PRIMARY CENTRAL NERVOUS SYSTEM TUMORS
In preparing *Primary Central Nervous System Tumors: Pathogenesis and Therapy*, we set out to write a textbook that would be comprehensive yet accessible. We wanted readers to have access to the cutting-edge advances in molecular biology and genomics that are revolutionizing neuro-oncology; at the same time, we required that our authors provide practical clinical information that is needed to make intelligent therapeutic decisions.

As you will see, we recruited some of the most accomplished neurologists, oncologists, cancer scientists, and nurses to participate as authors. We hope that you will find this book useful in your practice and highly informative.

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Contents

Part I  General Principles

1  Epidemiology and Risk Factors ............................................. 3
   Christine Lu-Emerson and Andrew D. Norden

2  Molecular Pathogenesis ..................................................... 27
   Howard Colman and Ken Aldape

3  Cellular Origins of Malignant Glioma: The Cancer Stem Cell Polemic .................................................. 45
   Christopher M. Taylor, Claire M. Sauvageot, Patrick Y.C. Wen,
   and Charles D. Stiles

4  Principles of Supportive Care ............................................. 55
   Jan Drappatz and Patrick Y.C. Wen

5  Principles of Clinical Trial Design and Response Assessment .... 85
   Nicholas Butowski and Susan Chang

6  Complications of Therapy .................................................. 103
   Derek R. Johnson, Jonathan B. Ashman, Paul D. Brown,
   Daniel H. Lachance, and Jan C. Buckner

7  Neuropsychological Function and Quality of Life .................. 143
   Jeffrey S. Wefel, Terri A. Armstrong, and Sadhna Kohli

Part II  Gliomas

8  Low-Grade Gliomas .......................................................... 173
   Jonathan H. Sherman, David Weintraub, M. Beatriz S. Lopes,
   and David Schiff

9  High-Grade Astrocytomas .................................................. 195
   Sith Sathornsumetee and David A. Reardon

10 Anaplastic Oligodendrogliomas and Mixed Gliomas ............... 233
    Jacoline E.C. Bromberg and Martin J. van den Bent
<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Ependymomas</td>
<td>249</td>
</tr>
<tr>
<td></td>
<td>Mark R. Gilbert, Roberta Ruda, and Riccardo Soffietti</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Uncommon Gliomas in Adults: Brainstem Gliomas, Pilocytic Astrocytomas</td>
<td>263</td>
</tr>
<tr>
<td></td>
<td>Ryan Merrell and Andrew D. Norden</td>
<td></td>
</tr>
<tr>
<td>Part III</td>
<td>Other Tumor Types</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Pediatric Tumors</td>
<td>285</td>
</tr>
<tr>
<td></td>
<td>Michelle A. Lee, Nathan J. Robison, Susan N. Chi,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sridharan Gururangan, and Mark W. Kieran</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Primary Central Nervous System Lymphoma</td>
<td>333</td>
</tr>
<tr>
<td></td>
<td>Elizabeth R. Gerstner and Tracy T. Batchelor</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Meningiomas</td>
<td>355</td>
</tr>
<tr>
<td></td>
<td>Marc C. Chamberlain</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Pituitary Adenomas</td>
<td>377</td>
</tr>
<tr>
<td></td>
<td>Gabriel Zada, Whitney Woodmansee, Ursula Kaiser,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and Edward R. Laws</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Vestibular Schwannomas</td>
<td>401</td>
</tr>
<tr>
<td></td>
<td>Mohamed E. Abazeed, Frederick G. Barker, Scott R. Plotkin,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jay S. Loeffler, and Helen A. Shih</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Medulloblastomas</td>
<td>415</td>
</tr>
<tr>
<td></td>
<td>Alba A. Brandes and Enrico Franceschi</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Pineal Region Tumors</td>
<td>435</td>
</tr>
<tr>
<td></td>
<td>Harry C. Brastianos, Priscilla K. Brastianos, and Jaishri Blakeley</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Genetic Syndromes</td>
<td>457</td>
</tr>
<tr>
<td></td>
<td>Mikael L. Rinne and Scott R. Plotkin</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Rare Tumors</td>
<td>499</td>
</tr>
<tr>
<td></td>
<td>Erik J. Uhlmann and Andrew D. Norden</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Spinal Tumors</td>
<td>529</td>
</tr>
<tr>
<td></td>
<td>Camilo A. Molina, Ziya L. Gokaslan, and Daniel M. Sciubba</td>
<td></td>
</tr>
<tr>
<td>Index</td>
<td></td>
<td>549</td>
</tr>
</tbody>
</table>
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Part I
General Principles
Chapter 1
Epidemiology and Risk Factors

Christine Lu-Emerson and Andrew D. Norden

Keywords  Epidemiology  ·  Risk factors  ·  Prognosis  ·  Incidence  ·  Glioma  ·  Meningioma  ·  Ionizing radiation  ·  Cellular telephones  ·  Brain tumor

Introduction

It is estimated that at least 45,000 individuals in the United States will be diagnosed with a primary brain tumor in 2010. Currently, little is known about the specific causes or risk factors associated with brain tumor development. Epidemiologic studies are important for this reason as well as the morbidity and mortality associated with the diagnosis and treatment of these lesions. Descriptive studies have characterized the incidence, mortality, and survival rates for brain tumors overall as well as by tumor type and demographic characteristics of affected patients, including their age, sex, and geographic region. Databases in the United States that collect such information include the Central Brain Tumor Registry of the United States (www.cbtrus.org), the North American Association of Cancer Registries (www.naaccr.org), and the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) program (www.seer.cancer.gov). Analytic epidemiologic studies have either compared the risk of brain tumors in people with and without certain characteristics (cohort studies) or compared the histories of people with and without brain tumors (case–control studies) to provide information on a wide range of putative risk factors, including allergies, ionizing radiation, and variations in DNA repair genes. A number of large national and international case–control and cohort studies including both pediatric and adult patients are currently ongoing and more are planned for the near future. In addition, genetic and molecular studies have
yielded valuable information regarding genes that are now known to play a role in brain tumor progression or sensitivity to radiation or chemotherapy. The two most common types of brain tumors are gliomas and meningiomas, which together make up approximately 70% of all primary brain tumors; this chapter will focus on the epidemiology of these tumors.

**Gliomas**

*Population Epidemiology*

From 2002 to 2006, about 18.3 cases of new primary brain tumors were diagnosed per 100,000 person-years [1]. When adjusted by age, the incidence rate for females is statistically greater than for males (19.36 per 100,000 person-years vs 17.11 per 100,000 person-years) [1]. Analysis of this gender difference by histology reveals certain patterns. Males have a higher incidence of neuroepithelial tumors, especially gliomas and germ cell tumors, whereas meningiomas are more than twice as common in females [1]. Hormonal factors have been postulated as a possible explanation for these sex differences. In light of the observation that gender differences in glioblastoma rates begin to emerge around the time of menarche, one study theorized that female hormones may confer protection from glioblastoma development [2].

Descriptive epidemiologic studies have reported ethnic, racial, and geographic variations in the incidence of brain tumors, though many of these studies fail to control for confounding factors including inconsistent reporting, differences in diagnostic practices, and differences in accessibility to health care [3, 4]. However, certain trends consistently emerge. Overall, the incidence rate of all primary brain and central nervous system (CNS) tumors is greater in whites (18.52 per 100,000 person-years) than in blacks (15.81 per 100,000 person-years) [1]. Specifically, white non-Hispanics have a higher incidence (18.43 per 100,000 person-years) when compared to white Hispanics and black non-Hispanics (16.11 per 100,000 person-years and 15.71 per 100,000 person-years, respectively) [1]. In the United States, gliomas are at least twice as common in whites compared with blacks, whereas meningiomas and pituitary tumors are significantly more common among blacks [1]. Genetic differences are suspected to play a role in these discrepancies [5, 6].

Both the CBTRUS and SEER data have reported variations in incident rates of brain tumors by geographic location within the United States [1, 7]. There also appears to be variation worldwide. High-incidence countries, including those of Northern Europe, Australia, Canada, United States, and New Zealand, have a primary brain tumor incidence that is four times that of low-incidence countries, such as the Philippines and India [3, 4]. The incidence of malignant brain tumors in Japan is less than half of that in Northern Europe [4]. Unfortunately, various confounding factors render the meaning of these trends uncertain.
Between 2002 and 2006, the median age at diagnosis among all patients in the United States with primary brain tumors was 56 years [1, 7]. With the exception of germ cell tumors, the incidence of all major histologic tumor types increases with age, with the highest incidence among patients of ages 75–84 years [1]. Specifically, the incidence of glioblastoma and meningioma increases proportionally with advancing age, though a decline in the incidence rate for glioblastoma is seen in patients of ages 85 and older [1, 5, 7]. This correlation of incidence with age may reflect a number of factors, including the duration of certain exposures, the accumulation of genetic mutations required for transformation, and a progressive decline in immune surveillance [4]. The association between age and the incidence rates of high-grade versus low-grade tumors reveals an interesting pattern. The rates of high-grade and low-grade tumors are similar in patients younger than 45 years of age [8]. After the age of 45, the incidence of low-grade tumors decreases whereas the incidence of high-grade tumors remains stable or increases [8]. Whether this decreased rate of low-grade gliomas in older patients is due to some acquired protective factor or an increased likelihood of mutations needed for high-grade glioma development remains unknown. In the pediatric population, the incidence of germ cell tumors peaks in adolescence, whereas the rates of non-germ cell tumors decrease throughout childhood and adolescence [1]. These differences may reflect the inherent biologic variations of the tumors and the varied etiologic factors associated with histologic subtypes.

Survival and Prognosis

Survival time in brain tumor patients is strongly correlated with histologic type and patient age [1]. Patients with glioblastoma have the poorest survival in all age groups, and survival time decreases with advancing age within each tumor type [1, 7]. Thus, pediatric and young adult populations generally have improved survival compared to their older counterparts. The exception is those pediatric patients diagnosed before the age of 3; they have poorer survival than children of ages 3–14 years [9].

Between 2000 and 2005, the relative 2-year and 5-year survival probabilities from time of diagnosis for patients with primary malignant brain tumors were 32.5% and 23.7%, respectively [7]. Among glioma patients, the greatest improvement in survival occurred in patients with lower grade gliomas and in patients younger than 65 years of age [6]. Technological advances in radiology and molecular biology and increased accessibility to imaging likely play a role in this progress. Perhaps because of glioblastoma’s rapid growth rate, which ensures a brief prediagnosis period, patients with these tumors have not experienced a similar improvement in survival. In fact, very little change in 2-year survival has been observed among adults with primary malignant brain tumors. There was only a 1.4% difference between the 2-year survival rate among patients diagnosed in 1994 and those diagnosed in 2004 [6]. Over the past decade, the only treatment to definitively influence survival has
been temozolomide chemotherapy. As part of the standard treatment paradigm for glioblastoma, temozolomide improves median survival time by 2.5 months [10, 11]. More recently, bevacizumab received accelerated approval for recurrent glioblastoma based on two phase II clinical trials which showed an increase in response rate and 6-month progression-free survival; however, it is unclear if it confers an overall survival benefit [12, 13].

The poor survival associated with the majority of gliomas has important implications for the proper design and conduct of epidemiologic studies. Incident population-based studies often rely on proxy responders, who are surrogate responders for the individual enrolled in the study, due to the difficulties in identifying patients with aggressive disease prior to their death [4]. The recent interest in the use of serum biomarkers, such as levels of vascular endothelial growth factor (VEGF) and interleukin-8, offers the additional complication of dissecting whether the associations reflect etiologic or prognostic information [4, 14]. The use of hospital-based series may circumvent some of these issues, but it adds the challenge of identifying appropriate control subjects [4].

There is great interest in identifying prognostic factors associated with survival probability and survival time. Traditionally, the strongest prognostic indicators for primary malignant brain tumors are age and histology [1]. Other factors implicated in glioblastoma prognosis include the following: preoperative and postoperative tumor size, Karnofsky Performance Status (KPS), extent of resection, capacity for complete resection, degree of necrosis, enhancement on preoperative MRI studies, volume of residual disease, tumor location, patient condition prior to radiation therapy, presurgical serum albumin level, hyperglycemia, and marital status [15–20].

Recent studies have focused on the use of molecular and genetic markers as prognostic indicators. For example, the co-deletion of chromosomes 1p and 19q confers a favorable prognosis among patients with oligodendrogliomas [21]. An association study of 141 glioma cases reported two genotypes (GLTSCR-1 exon-1 and ERCC2 exon-22) associated with the minimal 19q deletion region as independent predictors for survival [22]. For glioblastomas and other gliomas, the following molecular markers have been implicated in prognosis: overexpression or amplification of epidermal growth factor receptor (EGFR), TP53 mutation and expression, CDKN2A alterations and deletions, and MDM2 amplifications [23–33]. To add another layer of complexity, survival appears to depend on a relationship between age at diagnosis and molecular markers. For instance, one group found that overall, there was no difference in survival regardless of the tumor’s expression of EGFR or TP53 [34]. However, a sub-analysis revealed that younger patients had a shorter survival time when their tumors overexpressed EGFR but were TP53 wildtype. This finding was reproduced in an additional 42 tumors from younger patients. The positive prognostic effect of allelic loss of chromosome 1p and the negative prognostic effect of CDKN2A/p16 alterations are also age-dependent [24]. This relationship between age and genetic changes in glioblastoma implies that the underlying pathogenetic mechanisms involved in glioblastoma formation may vary with age.
Epigenetic silencing of the MGMT promoter was found to be an independent favorable prognostic factor in glioblastoma patients, regardless of treatment type, with an increased survival benefit conferred to those patients undergoing radiotherapy and temozolomide, as compared to radiotherapy alone [35]. A follow-up analysis demonstrated an association between MGMT promoter hypermethylation and improved survival in younger patients with good initial performance status [36]. Human telomerase (hTERT) expression is an independent predictor of outcome in many cancers. In glioblastoma, survival differed significantly by the hTERT MNS16A genotype with median survivals of 25.1, 14.7, and 14.6 months for the SS, SL, and LL genotypes, respectively [37]. Thus, the MNS16A genotype may potentially be exploited as a biomarker of survival or treatment response.

Immunologic factors have also been implicated in glioblastoma prognosis. Patients with glioblastoma who had elevated immunoglobulin E (IgE) levels lived 9 months longer when compared to those with normal or lower IgE levels [33]. As will be discussed later, there is speculation that IgE levels may correlate with better antitumor defenses, less aggressive tumor, or with antitumor activity itself [38–40]. Interleukin-6 (IL-6) is a cytokine that may promote glioblastoma growth. Amplification of IL-6 is significantly associated with decreased survival in glioblastoma patients [41]. A recent study demonstrated that glioma stem cells preferentially express IL-6 receptors and that targeting of these receptors in glial stem cells increases survival of mice with intracranial human glioma xenografts [42].

Risk Factors

Only a few causal risk factors have been identified for brain tumors. Heritable syndromes, including the neurofibromatosis, Li–Fraumeni syndrome, and Turcot syndrome, have provided greater insight into some of the genetic factors involved in tumorigenesis. Thus far, the only firmly established exogenous environmental cause of gliomas is exposure to high-dose radiation [4, 43, 44]. Analytic epidemiologic studies with either cohort or case–control designs have sought to elucidate new risk factors and refine established risk factors.

Hormonal and Reproductive Factors

The risk of glioma is lower in women than in men. Incidence rates from the New York State Cancer Registry suggest that this protective effect of sex becomes evident at the age of menarche, greatest around the time of menopause, and then decreases in the postmenopausal years [2]. SEER data suggest that the rate of glioma in women is at least 40% less than in men for all age groups 30 years and older [7]. Comparison of premenopausal and postmenopausal women shows that postmenopausal women are at greater risk for gliomas and vestibular schwannomas [45]. Results linking parity to glioma risk are more ambiguous, with some studies suggesting lower risk among parous women and other studies demonstrating no association [45–49].
There have been inconsistent results documenting the use of oral contraceptive use or hormone replacement therapy as a risk factor for gliomas [47, 49, 50].

**Ionizing Radiation**

Strong and consistent results from prospective studies indicate that there is a linear dose–response relationship between ionizing radiation exposure and glioma risk [4, 43, 44]. A stronger association for meningiomas exists and will be discussed later in this chapter. In children who were treated with ionizing radiation for tinea capitis, there is a relatively increased risk for nerve sheath tumors (relative risk [RR] 18), meningiomas (RR 10), and gliomas (RR 3) [4, 44]. Atomic bomb survivors have demonstrated a high incidence of meningiomas, glioma, schwannoma, and pituitary tumors [51]. The effect of diagnostic and therapeutic X-rays of the head and neck on the risk of glioma and meningioma development is less clear. One study found that if radiographs were taken before the age of 20 or occurred before the year of 1945, there was an increase in meningioma risk [52–55]. Radiotherapy has also been implicated in glioma pathogenesis. A Finnish study found that second brain tumors occurred more frequently than expected among patients previously treated for brain tumors with radiotherapy; however, these findings may be confounded by the fact that patients treated with radiation have higher grade tumors and are more likely to have recurrence [56]. Finally, it should be considered that genetic factors likely influence the degree of risk from these exposures. As an example, a pediatric study found that children with acute lymphoblastic leukemia who were treated with cranial irradiation and antimetabolite therapy were significantly more likely to develop a subsequent brain cancer if they harbored germline polymorphisms leading to low or absent thiopurine methyltransferase activity [57].

**Cellular Telephone Usage**

With the increasingly frequent use of cellular phones worldwide, multiple studies have investigated the relationship between cell phone usage and brain tumor risk. Many early studies found no evidence for this relationship, though sufficient numbers of long-term cellular phone users were lacking [58–60]. A case–control study found that the RR associated with cumulative use of a cellular telephone for more than 100 h was 1.0 for all types of tumors combined, with no evidence of higher risks among people who used cellular telephones for 60 or more minutes per day or regularly for 5 or more years [60]. However, the authors admitted that there was no sufficient data to evaluate the risks among long-term heavy users. One of the largest population-based case-controlled studies consisting of 1,522 glioma cases and 3,301 control cases in 5 Northern European countries found no evidence of increased glioma risk associated with regular mobile phone use [61]. There was no significant association with duration of use, years since first use, cumulative number of calls, or cumulative hours of use. The authors did note a slightly increased odds ratio (OR) of glioma development in individuals with ipsilateral use of the phone for 10 or more years [61]. Another study looking at different histologic types of brain
tumor found that the relative risk is greater for vestibular schwannoma when compared to meningioma and glioma, especially with ipsilateral use [62]. Unfortunately, many of these studies are confounded by selection and recall biases. As the number of long-term phone users increases, it will be possible to identify more patients with glioma who are also long-term cellular phone users, increasing the statistical power to address this potential risk factor in well-designed studies.

Other Possible Environmental or Behavioral Risk Factors

Historically, head trauma has been implicated in the development in some brain tumors. A case–control study of 476 glioma patients and 101 controls did not find an association between head injury and adult glioma formation [55]. Other studies have found that when any type of head injury is considered, the relative risk for glioma and other brain tumors’ development is slightly higher, but this may be due to a recall or response bias [4]. In an attempt to circumvent this reporting problem, a large cohort study examining the incidence of intracranial tumors after head injury was performed in Denmark [63]. There was no increased risk of glioma or meningioma during the 8-year follow-up, except during the first year. The authors suggested that the increased incidence may be attributed to early detection, though there was no concomitant decrease in cases during the subsequent years.

Much interest has surrounded the possibility that diet affects one’s risk for brain tumors. Abundant animal data have identified N-nitroso compounds, which are found in both endogenous and exogenous sources, as neurocarcinogenic. Animal data show that in utero exposure is especially tumorigenic [64–66]. Some studies have found that prenatal and perinatal exposure may cause DNA damage involved in human brain tumor development [44, 67]. However, another study of human maternal exposure to N-nitroso drugs found no increased risk of childhood brain tumors [68]. Similarly, much attention has surrounded oxidizing agents and the use of antioxidants. Oxidizing agents, which cause cumulative DNA damage, are thought to play an etiologic role in cancer. They too can be found in endogenous (aerobic respiration, cytochrome P450 system, nitric oxide) and exogenous sources. Antioxidants, whether by removing or decreasing the concentration of oxidizing agents, are theorized to minimize DNA damage or enhance DNA repair. Unfortunately, past epidemiologic studies have shown mixed data supporting a relationship between diet and brain tumors [44, 67, 69–73]. One pediatric case–control study evaluated the role of maternal nutrition during gestation and found no association between the mother’s gestational intake of nitrate, nitrite, or vitamin C and risk of brain tumor in the child [71]. A population-based case–control study in Nebraska found no association between intake of nitrate, nitrite, vitamin C, vitamin E, saturated fat, cholesterol, dietary fiber, and risk of adult glioma [72]. However, a study in San Francisco found that adults, especially men, who had gliomas consumed a diet higher in nitrates and cured food and lower in vitamin C-rich fruits and vegetables [73].

Tobacco is known to play a causative role in lung cancer. As N-nitroso compounds are also found in tobacco, it has been theorized that smoking may be
involved in the development of brain tumors. A meta-analysis in 2000 found no clear association between a mother’s smoking habits during pregnancy and risk of a brain tumor in the child [74]. In adults, studies do not show a significant contribution of tobacco smoking to the risk of brain tumor [4]. Similarly, alcohol consumption has not been consistently associated with brain tumor risk. Though a study in China found that adults with meningioma or glioma were more likely than controls to report alcohol consumption, a systematic review found that half of the studies investigating the effects of tobacco on brain tumor risk reported relative risks of less than 1 for any versus no alcohol use [70, 75].

With the exception of ionizing radiation, published studies have not found any consistent associations between putative risk factors and brain tumors. However, these studies have many potential limitations including small sample sizes, the use of proxy respondents resulting in invalid or imprecise exposure measures, inherited variations in metabolic and repair pathways, disease heterogeneity, and unaccounted-for protective conditions [4–6]. The dismal prognosis of most brain tumor patients provides the impetus to continue searching for environmental factors that might be modified to prevent disease.

**Genetic Factors**

The proposed pathogenesis of brain tumors involves the progressive accumulation of genetic alterations that allow cells to evade normal regulatory mechanisms. With our increasing knowledge of the molecular pathways involved in tumorigenesis and with the advent of new technologies, there has been a renewed focus on examining associations between genotypes and diseases. We will not discuss genetic syndromes in this chapter as they are reviewed elsewhere in this book. Because only a small proportion of brain tumors are due to inherited mutations in highly penetrant genes, attention has been focused on polymorphisms in genes that may influence susceptibility to brain tumors in the setting of environmental exposures. Familial aggregation of gliomas implicates an underlying genetic influence, but studies have been limited by the ability to distinguish inherited characteristics from shared environmental exposures.

**Familial Aggregation**

About 5% of glioma cases are familial, though the pattern of inheritance is usually uncertain. For instance, one study attributed approximately 2% of glioma cases to an autosomal recessive gene; however, another study proposed that a low penetrant dominant gene, rather than an autosomal recessive gene, was responsible for the familial clustering of brain tumors in their study [76, 77]. A segregation analysis of families, including over 5,000 relatives of 639 probands, showed that a Mendelian polygenic model best explained the patterns of brain tumor occurrence [78]. The first molecularly based genetic evidence for familial aggregation used linkage analysis to demonstrate a novel susceptibility locus at chromosome 15q23–q26.3 [79]. In their
paper, the authors note that this region harbors several candidate genes including the oncogene FES, insulin-like growth factor 1 receptor, and the RECQL3 locus which is involved in Bloom syndrome, a tumor predisposition syndrome. Investigation of TP53 polymorphisms suggested that the CC–CG–CC-specific polymorphism combination conferred an increased risk of brain tumors when analysis was confined to those with a history of cancer in the family [80]. On the other hand, other epidemiologic studies of families have demonstrated a pattern of occurrence that implicates environmental causes.

Polymorphisms in Genes Relevant to Cancer

The majority of primary brain tumors are likely due to polymorphisms in genes that confer susceptibility to brain tumors in conjunction with environmental exposures. Potential candidates include genes involved in oxidative metabolism, carcinogen detoxification, DNA repair, and immune response. Studies focused on the cytochrome P450 system and glutathione-S-transferase (GST) system have yielded conflicting results. One study reported that presence of the CYP2D6 poor metabolizer polymorphism increased astrocytoma and meningioma risks, but another study could not replicate these results [81, 82]. A study of constitutive GST polymorphisms found little evidence for association of GST variants with glioma, though the GSTT1 deletion was nearly significantly more common among glioblastoma cases with p53 mutations [83]. An international population-based case–control study found no association between several GST polymorphisms and CYP1A1 and adult brain tumor risk, though a weak association between the G–C GSTP1 105/114 haplotype and glioma was found [84].

The DNA repair pathway has also been extensively investigated. The DNA repair system is complex, involving more than 130 genes, many of which are polymorphic. The ERCC1 and ERCC2 genes are important in nucleotide excision repair. Polymorphisms in ERCC1 and ERCC2 have been linked to glioma [22, 85, 86]. The gene XRCC7 is involved in non-homologous end joining break repair. The TT genotype of XRCC7 is more common in glioma cases than in controls and may represent a marker of glioma susceptibility [87]. It has been proposed that polymorphisms in the MGMT gene, which encodes another important repair enzyme, may be associated with tumor development. A case–control study found that the V1/wildtype heterozygous genotype of the MGMT gene was detected with significantly increased frequency in de novo glioblastomas and may contribute to the tumor’s pathogenesis [88].

Another feature of glioma pathogenesis is cell cycle dysregulation. MDM2 is a negative regulator of p53 and is critical for maintaining fidelity of the cell cycle process. One study showed that a polymorphism in the MDM2 promoter resulted in higher expression of MDM2 with a concomitant decrease in the expression of p53; this, in turn, was significantly associated with earlier age of tumor development and multiple tumor sites in patients with Li–Fraumeni syndrome [89]. Though there appears to be an inverse relationship between TP53 and MDM2, the complex association between these genes remains elusive.
Infections and Immunologic Factors

There is a consistent, inverse relationship between adult glioma and history of allergies, high serological levels of IgE, history of varicella-zoster virus (VZV) infection, and presence of immunoglobulin G (IgG) antibodies to VZV [40, 90–95]. A large population-based case–control study in the United Kingdom found that risk of glioma was reduced in subjects reporting a history of asthma, hay fever, eczema, and other allergies [40]. A meta-analysis found that self-reported allergies were associated with a 40% reduction in the risk of glioma [96]. Mechanisms underlying this protective effect have not been identified. Possible explanations include anti-inflammatory effects from the cytokines involved in allergic and autoimmune disease, increased immunosurveillance, or suppression of the immune system by the tumor [38–40]. One study demonstrated that total IgE levels were lower in glioma cases than in controls, supporting a relation between allergic disease and glioma risk [94]. One problem with earlier case–control studies is the reliance on self-reporting, which may be influenced by the presence of glioma. Furthermore, self-reporting often relies on the use of proxy respondents secondary to the low survival probability associated with glioblastoma [5]. These proxy reports may not be reliable, as proxy respondents report fewer allergic conditions for index subjects than do self-reporting respondents [92]. Consequently, much attention has focused on the use of germline polymorphisms in genes associated with asthma and allergies as potential biomarkers. One population-based case–control study looked at five single nucleotide polymorphisms (SNP) on three genes previously associated with asthma (IL-4RA, IL-13, and ADAM33) [91]. There was a clear inverse relationship between polymorphism–glioblastoma association and polymorphism–asthma association, consistent with past findings that patients with asthma or allergic conditions are less likely to have glioblastoma. Because this study evaluated germline polymorphisms, its results cannot be attributed to recall bias or effects the tumor has on the immune system. Another study confirmed that the same IL-13 SNP (C1112T CT, TT) was inversely associated with IgE levels in controls [93].

Human leukocyte antigen (HLA) polymorphisms are known to play a role in the course of various inflammatory diseases, immune disorders, and malignancies. These cell surface molecules mediate interactions between tumor cells and the host immune response. Several studies have reported associations between HLA polymorphisms and the risk of malignant glioma [97, 98]. The HLA genotype B*13 and the HLA haplotype B*07-Cw*07 are positively associated with glioblastoma [99]. Interestingly, B*07 and B*07-Cw*07 are much more common in Caucasians, who have a higher incidence of glioblastoma. A follow-up study could not confirm these findings, but found that the HLA genotype A*32, which had previously been shown to be linked with a favorable prognosis in glioblastoma patients, was negatively associated with occurrence of GBM [100].

A variety of viral infections, including papovaviruses, adenoviruses, retroviruses, herpes viruses, and influenza, have been proposed to play an etiologic role in primary brain tumor formation [5, 14, 101]. Conclusive results regarding roles of these infectious agents in human gliomas have remained elusive [3, 4]. Two studies found
that prior clinical infection with VZV and anti-VZV IgG levels may be inversely associated with the risk of glioma in adults [102, 103]. It is unclear whether this relationship stems from the specific immune system’s response to antigens or from exposure to the antigen itself [94, 95]. The SV40 virus was implicated in brain tumor formation when an unknown proportion of inactive and live polio viruses were contaminated [104]. A German study which followed children over a 20-year period found that those inoculated with contaminated polio vaccine had a higher occurrence of glioblastoma, medulloblastoma, and other brain tumors when compared to those children who did not receive the contaminated vaccine [105]. A study in the United States found no difference in tumor risk for glioma and meningioma when they compared the two groups of children, though one study did show the incidence of ependymoma to be greater in children who received the contaminated vaccine [104, 106]. Such findings need to be validated in studies which are able to detect and confirm infection.

**Meningiomas**

**Population Epidemiology**

Meningiomas are tumors derived from meningothelial cells and represent the most frequently diagnosed brain tumor, comprising 33.6% of all primary brain and CNS tumors in the United States between 2002 and 2006 [1]. According to the World Health Organization (WHO), these tumors are classified as grade I (benign), grade II (atypical), or grade III (malignant) [107]. The prevalence of meningioma is about 97.5 per 100,000 people in the United States, with the incidence rates increasing over the time [108]. Meningiomas are more than twice as common in females [1]. Unlike gliomas, the incidence rates for black non-Hispanics are higher than those for white non-Hispanics and Hispanics [1]. Similar to gliomas, the risk of meningioma increases with age [1]. The observed increase in incidence over time probably stems from increased availability and use of imaging and from the inclusion of benign brain tumors into state cancer registries [108]. The Benign Brain Tumor Cancer Registries Amendment Act (HR 5204) was passed in 2002 and mandates the registration of benign brain tumors including meningioma [109]. With this act implemented on January 1, 2004, one hopes that reported incidence rates and survival times will be more accurate. Thus far, epidemiologic data for meningiomas have been limited by incomplete reporting, potential selection bias, and limited follow-up information [108]. The unadjusted 5-year survival rate for meningioma patients is 69%; when stratified by age, the rate is 81% among patients younger than 65 years of age and 56% among patients of ages 65 years or older [110]. Patients with a benign meningioma (WHO grade I) have a 5-year survival probability of 70%, whereas those with atypical (WHO grade II) and malignant (WHO grade III) meningiomas have a 5-year survival probability of 75 and 55%, respectively [110].


**Exogenous Risk Factors**

**Ionizing Radiation**

As for gliomas, the main environmental risk factor for meningioma is exposure to ionizing radiation, though the risk of meningioma is higher, ranging from sixfold to tenfold [53, 111–114]. A study of atomic bomb survivors in Japan found a statistically significant dose-related excess of CNS tumors, including meningiomas, in the cohort who received high and moderate doses of radiation [112]. Radiotherapy for primary intracranial tumors has been linked to secondary brain tumors, including meningiomas [56, 113]. As mentioned above, the Tinea Capitis Cohort followed children who received low-dose radiation therapy for scalp ringworm between 1948 and 1960. The study found a RR of 9.5 for meningioma development [113, 115]. However, in the entire cohort, meningiomas developed in less than 1% of children who received radiation, suggesting that factors other than radiation are important [116].

The effect of diagnostic dental X-ray studies on the risk of meningioma development has garnered much interest, especially as it used to be the primary source of ionizing radiation to the head and neck. Results of epidemiologic studies in this area are mixed. Initial studies showed that individuals who underwent repeated full-mouth dental X-ray studies, especially before the age of 20 or before 1945, had a fourfold increased risk of meningioma development [54, 117–119]. These findings were not replicated in other studies [120, 121]. In a series of 200 meningioma patients, full-mouth dental X-rays performed at least 20 years previously were associated with a significantly increased risk of meningioma (OR 2.06, 95% confidence interval [CI] 1.03–4.17), although there was no evidence for a dose-dependent relationship [53]. Unfortunately, there is a paucity of large-scale studies of meningioma risk in the current era, which has seen a decrease in dental X-ray doses but an increase in new radiographic procedures such as computed tomography (CT).

**Hormones**

An association between hormones and meningioma risk has been proposed. This is based on several lines of evidence, including the increased incidence of meningioma in females; the presence of estrogen, progesterone, and androgen receptors on some meningiomas; an association between breast cancer and meningiomas; observations that meningiomas vary in size during the menstrual cycle and pregnancy; and reports of meningioma cell proliferation after estrogen exposure in vitro [108, 122].

The majority of benign meningiomas possess progesterone receptors [123–125]. These receptors may influence prognosis, including risk of recurrence and survival [123, 126, 127]. One study of 60 benign meningiomas found a positive association between recurrence and the absence of progesterone receptor [126]. A larger study of 239 patients with meningiomas analyzed the tumors for progesterone and estrogen receptor status [127]. The presence of progesterone receptors was
associated with favorable outcomes. However, a retrospective study looking at the prognostic value of progesterone receptors in meningiomas found no correlation between progesterone receptor status and recurrence rates in benign (WHO grade I) tumors [128]. To date, the significance of the progesterone receptor status remains unclear.

The significance of estrogen receptors in meningioma is even less certain. The prevalence rate has varied from 0 to almost 95% in the published literature, and there may be some variation based on estrogen receptor isoforms [123, 125, 129–131]. The issue of receptor isoform is particularly interesting because the breast cancer literature suggests that a particular isoform may influence the tumor’s response to therapy [132, 133]. In fact, tamoxifen and other antiestrogen drugs have been studied in meningiomas with mixed results [134–136]. Though there is no current data relating the various estrogen isoforms to meningiomas, one can theorize that further understanding in this arena may increase our ability to successfully select candidates for antiestrogen therapies.

The use of exogenous hormones such as oral contraceptives and hormone replacement therapy in the pathogenesis of meningioma has only begun to be explored [50, 122, 137–140]. A case–control study from the Nurse’s Health Study (NHS) cohort concluded that hormone replacement therapy is positively associated with meningioma risk [139]. In this analysis, the RR of meningioma in premenopausal women was almost 2.5 times higher than in postmenopausal women who had never used hormones. Also, postmenopausal women who had used hormones in the past had a RR of 1.86 (95% CI 1.97–3.24) when compared to postmenopausal women who were hormone naive [139]. There was no association between meningioma risk and past or current use of oral contraceptives. The Million Women Study, a prospective study which looked at the association between anthropometric and lifestyle factors in association with brain tumors, did not find a relationship between oral contraceptive use and meningioma risk and did not report results for hormone replacement therapy use [137]. The largest case–control study, the Interphone Group, reported an increased relative risk of meningioma among postmenopausal women who had ever used hormone replacement therapy, although the findings were of borderline statistical significance (OR 1.7, 95% CI 1.0–2.8) [50]. A retrospective cohort study between 1993 and 2003 supported the positive NHS findings of an association between hormone replacement therapy use and meningioma risk [138]. However, a case–control study of 219 meningioma cases between 1987 and 1992 reported a protective effect for oral contraceptive use (OR 0.2, 95% CI 0.0–0.8) and a non-statistically significant protective effect associated with hormone replacement therapy use [140]. Thus far, the data supporting increased meningioma risk among oral contraceptive users are limited, though the current literature does suggest an increased risk of meningioma associated with the use of hormone replacement therapy.

There are conflicting results when examining the relationship between meningioma risk and pregnancy and menstruation [48, 50, 122, 137–140]. When compared to women whose age of menarche was younger than 12, there was a non-significant RR of 1.29 (95% CI 0.86–1.92) for meningioma development in
women whose age of menarche was between 12 and 14 years [139]. This risk increased for women with age of menarche more than 14 years of age (RR 1.97, 95% CI 1.06–3.66). There was also a trend for increased risk of meningioma for parous women when compared to nulliparous women. A Swedish study found no association between either parity or age at first birth and meningioma risk, though the study was unable to account for other possible meningioma risk factors such as use of exogenous hormones or radiation history [48]. The Interphone Study found an increasing meningioma risk in women less than 50 years with an increasing number of live births (OR 1.8, 95% CI 1.1–2.9 for three vs no live births) but found no association with menopausal status [50]. Thus, available data do not conclusively demonstrate an association of pregnancy and the menstrual cycle with meningioma risk.

**Association with Breast Cancer**

Several reports have proposed an association between breast cancer and meningioma [108, 141, 142]. Both tumors have common risk factors including hormone exposure, hormone receptor status, acceleration of presentation during pregnancy, and a possible shared genetic predisposition such as variants in DNA repair polymorphisms [141]. Of four studies that specifically considered this relationship, three found a statistically significant association [142–145]. Unfortunately, most of these studies have small sample sizes and fail to control for risk factors shared by both tumors [108]. In a population-based retrospective cohort evaluating the risk of subsequent breast cancer in meningioma patients and vice versa, the risks were moderately elevated regardless of the sequence [142]. Recent data from the Interphone Study suggest that mutations in the breast cancer susceptibility gene 1 interacting protein (BRIP1) are associated with meningioma risk [141].

**Head Trauma**

Studies of head trauma as a potential risk factor for meningioma have yielded inconsistent results. In the 1980s, several small case–control studies reported an increased risk of meningioma following head trauma, but other studies were unable to reproduce those results [108]. A cohort study of Danish residents hospitalized for head injury showed a standardized incidence ratio (SIR), for meningioma after the first year, of 1.2 (95% CI 0.8–1.7) [63].

**Family History**

Though the majority of meningiomas are sporadic, there has been some interest in examining the relationship between meningioma risk and family history. The Tinea Capitis Cohort found that patients who developed meningiomas after radiation were more likely to have family members affected with radiation-induced cancer, raising the suspicion of an inherited susceptibility [146]. One study in Sweden examined cancer risk in spouses and first-degree relatives of brain tumor patients and found
that a diagnosis of meningioma bestowed a twofold increase in meningioma risk to first-degree relatives, but not to spouses of affected individuals [147]. A recent study using the Swedish and Norwegian Registry Databases reported an increased risk of meningioma in individuals with a first-degree relative with meningioma [148]. Individuals with both an affected parent and sibling were at very high risk for early onset meningioma (SIR 265.2, 95% CI 25.0–975.2). In contrast, the SIR was 1.6 for individuals who were the children or siblings of an affected individual (95% CI 1.3–2 and 95% CI 1.2–2.2, respectively). At present, there is no published data from family-based linkage or segregation studies in meningioma.

**Genetic Polymorphisms**

With the advent of genomic studies, there is increased interest in examining the relationship between genetic variants and meningioma risk. Similar to gliomas, attention has been focused on genes involved in DNA repair, cell cycle regulation, and metabolic pathways [80, 81, 84, 114, 149, 150]. The Interphone Study reported 12 SNPs from DNA repair genes that were associated with meningioma [141]. In addition, this group reported a novel association between meningioma risk and three variants in the gene encoding *BRIP1*, which is involved in DNA repair of double-strand breaks via homologous recombination. As alluded to above, defects in *BRIP1* are linked to breast cancer susceptibility, implying that the association between meningioma and breast cancer may lie in DNA repair genes rather than or in addition to hormonal risk factors. Another gene found to be associated with meningioma risk is *ataxia telangiectasia mutated* or *ATM*, also involved in homologous and non-homologous DNA break repair [114, 141]. These DNA repair genes may also play a role in meningioma tumorigenesis in the setting of ionizing radiation. Polymorphisms in *TP53*, a well-known tumor suppressor gene, have not been associated with an increased risk of meningioma development; however, when the analysis was restricted to individuals with a family history of cancer, the CC–CG–CC variant was found to confer a 5.69-fold increase in meningioma risk (95% CI 1.81–17.96) [80].

**Conclusion**

Only a few causal factors have been identified for brain tumors. These include ionizing radiation and relatively rare inherited genetic syndromes. Advances in molecular biology have identified variants in specific genes, including those involved in DNA repair or cell cycle regulation, that play a role in tumorigenesis. Genetic studies have uncovered important genes or chromosomal abnormalities, such as 1p and 19q deletions in oligodendrogliomas, that are informative with respect to prognosis. Unfortunately, many studies looking at other potential etiologic factors have been inconclusive. This suggests that a complex interplay between genetic and environmental factors underlies the pathogenesis of most tumors. Future studies should be conducted on a large scale within collaborative group settings in order to achieve
sufficient patient numbers and adequacy of follow-up. With advances in molecular biology, genetics, and immunology, one hopes that the incorporation of genomic assays and biomarkers into brain tumor studies will help to identify additional etiologic and prognostic factors for these tumors.

References


1. Epidemiology and Risk Factors


Chapter 2
Molecular Pathogenesis

Howard Colman and Ken Aldape

Keywords  Molecular pathogenesis · Signal transduction pathway · Biomarker · p53 · EGFR (epidermal growth factor receptor) · IDH1 (isocitrate dehydrogenase 1) · IDH2 · Brain tumor

Introduction

Several decades of concentrated efforts have improved the understanding of the molecular biology and pathogenesis of primary brain tumors. Historically, primary brain tumors have been diagnosed and graded based on histopathologic criteria. However, as more data have accumulated regarding the molecular alterations underlying specific tumors, it has become clear that a number of key molecular alterations are associated with the initiation, progression, and clinical outcome of specific tumor histologies and grades. In addition, recent large-scale efforts at high-throughput molecular profiling of large cohorts of tumors, such as The Cancer Genome Atlas (TCGA) effort focused on glioblastoma (GBM) tumors, have identified novel molecular features that define specific clinically important tumor subgroups. Thus, in addition to contributing to a more detailed understanding of the origins and biology of primary brain tumors, these findings have contributed more refined definitions and knowledge of their molecular heterogeneity, and this knowledge plays an increasingly important role in the current approaches for diagnosis, grading, and treatment decisions. Together, these efforts have further refined our understanding of the molecular pathogenesis of these tumors and provided a basis for potential “personalization” of therapy based on the molecular features of individual tumors.
Gliomas

Gliomas are the most common primary tumors in adults. The most common histopathologic subtypes of gliomas are astrocytomas and oligodendrogliomas. These tumors are named for morphologic and immunohistochemical similarities between the normal glial cell types (astrocytes and oligodendrocytes) and the tumor cells in these histologies. Under the current WHO criteria, these tumors are also graded based on histopathologic features and criteria [1]. As described below, while these tumors share histologic features of glial lineages, the molecular alterations, biology, and natural history observed in the different histologies and different grades of tumors are quite distinct. These findings indicate that there are biologic and clinically important differences in either the cell of origin, initiating events, and/or molecular pathogenesis of progression between tumor types.

Low-Grade and Intermediate-Grade Gliomas

Diffuse Astrocytoma, WHO Grade II

p53

The tumor suppressor gene TP53 which encodes for the p53 protein has been clearly implicated in the pathogenesis of diffuse low-grade astrocytomas. This multifunctional molecule has been called a “guardian of the genome” (PMID: 7475551) and plays an important role in multiple cellular pathways related to oncogenesis including cellular response to DNA damage, cell cycle regulation, and cell death (apoptosis). Cells without functional p53 are thus prone to DNA instability and lack several of the key regulatory pathways that prevent survival and proliferation of cells with significant DNA damage.

The potentially important role of p53 in the molecular oncogenesis of low-grade astrocytoma is suggested by several observations. First, diffuse astrocytomas (along with higher-grade astrocytomas) occur at increased frequency in patients with inherited mutations in TP53 or Li–Fraumeni syndrome. Second, data from mouse models indicate that p53 mutations alone can contribute to immortalization and increased proliferation of astrocytes [2] and in combination with other genetic alterations can result in glioma formation [3, 4]. Perhaps most importantly, inactivating mutations in p53 are observed in a majority (>50%) of WHO Grade II astrocytomas [5, 6] and a slightly lower percentage of anaplastic astrocytomas (WHO Grade III). Together, these data suggest that p53 mutation or inactivation is an early and causative event in astrocytoma pathogenesis.

In addition to the previously described role of p53 in low-grade astrocytoma, new data suggest that this gene also plays a larger role in high-grade astrocytomas than previously recognized [7]. While prior data had suggested that p53 alterations were relatively rare in glioblastoma, recent results from the TCGA study reported a higher than expected rate of p53 mutation in these tumors. These findings suggest that either a larger percentage of GBM tumors arise from lower-grade tumors...
(see discussion of primary vs secondary GBM below) or that p53 alteration plays a more significant role in de novo high-grade astrocytoma than previously thought. Alternatively, a bias for secondary tumors in the sample set profiled by TCGA could also explain a higher p53 mutation rate in this data set compared to others.

Platelet-Derived Growth Factor (PDGF)

PDGF is a secreted protein that binds to the PDGFR tyrosine kinase. PDGF and PDGFR are often expressed by the same cells, resulting in the potential for both autocrine and paracrine stimulatory activities. PDGF plays an important part in neural development, particularly in the regulation of glial precursors [8]. PDGF has also been implicated in the pathogenesis of low-grade astrocytoma in several ways. Exogenous addition or overexpression of PDGF can result in increased proliferation or transformation of glial cells [9, 10]. Overexpression of both PDGF and PDGFR is also observed in low-grade astrocytomas [11].

However, it appears that PDGF overexpression alone is not sufficient for astrocytoma initiation and may depend on interactions with other molecular alterations. For example, alterations in p53 are highly correlated with PDGF overexpression in low-grade astrocytoma, suggesting a cooperative interaction [11]. In addition, the effects of PDGF overexpression in mouse models of tumor initiation depend on other alterations that are present. Overexpression of PDGF alone in glial progenitors led to tumors with an oligodendrogial phenotype, while overexpression of PDGF along with activation of Akt in these same glial progenitors resulted in a shift in tumor histology toward an astrocytic phenotype [12]. Thus, these data suggest that PDGF may play an important role in astrocytoma pathogenesis and that the effects of PDGF on tumor initiation and histology may be dependent on both the cell of origin and the status of the p53 and other signaling pathways.

IDH1 and IDH2 Mutations in Astrocytoma

Recent efforts at comprehensive sequencing to detect gene mutations in glioblastoma led to the novel observation of mutations in the isocitrate dehydrogenase genes IDH1 and IDH2 in a subset of these high-grade tumors [13, 14]. Additional studies demonstrated that mutations in these genes were also found in a large percentage (>50–80%) of low-grade astrocytomas and oligodendrogliomas [15–18]. High rates of mutations (>70%) were also observed in anaplastic astrocytomas (WHO Grade III) and glioblastomas (WHO Grade IV) that arose from lower-grade tumors, but generally not in primary glioblastomas that had no known lower-grade precursor. In addition, IDH1 mutations are highly correlated with both p53 mutation and 1p/19q loss (see below) in individual tumors [16]. While the biologic effect of IDH1/IDH2 mutation on oncogenesis remains unclear, these data indicate that mutation in IDH1 and/or IDH2 may be an important early step in the molecular pathogenesis of low-grade astrocytoma and oligodendroglioma, as well as secondary higher-grade gliomas and is a focus of ongoing investigations [19].
Other DNA Changes

Although much less prominent than in higher-grade astrocytoma, there are several less common alterations at the DNA and epigenetic level that have been noted in low-grade astrocytoma. These include the gain of chromosome 7q, loss of regions of chromosome 22q, and gains of regions of chromosomes 5p, 9, and 19p [20]. Combined loss of chromosomes 1p and 19q has also been observed in low-grade astrocytoma, although at much lower rates than in oligodendroglioma [21].

Recent genome-wide studies of DNA alterations associated with risk of glioma development have identified single nucleotide polymorphisms (SNPs) in several genes. These individual genes include CDKN2A and CDKN2B, which are involved in the regulation of cell cycle, and genes involved in regulation of telomeres including RTEL1 and TERT [22, 23]. The finding of increased risk of glioma in patients with germ line alterations in these genes strongly suggests a mechanistic role of these genes in glioma development.

Prognostic and Predictive Factors in Low-Grade Astrocytoma

While the list of potentially mechanistically important molecular alterations in low-grade gliomas continues to grow, the prognostic or predictive power of these markers to date has been less important in low-grade versus high-grade gliomas. Clinicopathologic factors that have been demonstrated to impact survival in low-grade astrocytoma include patient age, extent of resection, radiographic enhancement, and performance status [24–26]. Overall, neither mutation of p53 nor overexpression of PDGF has significant prognostic impact within low-grade astrocytomas [27, 28]. However, molecular markers of proliferation including MIB-1/Ki-67 labeling and phosphorylated histone H3 (pHH3) staining are prognostic in low-grade and intermediate-grade astrocytomas, with higher indices of proliferation associated with worse prognosis [29, 30]. Although data are still accumulating, the high rate of mutation of IDH1/IDH2 in astrocytoma and oligodendroglioma suggest that these alterations may be associated with tumor initiation. Whereas these mutations do not have prognostic significance for low-grade tumors, they are associated with a favorable prognosis in high-grade tumors (WHO Grades III and IV) [18, 31, 32].

Anaplastic Astrocytoma

The majority of anaplastic astrocytomas (WHO Grade III) appear to arise from lower-grade tumors and thus share many of the signature molecular alterations observed in Grade II astrocytomas [1]. However, the more aggressive histopathology and clinical course of anaplastic astrocytoma are associated with several important molecular alterations that are also seen at higher frequencies in a subset of GBM (Grade IV) tumors (see Refs. [1, 33, 34] for review). These alterations associated with progression from low to intermediate grade include defects in the Rb pathway (discussed in more detail below) including mutations in RB1 and loss of the
$Ink4a/Arf$ locus on chromosome 9. In addition, loss of chromosomes 19q and 11p is seen at higher frequency in anaplastic astrocytoma than in low-grade tumors. A subset of anaplastic astrocytomas also demonstrate loss of chromosome 10 and/or $PTEN$ mutations similar to many GBM tumors.

**Oligodendroglioma and Anaplastic Oligodendroglioma**

Overall, oligodendroglial lineage tumors demonstrate a significantly different spectrum of molecular alterations compared to astrocytic tumors. By far the most common alteration seen in both low-grade and intermediate-grade oligodendrogliomas is concurrent deletion of chromosomes 1p and 19q that is observed in up to 50–80% of cases [35, 36]. In the majority of tumors this is due to an unbalanced translocation [37]. These findings are potentially consistent with a central role of this alteration in the molecular pathogenesis of oligodendroglial tumors, however, the specific role of a number of candidate genes in these regions remains to be elucidated. Loss of chromosomes 1p and 19q is also an important prognostic factor in these tumors. Combined loss is associated with better prognosis and improved response to both radiation and chemotherapy and is often used clinically for treatment decision-making [38, 39]. More rarely, isolated loss of chromosome 1p or 19q is observed in oligodendroglioma, although these isolated losses are less prognostic than combined loss. Indeed, isolated loss of 19q is much more common in astrocytic tumors. Oligodendroglial tumors also demonstrate a high frequency of increased expression of both EGFR and PDGF/PDGFR and high rates of methylation of several genes including $p14$, $RB1$, $CDKN2A/CDKN2B$, and $MGMT$.

**Glioblastoma**

Glioblastoma (WHO Grade IV) represents the highest grade and most clinically aggressive form of glioma. Although these tumors represent a single histopathologic entity defined by WHO criteria and are distinguished from Grade III astrocytomas primarily by the presence of pseudopalisading necrosis and/or vascular proliferation [1], it is becoming increasingly clear that this single histopathologic entity actually comprises a surprisingly complex variety of molecular phenotypes.

**Secondary GBM**

Classically, glioblastomas have been described as primary or secondary based on their natural history and a series of findings over many years defining differences in molecular phenotype [1, 34]. Analyses of molecular alterations in glioblastoma have found that a minority of tumors demonstrated molecular alterations consistent with an evolution from a low-grade tumor and these tumors have been called “secondary” GBMs to describe their origins from lower-grade precursors. As described above, there are several molecular features found at high rates in low-grade tumors such as $p53$ [40] mutation or more recently $IDH1$ mutation [31, 41]. The origin of secondary
GBMs from lower-grade tumors is highlighted by the presence of these signature alterations in a minority of GBMs, in addition to evidence of additional important molecular alterations associated with tumor progression [40–42]. Secondary GBM is observed at higher frequencies in younger patients and is associated with better overall prognosis. Important molecular alterations associated with progression to anaplastic astrocytoma and finally secondary GBM include alterations in the Rb pathway and loss of parts of chromosome 10 and/or mutation of the tumor suppressor gene PTEN.

**Primary GBM**

In contrast, the majority of GBMs appear to arise de novo without any prior lower-grade lesion identified and have been called “primary” GBMs [1, 40]. These tumors typically lack the signature low-grade molecular alterations including p53 and IDH1/IDH2 mutation. Instead primary GBMs display a distinct spectrum of molecular alterations that at least to some extent are mutually exclusive with those of secondary GBM.

Secondary GBMs demonstrate a frequency of signature molecular alterations that several lines of data suggest are involved in the molecular pathogenesis of these tumors. First, these tumors have a high frequency of amplification of portions of chromosome 7 that include the epidermal growth factor receptor (EGFR) [43]. A subset of GBMs with EGFR amplification also demonstrate mutation of the receptor that results in loss of multiple exons and constitutive activation called the vIII mutant (EGFRvIII) [44]. In addition, primary GBMs have a high frequency of loss of the long arm of chromosome 10. This chromosome contains the important tumor suppressor gene PTEN that was initially identified based on its high rate of mutation in gliomas and other high-grade epithelial tumors [45–47]. In addition to loss of chromosome 10 in a high percentage of tumors, many GBMs also demonstrate mutation or loss of PTEN on the other chromosome. These observations along with the importance of this gene in key signaling pathways and mouse models of GBM demonstrate its importance in the molecular pathogenesis of these tumors. In addition to playing a role in primary GBM, alterations on chromosome 10 and in the PTEN gene are also seen in the progression of anaplastic astrocytoma to GBM, thus also implicating PTEN in the progression to secondary GBM. Primary GBMs are observed at higher frequencies in older patients and are associated with a worse prognosis.

**Key Functional Pathways in Glioma Pathogenesis**

The central molecular alterations described above impact several key signaling pathways in gliomas. Alterations at the DNA level (including chromosomal loss, gene amplification, or gene mutation) modulate pathway activity by virtue of gene dosage effects. Pathway activity may also be impacted by changes in gene expression levels or activation or inhibition of receptor-linked or intracellular signaling cascades.
These signaling pathways have been implicated in the molecular pathogenesis of gliomas through data from human tumor samples as well as preclinical and mouse models.

The p53 Pathway

As described above, the TP53 gene is an important tumor suppressor gene located on chromosome 17p13.1 that is centrally involved in multiple pathways regulating DNA integrity, cell cycle, and cell death [48]. In addition to mutation of the TP53 gene itself, the p53 pathway can be affected by alterations in several other regulatory genes/proteins. The MDM2 and MDM4 genes are antagonists of p53 that bind to the p53 promoter and inhibit its transcription. Amplification of both MDM2 and MDM4 has been identified in a subset of gliomas with intact p53 indicating an alternate mechanism for downregulation of this pathway [49]. In addition, a high proportion of gliomas contain deletions or mutations in the Ink4a/Arf locus which encodes regulators of both the p53 and Rb pathways [50–52]. Taken together, these data suggest that essentially all astrocytomas harbor important molecular alterations that affect the p53 pathway, although the frequency of specific alterations can vary by grade.

The Rb Pathway

Like TP53, the retinoblastoma (RB1) gene is a key tumor suppressor that has been implicated in the pathogenesis of many cancer types. The Rb protein plays a key role in regulating cell cycle progression and proliferation. Thus, cells with alterations in the Rb pathway have impaired regulation of these functions, resulting in increased cellular proliferation and a lack of response to anti-growth signals. The important role of several components of the Rb pathway in gliomagenesis has been demonstrated by alterations in these genes in human tumors and/or their mechanistic association with gliomagenesis in mouse models. The Rb pathway contains several positive and negative regulatory elements.

In normal, non-dividing cells, the Rb protein is inactive (hypophosphorylated) and binds to its regulatory partner E2F. Mutation or activation of Rb results in the dissociation from E2F and subsequent transcription of multiple genes involved in cell cycle progression and cellular proliferation. While mutations in the RB1 gene itself are relatively rare in low-grade astrocytoma, they can be seen in up to 30% of high-grade astrocytomas [53]. Alterations in other key genes/proteins in this pathway observed at significant rates in gliomas include the following: (1) amplification of the positive regulators CDK4, CDK6, and Cyclin D and (2) mutation, deletion, or decreased expression of the negative regulators p16, p15, and p27 [50–52, 54]. As with p53, the data suggest that while the specific component of the pathway altered in specific tumors can vary (and be mutually exclusive) essentially all gliomas demonstrate functional lesions in at least one key element of the Rb pathway.
Growth Factor Receptor Signaling and Angiogenesis

Receptor Tyrosine Kinases

A number of signaling pathways important in brain tumor pathogenesis involve specific growth factors and their associated receptor tyrosine kinases. Many of these growth factor receptors are cellular homologues of viral oncogenes and have been implicated in tumor initiation and progression of gliomas based on data from human tumors and mouse models. One example discussed above is PDGF, which is the cellular homologue of the oncogene v-sis. Another example is EGFR, the cellular homologue of the viral oncogene vErbB. EGFR binds the growth factors EGF and tumor growth factor (TGF-α). As discussed above, EGFR is implicated in the pathogenesis and progression of high-grade astrocytomas. As a result of their important role in tumor initiation and biology, these signaling pathways have also become central in the search for novel therapeutic agents for brain tumors and other cancers. A number of novel drugs and biologic agents have thus been developed to target individual or multiple signaling pathways that are in clinical trials or have been FDA approved for treatment of brain tumors. These therapeutic developments have been summarized in a number of reviews [55–62].

Downstream Signaling Pathways

Activation of EGFR, PDGFR, and other transmembrane receptors as a result of ligand binding or mutation affects a number of key intracellular signaling cascades. Three of the most important pathways in gliomas include the Ras/Raf/MAPK pathway, the PI3K/PTEN/AKT/mTOR pathway, and the angiogenesis pathways.

**Ras/Raf/MAPK**  Increased activation of the Ras/Raf/MAPK pathway has been implicated in promoting cell cycle progression and proliferation. One mechanism of activation of Ras in gliomas is the loss or negative regulatory activity of the NF1 protein as a result of mutations. While mutations in NF1 associated with development of low-grade pilocytic astrocytomas have been well described as part of the neurofibromatosis type 1 syndrome, they had not been described as prominent in high-grade astrocytomas. However, recent data from the TCGA effort have described mutation or somatic deletion of NF1 in 23% of sporadic GBM tumors [7, 63, 64]. The potential role of NF1 in the pathogenesis of high-grade astrocytomas is also demonstrated by the results of a number of mouse glioma model studies.

**PI3K/PTEN/AKT/mTOR**  The AKT pathway is also activated by a combination of transmembrane receptor signaling acting through PI3K and alterations at the DNA level involving PI3K and AKT in addition to PTEN. PTEN is a negative regulator of AKT and as described above, loss of chromosome 10 (containing the PTEN locus) and/or mutation or deletion of PTEN is seen in a high percentage of high-grade astrocytomas. In addition, recent data from the TCGA effort demonstrated lower percentages of mutations in PI3K subunits and AKT as potential novel mechanisms of activation of this pathway in GBM [7].
**Angiogenesis**  Increased vascularity and microvascular proliferation are important histopathologic features of GBM that separate it from lower-grade astrocytomas. One of the most important signaling factors associated with vascular proliferation in GBM and other tumors is VEGF which acts through multiple VEGF receptors (VEGFRs). VEGF can be secreted by tumor cells and is expressed at particularly high levels in areas of hypoxia and necrosis. Secreted VEGF binds VEGF receptors on vascular endothelial cells, resulting in growth and maturation of new blood vessels. Other signaling pathways including PDGF, EGF, and AKT can also promote angiogenesis both through activation of the VEGF/s VEGFR pathway and other mechanisms. Angiogenesis and angiogenesis-inducing signaling pathways have become an important therapeutic target in GBM and represent some of the most significant successes for targeted therapies in this disease [58, 59].

**Molecular Classification and Clinically Relevant Subtypes of Glioblastoma**

The molecular alterations associated with different histologies and grades of gliomas described above are derived from the work of many investigators over several years. However, recent technological developments have enabled more rapid and comprehensive investigation of the molecular characteristics and alterations of these and other tumors. While this global molecular understanding of glioma biology is still in evolution, these studies have already led to a number of novel observations that have potentially important clinical implications.

One of the key findings to come out of these global molecular profiling studies is that the single histopathologic entity defined by the WHO criteria as GBM actually consists of multiple molecular phenotypes that are characterized by significant differences in the molecular alterations observed at the DNA, RNA, and protein levels [7, 63–70]. One of the most powerful of these approaches has been global gene expression profiling in which the expression levels of 20,000 or more genes can be measured simultaneously from a single tumor sample. Application of various bioinformatic approaches to large data sets consisting of gene expression data from multiple tumors can be used to identify robust subgroups of tumors that share similar gene expression profiles. This approach has been taken by a number of groups [65–70]. While the names of the subtypes and the specific genes that define them vary between these studies, there are a number of aspects that are common across many analyses. In particular, the majority of these studies have identified at least one molecular subtype of GBM that is characterized by increased levels of expression of genes associated with mesenchymal differentiation, extracellular matrix, invasion, and angiogenesis. These “mesenchymal” tumors are associated with worse prognosis in most studies and may be associated with “primary” GBMs. Another molecular subtype of GBM that has been identified and validated in multiple data sets is characterized by increased expression of genes associated with normal neural tissues or neural development. These “proneural” tumors have been associated with better prognosis and “secondary” GBMs (and see below). Figure 2.1a and b highlights examples of gene expression subtypes identified in independent data sets.
The identification of robust molecular subtypes of GBM has been accelerated even further by the comprehensive effort to molecularly characterize a large cohort of GBM tumors as part of The Cancer Genome Atlas (TCGA) Network effort. Integrated analyses of GBM DNA copy number, mutation, and gene expression from this effort further highlight the potentially important links between molecular phenotype and clinical outcome [7, 63, 64]. These studies suggest that GBM tumors with proneural gene expression patterns were associated with high rates of point mutations in IDH1, amplification of PDGFRα, and mutation or loss of heterozygosity of TP53 [63]. Classical tumors in this gene expression classification were associated with high rates of amplification of chromosome 7 and EGFR amplification, while mesenchymal tumors were associated with higher rates of loss of chromosome 17q11.2 (containing NF1) and mutation of the NF1 gene [63]. These
data are summarized in Fig. 2.1c adapted from Verhaak et al. [63]. In addition, analysis of clinical outcomes in this retrospective study suggested that there was a differential response to therapy as a function of molecular subgroups.

Taken together, these data suggest that the prior classification of GBM tumors as primary or secondary can be further refined based on the prevalence of key molecular alterations observed within each subtype. The finding that a high proportion of low-grade astrocytomas and proneural GBM tumors demonstrate similar rates of p53 mutation, IDH1 mutation, and PDGF/PDGFR overexpression strongly suggests that the vast majority of secondary GBMs are actually proneural (and vice versa). On the other hand, primary GBMs appear to consist of several gene expression subtypes that are all associated with higher frequency of amplification of chromosome 7 and loss of chromosome 10 than proneural tumors. In addition, the distinct subtypes of primary GBM are also associated with additional specific alterations. For example, the mesenchymal subtype is associated with higher frequencies of chromosome 17q11 deletion (containing the NF1 gene) as well as higher frequencies of NF1 mutation. The newly described classical subtype is associated with higher level amplification of chromosome 7p11.2 and EGFR and loss of chromosome 9p21. A summary of this updated view of the pathogenesis of primary and secondary GBMs is shown in Fig. 2.2. Thus, while these data continue to evolve, it is highly likely that better understanding of these and other molecular alterations will eventually lead to both a more detailed understanding of the tumor biology and the identification of novel therapeutic targets for individual tumor subtypes.

![Fig. 2.2 An updated view of the development of primary and secondary glioblastoma highlighting key molecular alterations associated with specific tumor grades and/or molecular subtypes](image-url)
Prognostic and Predictive Markers

In addition to a better understanding of the molecular pathogenesis of gliomas, the growing molecular profiling data have led to the identification of molecular biomarkers that are beginning to be used to help guide patient therapy. Clinically relevant biomarkers can be roughly divided into those that are prognostic and predictive. Prognostic markers are associated with patient outcome or natural history of the disease in patients without treatment or in patients receiving non-targeted therapies. Predictive biomarkers are associated with differential outcome to treatment with a specific targeted therapy. Recent studies have identified several molecular markers prognostic of patient outcome to standard therapy (radiation and temozolomide [71]) in glioblastoma. These include MGMT promoter methylation [72] and a multigene predictor based on gene expression levels of multiple genes, many of which define the proneural and mesenchymal tumor types [73, 74].

Recent evidence from TCGA also identified an epigenetically defined tumor subset that appears independent of MGMT. The majority of low–intermediate-grade gliomas have been found to exhibit the CpG methylator phenotype (CIMP), analogous to prior descriptions of CIMP in colon cancer and other tumors [75]. CIMP-positive tumors are positively associated with IDH1 mutation and show improved prognosis, compared to CIMP-negative tumors. Future work will be required to define the causative role of CpG island methylation and gliomagenesis in CIMP-positive tumors.

The identification of molecular markers predictive of outcome to targeted therapies for GBM has been more problematic, due in part to the relative paucity of effective agents for this disease and the statistical difficulty of identifying responsive subgroups from the relatively small sample sizes in most GBM studies. For example, some studies found that high expression of EGFR [76] or presence of the vIII mutant of EGFR [77] was associated with improved outcome to EGFR inhibitors, while high levels of phosphorylated Akt [76] or low expression of PTEN [77] was associated with worse outcome to these agents. However, several subsequent studies in different types of GBM patients have failed to demonstrate a clear predictive power of these markers for treatment outcome with EGFR inhibitors [38]. Thus, the attempts to integrate and apply the growing body of high-throughput molecular profiling data in GBM to identify robust predictive biomarkers of outcome and sensitive or resistant molecular subtypes to specific targeted agents remain an active area of investigation in neuro-oncology.

Cell of Origin and the Tumor Stem Cell Hypothesis

Mouse Models

While our knowledge regarding important molecular events in the pathogenesis of gliomas is expanding exponentially, it is perhaps surprising that the cell of origin and key initiating events for initiation of specific tumor types remain obscure.
However, data from normal development, animal models, and recent identification of tumor stem cells from multiple primary brain tumors have shed some light on these important questions.

Gliomas are classified pathologically based on their resemblance to astrocytes and oligodendrocytes. While these cells have historically been hypothesized to be the cell of origin for astrocytomas and oligodendrogliomas, respectively, more recent data have brought this hypothesis into question. In particular, several lines of evidence from mouse models suggest that gliomas can originate from less differentiated normal cells (stem cells or progenitors) in addition to more differentiated cells (astrocytes or oligodendrocytes). Furthermore, both the cell of origin and initiating molecular events have a significant impact on the likelihood of tumorigenesis and ultimate tumor histopathology. For example, activation of Ras and AKT in neural progenitors resulted in high-grade astrocytoma but not when the same molecular alterations were targeted to more differentiated cells [78]. However, the addition of Ink4a/Arf deletion allowed tumor initiation in more differentiated cells with the addition of Ras, Ras + AKT [79], or EGFR [80]. Thus, tumor initiation depends not only on the oncogenic “hit” but also on the cell of origin. Additional oncogenic alterations in mouse models that result in different outcomes based on cell of origin and cooperating alterations include mutation of NF1, p53, and PTEN [81, 82], PDGF [83], and v-ErbB [84].

Tumor Stem Cells

Recent developments have highlighted the potentially important role of a subpopulation of cells within a tumor called tumor stem cells in many tumors including gliomas [85, 86]. The tumor stem cell hypothesis proposes that all the cells within a tumor are not equal, but rather that tumors contain a functional hierarchy of cells similar to that observed in the normal development of multiple human organs [87]. In this model, a small percentage of cells in the tumor called tumor stem cells possess the ability to self-renew and give rise to daughter cells that maintain the stem cell pool within the tumor. In addition, these tumor stem cells have the capacity to initiate tumors and divide and “differentiate” into a heterogeneous mix of cells that not only make up the bulk of the tumor but also actually lack the key stem cell properties of self-renewal and tumor initiation. Recent studies have identified populations of cells from GBM and other brain tumors with stem cell properties [88–98]. In some studies, these stem cells were defined by expression of the surface marker CD133 [89, 90]. However, other data suggest that while CD133 may be an enrichment marker for tumor stem cells, CD133-negative cells maintain tumor initiation properties in some cases [99, 100] and thus additional markers of brain tumor stem remain to be discovered. Other lines of evidence suggest that tumor cells with stem cell properties are associated with increased resistance to radiation and chemotherapy [101, 102], are associated with a perivascular location in human tumors [103], and may even promote angiogenesis [104]. Thus, while significant
controversy remains regarding the optimal functional and surface marker definitions of tumor stem cells in gliomas, there is increasing evidence that cells with stem cell properties play an important role in tumor initiation and treatment resistance in these and other tumors.

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Chapter 3
Cellular Origins of Malignant Glioma: The Cancer Stem Cell Polemic

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Keywords Glioma stem cells · CD133 · Neurospheres · Glioma cell of origin · Brain tumor

Introduction

Cellular heterogeneity is a distinctive feature of high-grade gliomas [1]. What are the cellular mechanisms that give rise to the collection of cell types that comprise glioblastoma multiforme? According to the clonal evolution model of tumor heterogeneity (also known as the stochastic model), tumor initiation occurs by an induced change in a single previously normal cell (Fig. 3.1a) [2]. This neoplastic cell has a selective growth advantage compared with the surrounding normal cells. Over time mutant cells are produced by acquired genetic instability, many of which are eliminated by the immune system or through a metabolic disadvantage. Occasionally, however, one of the mutant tumor cells acquires an additional selective advantage over the normal and tumor-initiating cells, making this new cell the precursor of a new tumor subpopulation. This model accounts for phenotypic as well as genetic heterogeneity within a given tumor and suggests that, through a selective evolutionary process, tumor cells become progressively more malignant. It also implies that all of the tumor cells retain some degree of tumorigenicity.

An alternative view of glioma heterogeneity is contained within the cancer stem cell model (also known as the hierarchical model) [3, 4]. The point of departure for this view of the oncogenic process is the discovery of multipotent neural progenitor cells in the postnatal brain by Reynolds and Wiess [5]. In accord with the cancer stem cell model, the cell of origin for a malignant glioma is a mutated, developmentally stalled neural progenitor that, like normal neural progenitors, is capable...
Fig. 3.1 Clonal evolution model versus cancer stem cell model. (A) Clonal evolution model. Through genetic and/or epigenetic changes, a somatic cell (white) acquires a proliferative advantage (yellow). Through genetic instability many variants are produced, but most die due to metabolic or immunologic disadvantage. Occasional changes increase the proliferative advantage (orange and red), allowing these variants to out-compete other existing clones. Over time, variants can become drug resistant and/or metastatic (black). In this model, the frequency of cancer cells with tumorigenic potential is high, suggesting that most or all cells should be targeted for therapy. (B) Cancer stem cell model. Following some transforming event, a stem cell (white) escapes one or more regulatory pathways, allowing it to proliferate unchecked (yellow). Through additional stable epigenetic changes the cancer stem cell can generate partially differentiated daughter cells with more limited potential for self-renewal. According to this model, cancer cells with tumorigenic potential are rare, suggesting a need to target a smaller subset of cells within the tumor. Compelling evidence exists for both models and they need not be mutually exclusive: clonal evolution can occur within the cancer stem cell model and some studies suggest that environmental conditions (such as hypoxia) could alter epigenetics, allowing differentiated tumor cells to revert to a more stem-like phenotype.
of self-renewal (Fig. 3.1b). Within a high-grade glioma, these malignant stem-like cells (which might be a minor component of the tumor cell population) give rise to partially differentiated daughter cells with potentially reduced malignant capability within the tumor.

Any discussion on the relative merits of the clonal evolution versus the stem cell models of gliomagenesis would be dry and pedantic if the focus was limited to the cellular heterogeneity of high-grade gliomas. However, there is an important clinical issue at stake. Why are malignant gliomas so notoriously resistant to radiation and cytotoxic drugs? The clonal evolution and stem cell models provide completely divergent explanations for the bleak prognosis of high-grade gliomas.

The clonal evolution model holds that resistance to genotoxic therapies is acquired [6, 7]. Advocates of clonal evolution would point out that gliomas are genetically unstable as evidenced by multiple karyotypic anomalies. Genetic instability can be exacerbated by standard-of-care therapeutic modalities (radiation, temozolomide) that are highly mutagenic. The combination of intrinsic and ectopic mutagenic events gives rise to occasional radiation/drug-resistant mutants that form the typical recurrent gliomas.

In stark contrast, the cancer stem cell hypothesis holds that resistance of gliomas to radiation and genotoxic drugs is intrinsic [4, 8]. Cancer stem cells, like their embryonic counterparts, are expected to cycle slowly, thereby limiting the response to radiation, and to express high levels of drug export proteins, thereby limiting the response to cytotoxic drugs. In addition, the rare stem-like cells that form the recurrent tumors may have growth factor requirements that are different from their partially differentiated daughter cells. Accordingly the stem-like tumor-initiating cells may not depend on the oncoproteins that are targeted by the new generation of small molecule protein kinase inhibitors.

So which of the two models is supported by the evidence? Supporters of the clonal evolution model argue that glioma stem cells are defined in operational ways, which may have little or no bearing on brain development. Even when their existence is conceded, the cellular and developmental origins of “glioma stem cells” can be contended. Do these cells arise from postnatal neural progenitors? Are glioma stem cells the progeny of mature glia or committed glial progenitors that have de-differentiated to a more stem-like state? In this chapter, we will attempt to shed light on these unresolved issues in cancer cell biology and malignant glioma. We will begin with a discussion of glioma stem cell biology, including supportive and negative data, followed by an overview of the candidates for “glioma cell of origin.”

Glioma Stem Cells

Neural stem cells are classically defined as cells, active in development, cell turnover, or repair, that are self-renewing and multipotent. Initially, the term “cancer stem cell” was created to reflect these two fundamental properties. However, there
is growing recognition that cancer stem cells, while self-renewing, cannot be considered multipotent because the differentiated progeny derived from a transformed precursor are genetically abnormal. The operational definition of a cancer stem cell is a tumor subpopulation that can self-renew in culture, perpetuate a tumor in orthotopic transplant in vivo, and generate diverse tissue or organ-specific progeny in vitro or in vivo.

Fresh surgical isolates of malignant gliomas contain cells with these properties. These glioma stem cells are frequently marked by CD133 (aka Prominin-1) – a cell surface antigen that is also a known marker of multipotent stem cells in blood and other tissues including the brain [9–11]. CD133-positive cells isolated from human brain tumors can initiate formation of “neurospheres” when cultured under non-adherent conditions in medium supplemented with growth factors (EGF and FGF), satisfying the stem cell quality of self-renewal. When these growth factors are removed and the tumor neurospheres are cultured under adherent conditions in serum-supplemented medium (or, in some studies, LIF-supplemented medium), individual cells can be seen that express marker proteins associated with neurons and glia, which satisfy the stem cell quality of multilineage potential [9, 10, 12, 13]. An important facet of these experiments is that the collection of marker proteins expressed under permissive conditions for differentiation recapitulates the markers present in the original tumor; thus, cancer stem cells from glioblastoma multiforme express markers associated with neurons, astrocytes, and oligodendrocytes. By contrast, stem-like cells isolated from pediatric brain tumors such as medulloblastoma or pilocytic astrocytoma express a more limited set of markers associated with neurons and astrocytes, respectively [9, 10, 12].

Consistent with the cancer stem cell model, these CD133-positive, neurosphere-forming cells, though typically a minor fraction of the tumor bulk, are by far the most tumorigenic component of the tumor. To illustrate this point, an intracranial inoculum of at least $10^5$ disaggregated glioma cells is required to initiate tumor growth in typical immunosuppressed mouse model for malignant glioma. By contrast as few as 100 CD133-positive cells will suffice to initiate similar tumor formation [14]. Also consistent with the cancer stem cell hypothesis, the CD133-positive glioma stem cells are selectively resistant to radiation [15].

**Glioma Stem Cell Caveats**

While several of the cellular properties noted above support the cancer stem cell model, experimental nuances provide an opening for skeptics. First, some gliomas contain CD133-negative cells that, in every other respect, fit the operational definition of a cancer stem cell [16]. Second, experiments with tumor xenograft models may lead to underestimation of the percentage of tumor-initiating or “tumor-sustaining” cells [17–19]. Third, it is possible that the cellular heterogeneity seen in high-grade gliomas may reflect partial recruitment of non-malignant neural or glial precursors into the tumor, which could complicate the interpretation of neurosphere
cell population in cell culture experiments [20]. Finally, single neurospheres are not usually derived from single cells. Even in the absence of agitation or manipulation, free-floating neurospheres show high motility. Timelapse video microscopy shows that, even in the absence of agitation or manipulation, free-floating neurospheres are rapidly drawn toward each other and merge to form larger neurospheres regardless of passaging density [21]. These neurosphere merger events are highly relevant to the property of multilineage potential, which is one of the defining characteristics of the cancer stem cell model.

Given the impact on targets and methodologies of cancer therapeutics, it is vital to develop biologically relevant assays to determine which model best represents any given cancer. These assays must determine the relative differentiation status as well as the tumorigenic potential of any given cell.

Do gliomas arise from neural progenitor cells? Stem-like properties in a neoplastic cell cannot be taken as conclusive confirmation of a developmental origin. Graphic evidence of the disconnect between a stem-like phenotype and a stem cell origin comes from studies on leukemias, which show that committed progenitor cells can be transformed into leukemia stem cells by misexpression of the oncopgenic fusion protein MLL-AF9 [22]. In the case of malignant glioma, there are at least three neural cell types that could, in principle, serve as cell of origin for glioma stem cells.

**Astrocytes or Astrocyte Progenitors as Cell of Origin for Glioma**

Historically, the first plausible candidates for glioma cell of origin were mature astrocytes or committed astrocyte progenitors. The very term “astrocytoma” reflects the traditional view that committed astrocytes or astrocyte progenitors serve as the cell of origin for malignant gliomas. For many years, conceptual problem with this lineage relationship was that astrocytes would somehow have to de-differentiate to a more primitive stem-like state to give rise to the mixture of cell types seen in high-grade gliomas. However, this theoretical barrier has been shattered by the expanding body of literature on induction of pluripotent stem cells from adult fibroblasts [23–26]. A variety of studies suggest that early cortical astrocytes can be induced to form tumors with convincing glioma histology in animal models [27–35]. However, these studies merit some close scrutiny. First, retroviral expression vectors only infect dividing cells. Second, these experimental methods only work for neonatal cortical astrocytes, not adult cortical astrocytes (which are actually quite difficult to grow in culture). Third, the “astrocytic marker” that is generally used, GFAP, is expressed in neural stem cells as well as some committed astrocyte progenitors and cortical astrocytes. Indeed, the lack of astrocyte-specific markers emphasizes the difficulty in interpreting experiments using targeting strategies to drive gene expression specifically in mature cortical astrocytes. Together, these results suggest that the in vitro and in vivo astrocyte targeting models may actually select for immature glial progenitor cells rather than mature astrocytes.
“Restricted” Neural Progenitors as Cell of Origin for Glioma

The discovery of replication competent, multipotent neural progenitors in the postnatal brain [5] brought with it an attractive alternative candidate for the glioma cell of origin. The machinery for self-renewal is already activated in these cells. Therefore, it is conceptually easier (i.e., require fewer mutations) to maintain self-renewal in these cells than it would be to induce self-renewal in mature progenitors [3]. Several replication competent cell types are now known to exist in the postnatal brain. The most actively cycling cells in the postnatal brain are NG2 cells [36, 37]. Unlike many of the replication competent cells in the brain, which are generally thought to be unipotent, NG2 cells have been reported to possess multipotent qualities [38, 39]. Interestingly, this multipotency can be regulated by epigenetic mechanisms. Also arguing in favor of NG2 cells as the cell of origin is the fact that most NG2 cells express the bHLH transcription factor Olig2, which is required for development of the oligodendrocyte lineage [40] and is necessary for glioma formation in a genetically relevant animal model of glioblastoma [41].

Multipotent Neural Progenitors as Cell of Origin

Multipotent neural progenitors, found in specialized niches, such as the dentate gyrus and subventricular zone (SVZ), have been extensively scrutinized and are plausible candidates for glioma-initiating cells [for reviews, see Sanai et al. [42] and Vescovi et al. [43]]. In rodents, the SVZ is the primary source of ongoing neurogenesis that contributes to the rostral migratory stream (RMS) required for neuron turnover in the olfactory bulb. Within the SVZ, several basic subclasses of progenitor cells can be distinguished on the basis of histology, immunohistochemical, and ultrastructural characteristics [44, 45]. A quiescent “Type B” stem cell that expresses the astrocytic marker GFAP and exhibits other morphological features of astrocytes is thought to give rise to transit-amplifying Type C cells that in most cases will go on to not only form neuroblasts of the RMS but can also give rise to oligodendrocytes [46, 47]. In an elegant set of studies, Jackson et al. [48] showed that the relatively quiescent, GFAP-positive type B stem cells express PDGFRα – a receptor tyrosine kinase hitherto associated only with oligodendrocyte progenitor cells. When the PDGF A:A homodimers (the specific activating ligand for PDGFRα) are infused into the lateral ventricles, neurogenesis is inhibited and the infused animals develop atypical hyperplasias within the subventricular zone. These hyperplasias show cellular atypia and pleomorphism associated with low-to-intermediate-grade human gliomas. There is an additional stem cell/glioma link embedded within this experiment. Normal markers of cells in the subventricular zone lineage are not expressed in the PDGF-driven B cell hyperplasias. However, Jackson et al. noted that the bHLH transcription factor Olig2 – a normally infrequent marker – becomes pervasive [48]. Ligon et al. have shown that Olig2 is expressed in 100% of human gliomas irrespective of grade but it is not expressed in brain
tumors of non-neural origin [49]. Moreover, Olig2 expression is required for tumor formation in a murine model of high-grade glioma that recapitulates two of the stereotypical genetic lesions found in human high-grade gliomas – namely loss of function \( p16^{\text{Ink4a}} / p19^{\text{Arf}} \) in the context of the constitutively active EGF receptor mutant EGFRvIII [41].

**Conclusion**

Malignant cells with stem-like properties have been found in a wide range of adult and pediatric brain cancers. Significant evidence suggests that these “cancer stem cells” arise from developmentally arrested progenitor cells that drive normal brain development and tissue repair. Against this backdrop, terms such as “tumor-initiating cells” or “tumor-propagating cells” are sometimes substituted for “cancer stem cells” because the latter term implies unwarranted insight into the tumor cell of origin. While the term “stem cell” may be somewhat prejudicial, the cancer stem cell hypothesis has provided a template for experimental design as well as incentive for neuro-oncologists to think about fundamental problems in brain development. The terms “cancer stem cell” and “glioma stem cell,” though possibly lacking strict scientific rigor, have served as consciousness-raising devices to spur the future development of cancer therapeutics and are therefore justified. Though additional work needs to be done to address the loopholes and caveats inherent to the cancer stem cell hypothesis, the practical overtones for targeted therapeutics are manifold.

**References**

Chapter 4
Principles of Supportive Care

Jan Drappatz and Patrick Y.C. Wen

Keywords Supportive care · Cerebral edema · Seizures · Venous thromboembolism · Neurocognitive symptoms · Brain tumor

The supportive care of patients who have brain tumors consists mainly of the treatment of seizures, peritumoral edema, venous thromboembolism, fatigue, and cognitive dysfunction. Effective medical management results in decreased morbidity and mortality and improved quality of life for affected patients.

Cerebral Edema

As a brain tumor grows, it produces focal symptoms by invasion and compression of surrounding brain tissue. More generalized signs and symptoms, such as headache, nausea, vomiting, and lethargy, result from increased intracranial pressure due to the space occupied by the tumor and the associated cerebral edema.

Cerebral edema is defined as a pathologic increase in the amount of total brain water content leading to an increase in brain volume [1] and is a significant and highly treatable cause of morbidity and mortality in brain tumor patients. Vasogenic edema occurs as tumor growth leads to disruption of the blood–brain barrier and increase in capillary permeability. This allows plasma-like fluid to enter the brain extracellular space through dysfunctional capillary endothelial tight junctions in tumors [2] (Fig. 4.1). The fluid may then spread throughout adjacent white matter. The process is mediated by vascular endothelial growth factor (VEGF) [3, 4], matrix metalloproteinases [5], and scatter factor/hepatocyte growth factor [6, 7], which are produced by the tumor and increase the permeability of tumor vessels [2, 6, 8, 9]. In addition, the membrane water channel protein aquaporin 4 (AQP4)
Fig. 4.1 The blood–brain barrier (BBB). Normal blood–brain barrier demonstrating tight junctions between endothelial cells that form a barrier between the circulation and the brain parenchyma. Peritumoral edema formation occurs through defective endothelial junctions of an abnormal blood–brain barrier. Reproduced with permission from Francis et al. [219]; ©Copyright 2003, Cambridge University Press

is upregulated around malignant brain tumors [2, 10]. AQP4-mediated transcellular water movement is important for fluid clearance in vasogenic brain edema, suggesting AQP4 activation or upregulation as a novel therapeutic target in vasogenic brain edema [2, 11, 12]. High VEGF expression has been reported in human anaplastic astrocytoma and glioblastoma (GBM) [13, 14], meningiomas [6, 15], and brain metastases [16, 17]. VEGF is especially critical when tumors outgrow their vascular supply. Hypoxia drives VEGF production in GBM and is the most important factor in neoangiogenesis and cerebral edema development in GBM [18].

Edema results in mass effect, increased intracranial pressure, and can lead to compromise of cerebral blood flow and brain herniation. Headaches, nausea and vomiting, altered mental status, and focal neurologic deficits are the typical symptoms of cerebral edema. The symptoms are often mild at onset and worsen
quickly over days and weeks. The classic syndrome is characterized by a dull morning headache that occasionally awakens the patient from sleep, is often aggravated by positional change, and may be associated with nausea and vomiting. All of these features in concert are rarely observed. Patients may also experience plateau pressure waves caused by the sudden elevation of intracranial pressure for brief periods [19], leading to an abrupt decline in mental status that may be confused with seizure activity.

On examination, papilledema can be seen and focal neurologic signs may be present, either due to tumor infiltration or due to mass effect. The shift of brain contents from one intracranial compartment to another may lead to herniation [20]. Both computed tomography (CT) and magnetic resonance imaging (MRI) are useful in the diagnosis of cerebral edema (Fig. 4.2). Treatment includes tumor-directed measures such as debulking surgery, radiotherapy, and chemotherapy, as well as the use of corticosteroids and more recently VEGF inhibitors [21]. Initial favorable effects on postoperative cerebral edema were noted by Ingraham in 1952 who used cortisone to treat adrenal insufficiency after craniotomies for craniopharyngioma [22]. Galicich [23] and French [24] established dexamethasone therapy as the standard treatment for tumor-associated edema in the 1960s. Despite their familiar side effects (Table 4.1), corticosteroids have remained the mainstay of treatment since. Recently, agents that block the VEGF pathway such as bevacizumab and cediranib have been shown to decrease vascular permeability and, thus, cerebral edema, by restoring the abnormal tumor vasculature to a more normal state. These “anti-angiogenic” drugs will likely gain an increasing role in the treatment of cerebral edema.
Table 4.1 Complications of corticosteroids

<table>
<thead>
<tr>
<th>Systemic complications of corticosteroids</th>
<th>Neurologic complications of corticosteroids</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>• Increased appetite</td>
<td>• Myopathy</td>
</tr>
<tr>
<td>• Weight gain</td>
<td>• Behavioral changes</td>
</tr>
<tr>
<td>• Cushingoid features (moon face, centripetal obesity, buffalo hump)</td>
<td>• Visual blurring</td>
</tr>
<tr>
<td>• Increased susceptibility to infections</td>
<td>• Tremor</td>
</tr>
<tr>
<td>• Candidiasis</td>
<td>• Insomnia</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td>• Reduced taste and smell</td>
</tr>
<tr>
<td>• Osteoporosis</td>
<td>• Cerebral atrophy</td>
</tr>
<tr>
<td>• Avascular necrosis</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac/vascular</strong></td>
<td><strong>Uncommon</strong></td>
</tr>
<tr>
<td>• Hypertension</td>
<td>• Psychosis</td>
</tr>
<tr>
<td>• Increased cardiovascular and cerebrovascular disease</td>
<td>• Hallucinations</td>
</tr>
<tr>
<td><strong>Eye</strong></td>
<td>• Hiccups</td>
</tr>
<tr>
<td>• Cataracts</td>
<td>• Dementia</td>
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<tr>
<td>• Glaucoma</td>
<td>• Seizures</td>
</tr>
<tr>
<td>• Central serous chorioretinopathy</td>
<td>• Dependence</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
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<tr>
<td>• Peptic ulceration</td>
<td>• Epidural lipomatosis</td>
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<tr>
<td>• GI bleeding</td>
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<tr>
<td><strong>Genitourinary and reproductive</strong></td>
<td></td>
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<tr>
<td>• Menstrual irregularities</td>
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<td>• Infertility</td>
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<td><strong>Hematologic</strong></td>
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<td>• Neutrophilia</td>
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<td>• Lymphopenia</td>
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<td><strong>Metabolic</strong></td>
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<td>• Hyperglycemia</td>
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<td>• Hypokalemia</td>
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<td>• Hyperlipidemia</td>
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<tr>
<td>• Fluid retention</td>
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<tr>
<td><strong>Skin</strong></td>
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<td>• Hirsutism</td>
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<tr>
<td>• Fragile skin</td>
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<tr>
<td>• Purpura</td>
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<tr>
<td>• Acne</td>
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<tr>
<td>• Striae</td>
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</table>

Adapted with permission from Wen et al. [218]

edema [21]. In contrast, the mechanism of action of corticosteroids remains poorly understood [25, 26].

Dexamethasone is the most commonly used glucocorticoid as it has relatively little mineralocorticoid activity and possibly a lower risk of infection and cognitive impairment, compared to other corticosteroids [27]. The initial dose is somewhat
arbitrary and depends on the clinical situation. The usual starting dose is a 10-mg load, followed by 16 mg split twice to four times per day in patients with symptomatic edema. Lower doses may be as effective, especially for less severe edema [28]. The dose may be increased up to 100 mg/day if required [29]. Although, dexamethasone can be given twice daily, many clinicians prescribe it three or four times daily. As a rule, patients should receive the minimum effective dose to avoid the harmful effects of steroids. Patients with peritumoral edema on imaging studies but without symptoms should not receive corticosteroids. The therapeutic effects of dexamethasone are usually seen within 24 h. Symptoms such as headache and lethargy often respond better than focal neurologic deficits. The contrast enhancement of tumors can decrease, suggesting partial restoration of the blood–brain barrier, whereas tumor perfusion can increase due to reduced peritumoral water content and local tissue pressure [30, 31].

When patients present with significant mass effect and have signs of impending herniation, additional measures to more quickly alleviate brain edema include elevation of the head of the bed, fluid restriction, mannitol, barbiturates, hypertonic saline, thiazide diuretics, and hyperventilation [32, 33].

Surgical debulking, if feasible, will more permanently reduce mass effect and will allow for tapering of steroids. The taper can start within a week after surgery but should be delayed in symptomatic patients undergoing radiotherapy, which may temporarily worsen edema. Patients with brain tumors exerting significant mass effect should receive steroids for 24 h prior to starting radiotherapy to reduce intracranial pressure and minimize neurologic symptoms.

**Complications of Corticosteroids**

Steroids have many potential harmful side effects and drug–drug interactions. A clinically important interaction exists with cytochrome P450 (CYP450) enzyme-inducing anti-epileptic drugs (EIAEDs), which may decrease steroid effectiveness [34, 35]. Dexamethasone may also induce specific CYP450 isozymes, potentially interacting with other drugs that are metabolized by this system.

In general, longer treatment durations and higher doses are associated with greater toxicity [36]. The stigmata of chronic steroid use include truncal obesity, moon facies, an acneiform rash, purpura, and striae distensae. Potentially debilitating complications are proximal myopathies [37], osteoporosis and avascular bone necrosis [38, 39], diabetes mellitus [40], cognitive dysfunction [41], gastrointestinal hemorrhage [42], bowel perforation [43] and opportunistic infections such as oropharyngeal candidiasis [44], and *Pneumocystis jirovecii* pneumonia [45].

**Gastrointestinal Complications**

Although many brain tumor patients receiving corticosteroids are treated with histamine (H2) blockers or proton pump inhibitors to prevent gastrointestinal (GI) bleeding or peptic ulcer disease, recent studies evaluating GI complications in patients receiving steroids have found a very low incidence of peptic ulceration
and GI bleeding when corticosteroids are used alone [46]. The use of proton pump inhibitors and H2 blockers in brain tumor patients should therefore be restricted to patients in the perioperative setting, patients with a history of GI bleed, and patients receiving anticoagulation or non-steroidal inflammatory agents (NSAIDs).

Bowel perforation is not common, but the risk may be increased in patients with constipation and who receive concurrent treatment with VEGF inhibitors such as bevacizumab [47]. Because corticosteroids mask many of the inflammatory signs of perforation, this diagnosis needs to be entertained in any brain tumor patient with abdominal pain, fever, or unexplained leukocytosis.

**Musculoskeletal Complications**

Steroid myopathy is the most common and disabling complication of steroid therapy in brain tumor patients with a reported incidence of 7–60% [48, 49]. The largest published series reported symptomatic steroid myopathy in 10.6% of patients [49]. It is more common in older patients and after prolonged use of higher doses. Typical symptoms are muscle atrophy and weakness, especially in the proximal lower extremities.

The pathophysiologic mechanism involves inhibition of protein synthesis primarily in type II muscle fibers [50]. Patients typically report difficulties arising from the seated position. Assessment of hip flexor strength is the most sensitive clinical test for steroid myopathy, but upper extremity muscles, neck muscles, and even respiratory muscles can be involved [51]. Muscle enzymes, electromyography (EMG), and muscle biopsy are often normal. Occasionally, EMG demonstrates myopathic changes or biopsy reveals atrophy of type IIb muscle fibers, variation of the fiber size, and centralization of the nuclei without evidence of inflammation [48].

The development of steroid myopathy can be minimized by using the lowest necessary dose for as short a time as possible. Once a patient has developed symptoms, treatment is limited to physical therapy. If possible, corticosteroids should be discontinued or tapered. Upon discontinuation, patients will gradually recover their muscular strength, a process that can take up to several months [52].

Use of non-fluorinated steroids such as prednisone and methylprednisolone instead of dexamethasone may lower the risk for steroid myopathy. Regular exercise can attenuate the symptoms.

Glucocorticoid-induced osteoporosis is the most common cause of secondary osteoporosis [53, 54]. Older patients and especially postmenopausal women not on estrogen replacement are at increased risk for fractures. The most important effects of steroids include reduction in osteoblasts and increased osteocyte and osteoblast apoptosis leading to decreased bone formation [55, 56]. They also lead to an increase in the expression of receptor activator of nuclear factor-kappa B ligand and colony-stimulating factor-1 and to decrease in the expression of osteoprotegerin [57].

The diagnosis of osteoporosis is made with a bone mineral density (BMD) test. Calcium and vitamin D supplementation have been evaluated in randomized trials. The American College of Rheumatology recommends calcium and vitamin D supplementation for all patients on chronic glucocorticoids [58]. Patients receiving
chronic corticosteroid therapy should be given calcium supplements (1,500 mg/day) with vitamin D (800 IU daily) or an activated form of vitamin D (e.g., alfacalcidol at 1 μg/day or calcitriol at 0.5 μg/day) [58]. Bisphosphonates such as etidronate, alendronate, ibandronate, risedronate, and zoledronate were extensively studied for the treatment of glucocorticoid-induced fractures since the mid-1990s [59]. A Cochrane Systematic Review demonstrated a positive effect on BMD; however, results regarding fractures were inconclusive [60]. A recent systematic review demonstrated a risk reduction of vertebral fractures from 1.4 to 11% with bisphosphonates [59]. Other therapies include calcitonin, which is less effective than bisphosphonates [61], and teriparatide, a human recombinant 1–34 parathyroid hormone [62]. Very high-risk patients such as postmenopausal women and elderly men who require prolonged steroids might benefit from preventive use of bisphosphonate therapy.

The weekly formulations are more convenient for patients (alendronate 35 mg/week for prevention; 70 mg/week for treatment; risedronate 35 mg/week for prevention or treatment). For patients who develop severe pain from compression fractures, kyphoplasty may provide pain relief [63]. A recent randomized, placebo-controlled trial, however, demonstrated no improvement of pain control when kyphoplasty was compared with a sham procedure [64]. Another complication of steroid use is avascular necrosis of the hip or other bones. In patients with smaller lesions and who are not severely symptomatic, the treatment is conservative.

Psychiatric Complications
Mild psychiatric symptoms develop in up to 28% of patients receiving steroids and severe reactions are seen in 6% [65, 66]. Typically, corticosteroid-induced psychiatric symptoms are affective, including mania and depression. Frequently, patients receiving short-term corticosteroid therapy present with euphoria or hypomania, while chronic exposure leads to depressive symptoms which, when severe, can include suicidal ideation [66, 67]. Increased distractibility and memory loss have also been reported [68] and may be related to hippocampal dysfunction [69]. As with all steroid-related adverse events, the dosage is the most important risk factor for the development of psychiatric symptoms; the incidence of psychiatric disturbance is 1.3% in patients receiving 40 mg/day or less and 18.4% in patients receiving more than 80 mg/day of prednisone [70] and seems to be independent of prior psychiatric illness [71]. Discontinuation of corticosteroid therapy generally leads to a full recovery. Psychosis, aggression, or agitation should be treated with atypical antipsychotics such as risperidone, olanzapine, or quetiapine. Patients with persistent affective symptoms who are receiving chronic corticosteroid therapy must be evaluated for suicidal ideation and should be treated with antidepressants for dysphoria and with a mood stabilizer for manic symptoms.

Immunosuppressive Effects and Infectious Complications of Corticosteroids
Corticosteroids are immunosuppressive drugs. The use of moderate to high doses of glucocorticoids can result in clinically significant suppression of the immune system
and susceptibility to opportunistic infections. The immune system in patients receiving additional chemotherapy such as prolonged courses of daily temozolomide may be further compromised and these patients are at especially increased risk for developing *P. jirovecii* pneumonia (PJP) [72–76]. *P. jirovecii* is an archiascomycetes fungus capable of causing life-threatening pneumonitis in immunocompromised patients [77, 78]. The nomenclature for the species of *Pneumocystis* that infects humans has recently changed from *Pneumocystis carinii* to *P. jirovecii*; this was done to distinguish it from the species that infects rats. PJP is most common in AIDS patients, organ transplant recipients, and patients with hematologic malignancies [79]. Patients with a CD4 count below 200 cells/mm$^3$ are at particularly high risk. Although PJP is relatively rare in brain tumor patients, patients receiving corticosteroids or prolonged courses of daily temozolomide are at increased risk for developing PJP. Small cohort studies estimate the incidence in brain tumor patients between 1.7 [72] and 6.2% [74]. Patients are particularly susceptible when steroids are being tapered.

The diagnosis of PJP should be considered in any brain tumor patient at risk who develops new respiratory symptoms, typically fever with dry cough. Diagnosis of PJP requires identification of the organism in respiratory secretions, which is most commonly achieved by staining of an induced sputum specimen or broncho-alveolar lavage fluid. Staining is necessary because *Pneumocystis* cannot be cultured. The treatment of choice is trimethoprim–sulfamethoxazole (TMP–SMZ) and is reviewed in more detail elsewhere [79].

All brain tumor patients receiving chronic steroids or prolonged daily courses of temozolomide should receive prophylactic therapy against PJP. TMP–SMZ is highly effective in preventing PJP when administered as a single double-strength tablet (160 mg of trimethoprim plus 800 mg of sulfamethoxazole) twice a day for 3 consecutive days each week or once daily three times a week, during steroid administration and for 1 additional month afterward [78, 79]. Aerosolized pentamidine, dapsone, or atovaquone are alternatives that should be considered in patients allergic or otherwise intolerant to TMP–SMZ (Table 4.2).

| Table 4.2 Prophylaxis of *Pneumocystis Jirovecii* pneumonia |
|-----------------|-----------------------------|
| **Regimen**     | **Dose**                    |
| Trimethoprim–sulfamethoxazole | Double strength (800 mg sulfamethoxazole and 160 mg trimethoprim) three times weekly or single strength (400 mg sulfamethoxazole and 80 mg trimethoprim) daily |
| Aerosolized pentamidine | 300 mg monthly |
| Dapsone         | 50 mg twice daily or 100 mg daily |
| Atovaquone      | 1,500 mg daily |

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Candidiasis is the most common opportunistic infection secondary to immunosuppression from steroids. Most candidal infections are mucocutaneous or oropharyngeal and easily treated with nystatin, clotrimazole, or topical antifungal agents. Occasionally, esophageal or systemic candidiasis may occur and require systemic therapy with agents such as fluconazole or itraconazole.

Other Steroid Side Effects
Epidural lipomatosis is a rare disorder seen in patients receiving chronic steroid treatment in which excess adipose tissue is deposited within the epidural space and has been occasionally described in brain tumor patients [80]. It can present as back pain, radiculopathy, or frank spinal cord compression. Treatment is directed at decreasing the steroid dose and in severe cases, multi-level decompressive laminectomy might become necessary to alleviate the neurological symptoms caused by spinal cord compression [81]. Longer-term corticosteroid use may result in occurrence of glaucoma [82] and cataract formation [83], the severity of which corresponds to the dose and duration of therapy [84, 85]. Corticosteroids can also cause hiccups [36, 86]. These can occasionally be troublesome and may respond to treatment with metoclopramide, chlorpromazine, or baclofen [87]. Glucocorticoid use is also associated with hyperglycemia. Mild blood sugar elevations can often be managed with oral agents. Marked hyperglycemia, especially in diabetic patients, usually requires insulin [88]. Steroid pseudorheumatism [89] is caused by withdrawal of patients from corticosteroids. It is manifested by diffuse arthralgias. Reintroduction of steroids followed by a slower taper or treatment with NSAIDs may lead to improvement.

Novel Therapies for Cerebral Edema
VEGF plays an important role in the pathogenesis of peritumoral edema [90]. VEGF inhibitors including bevacizumab [91, 92] and cediranib [21, 93, 94] have been shown to reduce tumor-related edema. In patients receiving this class of drug, steroid requirements typically decrease and often patients can come off steroids altogether. Although their role in treatment of cerebral edema is presently not well defined, VEGF inhibitors may eventually prove to be more effective, and less toxic, alternatives to corticosteroids.

Seizures

Epidemiology and Pathophysiology
The risk of seizures among brain tumor patients is related to tumor type [95, 96]. Low-grade gliomas present more frequently with seizures (60–85%) than high-grade primary brain tumors (20–40%) or metastases (15–20%) [97–100]. Cortical
lesions are more likely to cause seizures than infratentorial or white matter tumors [98]. Several mechanisms are implicated in seizure development. These include an imbalance between inhibitory and abnormal excitatory, mainly glutamatergic, mechanisms [101, 102], changes in peritumoral brain tissue, and the relative deafferentation of cortical areas, known to induce epileptogenic foci, often removed from the tumor site (secondary epileptogenesis) [100, 102]. Seizures are a major cause of morbidity associated with brain tumors.

**Prophylactic Treatment**

The use of prophylactic anti-epileptic drugs (AED) in brain tumor patients is often based on individual preference of the treating physician rather than clinical evidence. A meta-analysis of 5 randomized trials, including a total of 403 patients diagnosed with glial tumors, meningiomas, and brain metastases [103–107], found no benefit supporting anticonvulsant prophylaxis with phenobarbital, phenytoin, or valproic acid in patients with no history of seizures, regardless of the type of tumor [108]. A meta-analysis of randomized controlled trials exploring the potential value of AED prophylaxis after supratentorial surgery favored the use of phenytoin to prevent early seizures. However, there was no evidence that long-term treatment with phenytoin or carbamazepine reduced the incidence of late seizures compared with placebo or no treatment [109]. Similar findings were also obtained in patients undergoing craniotomy for a variety of other conditions, including vascular malformations and abscesses.

Known adverse effects with anticonvulsant therapy include rash (including Stevens–Johnson syndrome), myelosuppression, ataxia, hepatotoxicity, osteomalacia, tremor, cognitive dysfunction, and drug–drug interactions. The incidence and severity of these side effects is higher in brain tumor patient than in other patients receiving AEDs [110, 111]. Overall, one-fourth of brain tumor patients on AEDs experience side effects severe enough to warrant a change in or discontinuation of AED therapy [110].

Considering the lack of evidence supporting the use of prophylactic AEDs, the American Academy of Neurology issued a practice parameter which states that prophylactic AEDs should not be administered routinely to patients with newly diagnosed brain tumors (standard) and should be tapered and discontinued in the first postoperative week in patients who have not experienced a seizure (guideline) [110]. Despite these recommendations, 89% of patients in a recent study looking at practice patterns in adult glioma patients received AEDs, whereas only 32% presented with seizures [112].

Long-term treatment with AEDs is indicated once a brain tumor patient suffers a seizure due to the high risk of recurrence. Even if complete seizure control cannot be achieved, AED therapy may decrease seizure severity and frequency. The selection of a particular AED requires consideration of the treatment the patient is receiving. Several of the commonly used AEDs (phenytoin, carbamazepine, oxcarbamazepine, and phenobarbital) induce CYP450 enzymes, leading to a clinically
significant reduction in the plasma levels of many antineoplastic drugs. Valproic acid is a CYP450 inhibitor and may decrease clearance of other drugs metabolized by this pathway. Most of the newer agents (levetiracetam, gabapentin, pregabalin, lamotrigine, topiramate, tiagabine, zonisamide, lacosamide) do not induce the CYP450 system and are increasingly used in patients with brain tumors. Enzyme-inducing AEDs (EIAEDs) also interact with dexamethasone, which is frequently used to treat peritumoral edema. Dexamethasone induces CYP450 enzymes, potentially lowering levels of AEDs metabolized by the cytochrome P450 system. Conversely, the use of EIAEDs may result in the need to increase the dose of dexamethasone to produce the same therapeutic effect [35, 113, 114].

The general principles for management of epilepsy apply to brain tumor patients. Patients should be treated with a single agent at the lowest dose that effectively controls seizures. Table 4.3 lists commonly used AEDs with their doses, side effects, and the Food and Drug Administration’s (FDA) approved indication. If the initial drug does not work at the highest tolerated dose then patients should be switched to monotherapy with a second drug. The use of multiple AEDs should be reserved for refractory cases as side effects increase with the number of AEDs used. Although the FDA has approved the marketing of some AEDs for adjunctive use only, many of the non-EIAEDs are frequently used as monotherapy [115]. The choice of an AED for an individual patient is usually made based on considerations of side-effect profile, pharmacokinetic properties, administration, and mode of action.

Some AEDs have useful concomitant effects. Topiramate and zonisamide can cause weight loss, while topiramate may alleviate chronic headaches in some patients. Lamotrigine and valproic acid are mood stabilizers.

**AED Interactions with Antineoplastic Agents**

Many chemotherapy agents commonly used in brain tumor patients, such as cisplatin, carboplatin, carmustine, and methotrexate, interact with AEDs such as phenytoin, reducing their bioavailability [116–118]. The mechanisms implied include impaired AED absorption, cytochrome P450 enzyme induction, and altered protein binding. EIAEDs in return accelerate the metabolism of many chemotherapeutic agents including thiotepa, taxanes, and irinotecan [119–121] as well as many of the newer targeted molecular agents. Glucocorticoids such as dexamethasone also induce the cytochrome P450 system [122]. If given with dexamethasone or prednisone, phenytoin concentrations should be monitored closely and the dose should be adjusted if necessary. Temozolomide is not known to have interactions with anticonvulsants. Valproic acid inhibits the glucuronidation of SN-38, the active metabolite of irinotecan, leading to a 270% increase in the area under the curve (AUC) of SN-38 in rats [123]. Additionally, it has been shown to inhibit histone deacetylase, a target of several therapeutic agents in development for gliomas and other cancers; its use in patients receiving these drugs should therefore be avoided [124].
<table>
<thead>
<tr>
<th>EIAEDs</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Approved for monotherapy in USA</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Carbamazepine</em> (Tegretol, Tegretol XR, Carbatrol)</td>
<td>400–2,400 mg/day (bid to qid) (TPC: 8–12 μg/ml)</td>
<td>Drowsiness, dizziness, diplopia, bone marrow suppression (especially leukopenia), rash, hyponatremia, hepatotoxicity, arrhythmia</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Oxcarbazepine</em> (Trileptal)</td>
<td>1,200–2,400 mg/day (bid–qid) (TPC: 12–30 μg/ml)</td>
<td>Drowsiness, dizziness, diplopia, rash, nausea, hyponatremia, lymphadenopathy, hepatotoxicity</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Phenytoin</em> (Dilantin, Phenytek)</td>
<td>15–20 mg/kg load and then 3–5 mg/kg/day (qd–bid) (TPC: 10–20 μg/ml)</td>
<td>Drowsiness, dizziness, rash, gingival hyperplasia, hirsutism, bone marrow suppression, hepatotoxicity, neuropathy, cerebellar degeneration, folate deficiency, osteomalacia, lupus, lymphadenopathy</td>
<td>Yes</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>10–20 mg/kg load and then 1–3 mg/kg/day (qd) (TPC: 15–40 μg/ml)</td>
<td>Sedation, dizziness, impaired cognitive function, hyperactivity, rash, bone marrow suppression (rare), hepatotoxicity (rare), frozen shoulder, Dupuytren’s contracture, reduced libido</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Primidone</em> (Mysoline)</td>
<td>750–2,000 mg (tid) (TPC: primidone 5–12 μg/ml; phenobarbital 15–40 μg/ml)</td>
<td>Similar to phenobarbital</td>
<td>Yes</td>
</tr>
<tr>
<td>Non-EIAEDs</td>
<td>Dose</td>
<td>Side effects</td>
<td>Approved for monotherapy for partial or secondary generalized seizures in USA</td>
</tr>
<tr>
<td><em>Clonazepam</em> (Klonopin)</td>
<td>2–20 mg/day (qd–qid)</td>
<td>Drowsiness, ataxia, behavior problems, hyperactivity, hypersalivation, seizure exacerbation, hepatotoxicity, blood dyscrasia</td>
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</tr>
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Table 4.3 (continued)

<table>
<thead>
<tr>
<th>EIAEDs</th>
<th>Dose</th>
<th>Adverse effects</th>
<th>Approved for monotherapy in USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin (Neurontin)</td>
<td>900–4,800 mg/day (tid–qid)(^a)</td>
<td>Drowsiness, dizziness, fatigue, ataxia</td>
<td>No</td>
</tr>
<tr>
<td>Lamotrigine (Lamictal)</td>
<td>300–500 mg/day; 100–150 mg/day if taking valproic acid (qd–bid) (TPC: 3–14 μg/ml)</td>
<td>Drowsiness, dizziness, fatigue, ataxia, rash, hepatotoxicity</td>
<td>Conversion to monotherapy</td>
</tr>
<tr>
<td>Levetiracetam (Keppra)</td>
<td>1,000–3,000 mg/day (bid)(^a)</td>
<td>Drowsiness, fatigue, nervousness, headaches</td>
<td>No</td>
</tr>
<tr>
<td>Pregabalin (Lyrica)</td>
<td>150–600 mg/day (bid–qid)</td>
<td>Drowsiness, dizziness, edema, impaired concentration, blurred vision, weight gain, ataxia, possible dependency</td>
<td>No</td>
</tr>
<tr>
<td>Tiagabine (Gabitril)</td>
<td>32–56 mg/day (bid–qid)(^a)</td>
<td>Drowsiness, dizziness, fatigue, nervousness, tremor, decreased concentration</td>
<td>No</td>
</tr>
<tr>
<td>Topiramate (Topamax)</td>
<td>200–400 mg/day (bid)(^a)</td>
<td>Drowsiness, fatigue, decreased concentration, paresthesias, weight loss, kidney stones</td>
<td>Yes</td>
</tr>
<tr>
<td>Valproic acid (Depakote, Depakene)</td>
<td>15–60 mg/kg/day (tid–qid) (TPC: 50–100 μg/ml)</td>
<td>Drowsiness, nausea, tremor, thrombocytopenia, hepatotoxicity, weight gain, hair loss, pancreatitis</td>
<td>Yes</td>
</tr>
<tr>
<td>Zonisamide (Zonegran)</td>
<td>200–600 mg/day (qd–bid) (TPC: 10–30 μg/ml)</td>
<td>Drowsiness, dizziness, anorexia, nausea, headache, difficulty concentrating, weight loss, renal stones</td>
<td>No</td>
</tr>
<tr>
<td>Lacosamide (Vigabatrin)</td>
<td>200–400 mg/day</td>
<td>Dizziness, ataxia, vomiting, diplopia, nausea, vertigo, and blurry vision</td>
<td>No</td>
</tr>
</tbody>
</table>

\(^a\)Therapeutic plasma concentration not established

TPC: target plasma concentration; EIAED: enzyme-inducing anti-epileptic drug

Reproduced with modifications and permission from Wen et al. [218]
Surgical Management of Seizures

Seizures in brain tumor patients may occasionally be refractory to medical management. Surgical treatment of brain tumor-related epilepsy is generally only indicated in patients with slow-growing tumors with a good prognosis. The best results are obtained when the pathologic lesion and adjacent epileptogenic cortex are resected [125].

Thromboembolic Complications

Epidemiology and Pathophysiology

Venous thromboembolism (VTE) is the second leading cause of death in cancer patients [126]. The association between brain tumors and thromboembolic disease is well known and contributes significantly to morbidity and mortality. The incidence of deep vein thrombosis (DVT) or pulmonary emboli (PE) in brain tumor patients varies significantly between different studies (3–60%) [127–131]. In patients with high-grade gliomas outside the perioperative period the incidence is approximately 20–30% [130, 132–135]. This risk is generally greater in the postoperative period and in patients with hemiplegia, in geriatric patients, glioblastoma histology, large tumor size, use of chemotherapy, hormonal therapy, operation length greater than 4 h, and A or AB blood group types [136]. In contrast to adults, children with brain tumors have a lower incidence of VTE [137]. Early recognition of the signs and symptoms and judicious therapy of VTE are essential. Left untreated, nearly 50% of all patients with symptomatic, proximal deep venous thromboses will develop pulmonary emboli (PE) [138] with mortality rates of 10–34% [139–142]. The VTE risk persists throughout the clinical course of the disease. A prospective study of 77 high-grade glioma patients reported a 21% risk of DVT at 12 months, which increased to 32% at 24 months [132].

The pathogenesis of VTE in brain tumor patients is not completely understood [143, 144]. Normal brain tissue is a rich source of tissue factor (TF), the cell surface receptor of factor VII/VIIa that plays a central role in the initiation of the coagulation cascade [145]. Higher-grade tumors express higher levels of TF, leading to greater activation of the coagulation cascade [146, 147]. The release of brain-derived TF and other procoagulants and fibrinolytic inhibitors from tumor and surrounding cerebral tissue into the systemic circulation is thought to activate the coagulation cascade and result in chronic disseminated intravascular coagulation [146, 148, 149]. Elevated levels of D-dimer, homocysteine, lipoprotein(a), VEGF, tissue plasminogen activator (tPA), and plasminogen activator inhibitor (PAI) are found in patients with malignant gliomas and contribute to the hypercoagulable state in patients with brain tumors [136].
**Diagnosis**

Duplex ultrasonography in combination with clinical evaluation generally provides an adequately precise and non-invasive approach to diagnosing DVT [150]. For proximal DVT, ultrasonography has sensitivity of 89–96% and specificity of 94–99% [151]. However, for symptomatic calf DVT, the sensitivity drops to 73–93% [151, 152] and for asymptomatic patients ultrasonography has a sensitivity of only 50% [151]. Repeat ultrasound or venography may be required for patients who have suspected calf vein DVT and a negative or technically inadequate ultrasound. Contrast venography is still considered the gold standard to rule out the diagnosis of DVT but is rarely performed. For patients with a low clinical suspicion of DVT, a normal D-dimer is sufficient to exclude DVT and an ultrasound can be safely omitted in these cases [153].

For patients with suspected PE, imaging is necessary. The first-line diagnostic tool is CT pulmonary angiography (CTPA) [154]. Ventilation–perfusion (V/Q) scans are only rarely performed.

**Prophylactic Treatment**

Because of the high risk of developing VTE, brain tumor patients undergoing craniotomy require adequate prophylaxis. The methods used for VTE prophylaxis are mechanical, pharmacological (unfractioned heparin [UFH] or low molecular weight heparin [LMWH]), or a combination of both. The optimal prophylactic regimen has not been established. Mechanical methods include early ambulation, compression stockings, electrical calf muscle stimulation [155], and intermittent external pneumatic compression devices. Each of these helps to limit venous stasis and to enhance systemic fibrinolysis. Studies of mechanical prophylaxis in neurosurgery patients have demonstrated up to a 50% reduction in VTE compared with controls [156–158], with the greatest effect derived from the use of pneumatic compression, although failure rates in some studies were as high as 9.5% [159]. Studies in patients who have undergone craniotomy comparing pneumatic compression devices with heparin suggest that heparin reduces the frequency of DVT and PE by 40–50% [160, 161]. However, the rate of major postoperative intracranial hemorrhage may increase from its baseline of 1–3.9% to as high as 10.9% with heparin [127, 162, 163]. A meta-analysis of four trials of thromboprophylaxis in predominantly brain tumor patients found that LMWH and UFH reduced the risk of VTE from 12.5 to 6.2% and carried only a 2% risk of major bleeding [164]. Nonetheless, many neurosurgeons continue to associate heparin compounds with bleeding complications and use mechanical methods only [165, 166].

The high incidence of VTE in patients with malignant gliomas beyond the perioperative period could potentially be reduced with prophylactic anticoagulation. The extended use of LMWH as primary prophylaxis of VTE in patients with newly diagnosed malignant glioma was assessed in the PRODIGE trial [167]. The trial was
terminated early because of the unavailability of placebo. Overall, 186 patients were randomly assigned to 6 months of treatment with dalteparin or placebo. The incidence of VTE at 6 months was reduced in patients receiving dalteparin (11% vs 17% with placebo), but the difference did not reach statistical significance, and statistical power at the time of termination was inadequate. Intracranial hemorrhages were seen more frequently in patients treated with dalteparin (5% vs 1% with placebo). Since there is no clear evidence, primary prophylaxis with anticoagulants is not generally recommended in patients with brain tumors except in the perioperative period [147].

**Symptomatic Treatment**

The main goals in the treatment of VTE are to prevent PE and to alleviate leg edema and associated pain. Unfractionated heparin and particularly LMWH are widely used for the treatment of VTE and reduce the frequency of recurrent thromboembolic complications. Meta-analyses comparing UFH and LMWH for the treatment of DVT have shown better outcomes, with a reduction of major bleeding complications, in patients treated with LMWH [168, 169]. Numerous studies have demonstrated the relative safety of properly monitored anticoagulation in patients with primary and metastatic brain tumors [170–174] and this topic has been reviewed extensively in the neurosurgical and neuro-oncologic literature [143, 144, 170, 175–178]. The incidence of cerebral hemorrhage in these studies was generally not significantly increased in anticoagulated patients [170, 173], while systemic bleeding was generally minor and infrequent [171, 179]. When hemorrhagic complications occur, they are seen most commonly in the context of supratherapeutic anticoagulation [180, 181].

Only patients with strict contraindications for therapeutic anticoagulation should be treated with inferior vena cava (IVC) filters. IVC filters have a higher complication rate and are less effective in preventing PE compared to anticoagulation. A retrospective study of patients with brain tumors identified complications in up to 62% of patients after IVC filter placement including procedure-associated morbidity (such as pneumothorax, infection, bleeding, and IVC wall damage), as well as thrombotic events, including a 12% risk of recurrent PE, 26% incidence of IVC thrombosis, and 10% risk of postphlebitic syndrome [182]. Four out of ten patients with brain metastases who received IVC filters in a case series reported by Schiff and Deangelis had recurrent VTE [171]. The use of IVC filters should therefore be reserved for patients with recent craniotomy, intracranial hemorrhage, frequent falls, poor compliance, or prolonged thrombocytopenia from chemotherapy. In patients with temporary contraindications, an IVC filter followed by delayed anticoagulation may limit future thromboembolic complications.

Warfarin remains widely used as a long-term anticoagulant in brain tumor patients. There is, however, accumulating evidence that LMWHs are more effective and safer in cancer patients. Thus far, no randomized trials have directly compared LMWH with warfarin anticoagulation specifically in patients with brain tumors.
In a randomized trial of secondary prevention of VTE in patients with systemic cancer, warfarin when compared with enoxaparin (1.5 mg/kg daily) was associated with a higher frequency of bleeding; there were six deaths owing to hemorrhage in the warfarin group compared with none in the enoxaparin group [183].

LMWH was compared to warfarin in the randomized CLOT trial that included 673 cancer patients with VTE. This trial was not designed to assess the risk of intracranial hemorrhage, and the study included only 34 patients with primary brain tumors and an unknown number with brain metastases. Overall, LMWH was more effective than oral anticoagulation in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding [184]. As brain tumor patients frequently receive concurrent therapy with medications that interact with warfarin, close monitoring of the international normalized ratio (INR) is necessary. The use of LMWHs in lieu of warfarin avoids the difficulties of fluctuating INRs due to the many drug–drug interactions with warfarin. For these reasons, we favor LMWH over warfarin for secondary prevention of VTE, although more evidence is certainly desirable before applying this approach routinely in this patient population. Before initiation of therapeutic anticoagulation, a screening head CT or MRI should be performed to rule out recent intracranial bleeding. Evidence of recent spontaneous bleeding is generally considered a contraindication to anticoagulation. Anticoagulation should probably also be avoided in patients with active brain metastases from melanoma, choriocarcinoma, renal or thyroid cancer as these tumors are associated with an increased rate of hemorrhage.

Currently US FDA-approved LMWHs for treatment of VTE include ardeparin, dalteparin, enoxaparin, nadroparin, reviparin, and tinzaparin [147]. The advantages of LMWH compared to UFH consist of better bioavailability and longer half-life, more predictable dose response, reduced requirements for laboratory monitoring, lower frequency of heparin-induced thrombocytopenia, and possibly less heparin-associated osteopenia [181, 185]. Because of their improved safety and ease of use, stable patients with DVT are usually treated with LMWH in the outpatient setting, while transitioning to oral anticoagulation with warfarin to reach therapeutic INR levels [186–188]. There is also evidence that LMWHs are modestly superior to UFH for initial treatment of DVT and are at least as effective as UFH for treatment of pulmonary emboli [151]. Treatment with UFH is nowadays reserved for patients with serious PEs and high-risk patients where the longer half-life and incomplete protamine reversibility of LMWHs make them less attractive. When administering UFH, a bolus of UFH should be reserved for high-risk patients with symptomatic PE where the risk of further thrombotic complications outweighs the potential bleeding risk associated with more aggressive initial anticoagulation. The duration of anticoagulation depends on the patient’s overall clinical status. As most neurologic cancers are incurable, anticoagulation is continued indefinitely in most patients. When the underlying cause of the hypercoagulable state no longer exists, anticoagulation can be discontinued after approximately 3–6 months.

Patients with heparin-induced thrombocytopenia (HIT) must not receive heparin products. In lieu of heparin, direct thrombin inhibitors such as lepirudin, argatroban, or bivalirudin can be considered, although limited data exist to guide their
use in patients with brain tumors. Fondaparinux is a synthetic pentasaccharide which binds to antithrombin, thereby indirectly and selectively inhibiting factor Xa. Fondaparinux demonstrated efficacy comparable to LMWH in randomized clinical trials and is FDA-approved for the prevention and treatment of VTE. Since it does not bind to platelets or platelet factor 4, it should not produce heparin-induced thrombocytopenia, and although not FDA-approved for this indication, its use might be considered in brain tumor patients who have developed heparin-induced thrombocytopenia.

**Intracranial Hemorrhage**

The most concerning complication of anticoagulation in patients with brain tumors is intracranial hemorrhage. Any rapid change in neurologic symptoms or sudden onset of severe headaches should lead to urgent brain imaging. If hemorrhage is confirmed, anticoagulation will need to be reversed and a neurosurgeon should be consulted. Protamine reverses UFH completely. However, it incompletely reverses LMWH and has an even less effect on fondaparinux and the direct thrombin inhibitors [143, 189]. Vitamin K reverses the effect of warfarin but requires hours to days to take effect [190]. In these cases, blood products such as fresh frozen plasma, recombinant human factor VIIa, or prothrombin complex concentrates should be used [191–193]. Recombinant factor VIIa may also reverse the anticoagulant effects of LMWHs, direct thrombin inhibitors, and fondaparinux [194, 195].

**Neurocognitive Symptoms**

The majority of brain tumor patients experience distressing neurocognitive symptoms. These patients often present with neurological signs or deficits that reflect the location of the tumor. The side effects of the currently available therapies further exacerbate their symptoms. Cognitive symptoms include slowed cognition, personality changes, mood changes, and a deficit in language, concentration, or memory, and fatigue and contribute to a marked reduction of quality of life [196]. Appropriate assessment of these symptoms is critical in all brain tumor patients. Potential etiological factors and comorbidities need to be examined with specific attention to factors that may be correctable (such as anemia, nutritional status, endocrine dysfunction, depression, and anxiety).

**Fatigue**

Fatigue adversely affects the quality of life of the majority of brain tumor patients [197, 198]. In one survey of patients with primary brain tumors, nearly half reported low energy levels on the Functional Assessment of Cancer Therapy-Brain Scale (FACT-BR) [197]. Several studies assessing the quality of life in patients with malignant gliomas found that fatigue was the most frequently reported and troublesome
of all symptoms [198, 199]. Fatigue tends to be more common in patients with high-grade gliomas than low-grade tumors [200] and is especially troublesome following treatment with radiotherapy (RT) [201, 202]. Fatigue tends to increase with the number of radiation fractions, reaching a maximum at the end of RT and provides an opportunity for intervention to improve the quality of life of these patients. AED use, chemotherapy, anemia, metabolic disturbances, depression, endocrine dysfunction, and weight gain from chronic steroid use all contribute to fatigue. It is important to exclude hypothyroidism and hypocortisolism, reduce or eliminate unnecessary AEDs, and treat anemia and depression. Psychostimulants may play a role in the treatment of brain tumor-related fatigue. The psychostimulants available include methylphenidate, pemoline, dextroamphetamine, modafinil, and armodafinil. These drugs are generally well tolerated in brain tumor patients and can act as augmenters of antidepressants [203–206]. A pilot study of modafinil for treatment of neurobehavioral dysfunction and fatigue in adult patients with brain tumors showed improvement across cognitive, mood, and fatigue outcome measures [207]. Stimulants may have a role in the treatment of fatigue during radiotherapy. A randomized, placebo-controlled trial of its R-enantiomer armodafinil is currently ongoing.

Cognitive Impairment

Cognitive deficits include short-term memory loss, concentration difficulties, personality changes, emotional lability, loss of executive function, and decreased psychomotor speed. These complaints can be tumor-related and exacerbated by chemotherapy and RT as well as AEDs and steroids [208]. Whole brain RT alone or in combination with high-dose chemotherapy results in greater cognitive decline than partial RT or high-dose chemotherapy alone [209]. Patients undergoing treatment should have a baseline cognitive assessment so that changes can be identified and patient reports quantified [208]. The cognitive impairment may be associated with behavioral disturbances and require psychosocial interventions. Medications such as methylphenidate may be helpful in improving motivation, attention, and neurologic functioning [210]. Acetylcholinesterase inhibitors approved for Alzheimer’s disease, such as donepezil, have shown to improve cognitive functioning, including memory, mood, and quality of life in brain tumor patients after RT [211]. Glutamate inhibitors such as memantine may also be helpful. Atypical antipsychotics can be effective in improving psychotic symptoms, anger, agitation, and poor impulse control [212]. Patients with cognitive impairment, frontal gait disorder, and urinary incontinence should be evaluated for the presence of communicating hydrocephalus and may benefit from ventriculo-peritoneal shunting [213].

Approaches to cognitive rehabilitation can be divided into retraining and compensation. Retraining methods are based on the assumption that, owing to the plasticity of the brain, practice can restore impaired brain functions. In contrast, compensation methods focus on learning strategies to compensate for the
neuronal damage \[214\]. As the delayed cognitive effects of radiotherapy are being increasingly recognized in long-term survivors, their risk will need to be considered when planning treatment \[215, 216\].

**Depression and Anxiety**

Depression and anxiety are common symptoms in brain tumor patients. Depression may be related to frontal lobe tumor location or medications (dexamethasone and levetiracetam in particular) or it may be part of the psychological response to the tumor diagnosis and fear of death. Estimates of the rates of depression vary between studies and depend on the assessment method. In the Glioma Outcomes Project, there was significant discrepancy between the rates of depression reported by patients and physicians \[217\]. Among the 598 patients with malignant glioma, physicians diagnosed depression using DSM-IV criteria in 15% of the study subjects in the early postoperative period. However, a total of 93% of these patients reported symptoms of depression during this period \[217\]. As survival is shorter among depressed patients \[217\], the importance of diagnosis and treatment cannot be underestimated. Depressed patients require adequate psychosocial support and should be considered for antidepressant pharmacotherapy. Commonly used antidepressants include selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram), serotonin/norepinephrine reuptake inhibitors ( duloxetine, milnacipran and venlafaxine), and noradrenergic and specific serotonergic antidepressants (mirtazapine) and are generally well tolerated. The norepinephrine–dopamine reuptake inhibitor bupropion is associated with lowering of the seizure threshold and should be avoided in brain tumor patients.

**Summary**

Seizures, cerebral edema, thromboembolic complications, neurocognitive dysfunction, and depression are common challenges in brain tumor patients and account for significant morbidity and mortality. Effective medical management of these complications can significantly improve quality of life. Current evidence suggests that anticoagulation for VTE in brain tumor patients does not significantly increase the risk for intracranial hemorrhage, unless there is a clear contraindication. However, further studies are required to define the optimal prophylaxis and treatment of VTE. AEDs should only be prescribed to patients who have had a seizure. There is no evidence that prophylactic AEDs are beneficial in brain tumor patients who have not had seizures. To minimize interactions with other drugs, non-EIAEDs should be considered. Corticosteroids effectively treat brain tumor-related edema, but have unfavorable side effects and should be used in the smallest effective dose and for the shortest duration possible. Fatigue and depression are often not recognized or treated in patients with primary brain tumors, but effective therapy can have a major impact on the patient’s quality of life.
References


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Chapter 5  
Principles of Clinical Trial Design and Response Assessment  

Nicholas Butowski and Susan Chang  

Keywords  Clinical trials · Brain tumor · Neuro-oncology  

Introduction  

The prognosis for patients with primary brain tumors remains poor; yet, there is excitement in the oncology community that a shift away from the sole use of traditional cytotoxic agents toward the use of molecularly targeted agents may provide more effective treatment options. Before a new therapy can be tested in patients, preclinical research is performed to determine the new agent’s mechanism of activity, its relevance to treatment, and its toxic effects. Only once the preclinical research is completed and thought promising is the new agent tested in clinical trials.  

The aim of therapeutic cancer clinical trials is to determine the effectiveness and safety of a new agent, whether used alone or in combination with another drug. These trials are carefully performed in an effort to avoid the use of ineffective or toxic therapies. Clinical trials are scientific experiments with four main requirements: (1) a well-defined question within a specific patient population; (2) a prospective plan with clear objectives and endpoints; (3) conduct under controlled conditions; and (4) statistical rigor. Failure to conduct a study with attention to these areas threatens the validity of the results.  

No matter the clinical trial phase, several components of a clinical trial require prospective planning (see Table 5.1). First, the scientific background of the experimental agent including the mechanism of action, preclinical data, and any clinical data needs careful review and documentation in the introduction of the protocol. Next, the objectives and endpoints should be thought out and defined clearly. Patient eligibility criteria should also be unambiguously defined with strict attention to the

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Table 5.1 Important components of clinical trials

(1) Scientific background and rationale
(2) Objectives and endpoints
(3) Eligibility criteria
(4) Treatment plan and design
(5) Drug information
(6) Toxicity assessment and modifications
(7) Statistical considerations
(8) Regulatory considerations including consent and data safety monitoring plan

method of enrollment. All patients should be included in the final report. The design of the study and the treatment plan including a detailed description of dose administration and schedule and frequency of evaluation should be constructed so that it can be reproduced. Expected toxicities and methods of toxicity assessment with dosage modifications or early stopping rules should be created. One must also determine which statistical approaches will be used to analyze the data. Lastly, an informed consent document must be created and written in a manner that allows the patient to understand the objectives of the study and that he/she has the freedom to withdraw at any time.

A comprehensive review of cancer clinical trials is beyond the scope of this chapter. Instead, we provide an overview of the basic principles of therapeutic cancer clinical trials (see Table 5.2) and specifically address the challenges of clinical trials in neuro-oncology. Several other reviews of this topic are available [1–5].

Table 5.2 Summary of typical conditions for the different types of clinical trials

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>All refractory tumor</td>
<td>Tumor specific</td>
</tr>
<tr>
<td>Dose of drug</td>
<td>Escalating</td>
<td>Specified</td>
</tr>
<tr>
<td>Primary objective</td>
<td>Establish Phase II dose</td>
<td>Antitumor activity</td>
</tr>
<tr>
<td>Study design</td>
<td>Single arm</td>
<td>Usually single arm</td>
</tr>
<tr>
<td>Number of patients</td>
<td>&lt;30</td>
<td>20–60</td>
</tr>
<tr>
<td>Typical endpoint</td>
<td>Toxicity</td>
<td>Response</td>
</tr>
<tr>
<td>Statistical design</td>
<td>Escalating cohorts</td>
<td>Two-stage design</td>
</tr>
</tbody>
</table>

Phase 0 Trials

Phase 0 clinical trials were developed in response to the US Food and Drug Administration exploratory Investigational New Drug (IND) guidance [6]. These trials are intended to accelerate the evaluation of new molecular agents. Specifically, the exploratory IND supports the performance of first-in-human testing of
investigational agents at subtherapeutic doses based on reduced manufacturing and toxicity requirements, allowing the demonstration of drug–target effects and assessment of pharmacokinetic–pharmacodynamic relationships in humans [7, 8].

The sole objective of Phase 0 cancer clinical trials is to establish whether an agent is modulating its target in a tumor and consequently whether further clinical development is reasonable. A Phase 0 study has no therapeutic or diagnostic intent, being by definition a dose too low to cause any therapeutic effect. Thus, Phase 0 trials are not meant to replace traditional Phase I dose escalation studies which define dose-limiting toxicities and the maximum tolerated dose. If such endpoints are important for a specific therapeutic agent, then a traditional Phase I trial is required. Drug companies often carry out Phase 0 studies to rank agents in order to decide which has the best pharmacokinetic parameters in humans to further develop. These decisions are based on human models instead of relying on animal data. Questions have been raised about whether Phase 0 trials are truly useful, ethically acceptable, and save money [9]. For example, most cancer patients participate in clinical studies with the hope of obtaining therapeutic benefit. Because of the strict limitation in duration and dosing (the novel agent is generally given for 7 days or less) and the mandatory lack of therapeutic or diagnostic intent of Phase 0 studies, some have questioned whether cancer patients will agree to participate in these types of clinical trials. However, it appears that physicians and patients alike, especially in the oncology community, believe that Phase 0 trials represent a valid attempt to change a previously over-conservative approach to drug development by accelerating the clinical testing of experimental therapeutic agents [10, 11].

Little has been completed in the realm of Phase 0 studies for primary brain tumors. This is in part not only due to the comparative rarity of primary brain tumors but also due to the fact that Phase 0 studies are limited to small molecules and well-characterized therapeutic biological products such as recombinant proteins and monoclonal antibodies. Such trials are not to be used for other biological reagents such as human cell or tissue products, blood proteins, vaccines, or devices [6, 10]. Some articles do address the need for and complex design of Phase 0 studies in primary brain tumors [1]. Such near term studies should be designed within the FDA guidelines that describe three types of representative Phase 0 trials (all of which are potentially relevant to oncology) [12, 13]: (1) The first type of Phase 0 trial is a microdose study of pharmacokinetics or imaging. Such studies are designed to evaluate the pharmacokinetics, metabolism, and/or imaging distribution of specific agents. They are referred to as microdose studies because in the terminology of the exploratory IND, a microdose is defined as less than one-hundredth of the dose calculated (based upon animal data) to yield a pharmacological effect of an experimental agent, with a maximum dose limit of \( \leq 100 \mu g \). Multiple related compounds may be studied in this type of design under a single exploratory IND which may represent a savings of preclinical resources. The possible shortcoming of this design is that microdose pharmacokinetic experiments may not predict drug behavior at higher doses because of non-linear kinetics. An advantage of a microdose Phase 0 study is the reduced preclinical testing requirements needed prior to the initiation of a clinical trial.
The second Phase 0 trial type is a pharmacological endpoint study. This trial is designed to examine the pharmacological effects of the candidate product, but it does not attempt to define the maximum tolerated dose. The doses used will be higher than in a microdose trial, and as a consequence, more extensive preclinical safety data are required. However, the amount of preclinical information is still less extensive than that needed to support a Phase I trial. The duration of dosing generally is limited to 7 days.

The third type of Phase 0 study is designed to evaluate the specific mechanisms of action of a new agent. These trials are similar to the pharmacological endpoint Phase 0 studies, but they focus on the target tissue and on an agent’s proposed mechanism of action. These studies have the most relevance to oncological drug development [11]. Endpoints related to the mechanism of action could include the degree of receptor saturation in target tissue, the inhibition of an enzyme or signaling pathway in tumor cells, the altered expression of a specific gene product, or other biomarker endpoints. However, these trials require specific pharmacodynamic biomarkers which must be validated in preclinical experiments in order to become the primary endpoints for the clinical study. The conclusions of such a study will only be as good as the biomarker assay used as an endpoint. Of course, this challenging issue is not limited to Phase 0 trials but applies to any biomarker-guided study.

Phase I Trials

Cytotoxic Agents

Phase I trials are designed to identify the recommended Phase II schedule and dose and describe the pharmacological characteristics of the drug and its toxic effects. Phase I studies of traditional cytotoxic drugs determine the recommended Phase II dose based on the maximum tolerated dose (MTD) of a new agent. This toxicity-based approach originates from the supposition that the therapeutic effect and toxic effects of the agent parallel each other as the dose is increased and that the same mechanism of action produces the therapeutic and toxic effects.

The guiding principle for dose escalation in Phase I trials is to avoid exposing too many patients to subtherapeutic doses while preserving safety and maintaining rapid accrual. Customarily, the starting dose for a new drug is based on preclinical animal toxicity studies unless other investigations warrant a modified dose (e.g., a study reveals that human bone marrow is more sensitive to the new drug than is animal bone marrow). Previously, the starting dose was deduced on the basis of one-tenth of the dose at which 10% of the most sensitive animal species died. However, a recent retrospective analysis of 21 Phase I trials revealed that this starting dose was inappropriately low in most cases [14]. In an attempt to remedy this, the US Food and Drug Administration released draft guidelines that may help determine a better estimation of the recommended starting dose [15]. These guidelines incorporate...
factors such as selection of the most appropriate species from which to extrapolate data and the human equivalent dose calculation. The dose schedule for the new agent is determined by the mechanism of action, clinical pharmokinetics (half-life), and any previous clinical experience. For central nervous system (CNS) tumors it is important to ensure that appropriate studies have been done which demonstrate drug distribution into the CNS.

One well-accepted standard Phase I design involves the accrual of cohorts of three to six patients, which are treated at an initial starting dose with pre-planned increases in dose levels after enough time has elapsed to observe acute toxic effects. Toxicity is standardly measured using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0. The recommended Phase II dose is defined as one dose level below that which resulted in dose-limiting toxicity in two or more of the three to six patients treated.

Different dose escalation designs exist. Historically, a modified Fibonacci escalation sequence (higher escalation steps have decreasing increments, e.g., 100, 65, 50, and 40) is used. However, evidence suggests that the use of the Fibonacci method is not necessary to ensure safety or statistical rigor [14]. Other dose escalation designs such as statistically based methods, continual reassessment methods, and accelerated titration designs can also be used [16]. All methods have the same goal of defining the MTD but differ in the amount of importance they assign to such factors as the number of patients treated at a specified dose level, rapidity of accrual, and pharmokinetic modeling. In comparison to the Fibonacci method, these alternative dose escalation designs may reduce the number of patients treated at potentially subtherapeutic dose levels or at doses that exceed the MTD.

Bearing in mind that the goal of Phase I trials is not therapeutic effect, patient selection is generally open to patients with a broad spectrum of cancers that are refractory to standard therapy or who have no other reasonable therapeutic option. Still, it is important to control patient characteristics that could confound toxicity evaluation. Factors such as general medical health, performance status of the patient, normal organ function, and concomitant medications can alter the new drug’s toxic effect. Additionally, one must take into account that many cytotoxic agents possess similar toxicities (hematological, nausea, vomiting) and as such, patients who have been pretreated with standard cytotoxic agents may be less tolerant of a new cytotoxic agent than a newly diagnosed patient would be.

Phase I studies also usually incorporate pharmokinetic studies (absorption, distribution, metabolism, and excretion) of the new agent in relation to patient characteristics like age, organ function, and degree of toxic effect. Such considerations may aid in refinement of the recommended Phase II dose. Also studied is the influence of agents that may alter metabolism of the study agent. For instance, several commonly used anti-epileptic drugs (AEDs) induce the hepatic cytochrome P450 system and alter the metabolism of the treatment agent [17, 18]. Corticosteroids may also produce this effect. Due to these effects, Phase I neuro-oncology studies often stratify patients into two different dose escalation cohorts of those on and off enzyme-inducing anti-epileptic drugs; they also document corticosteroid use.
Lastly, Phase I studies have a predefined schedule and method of reporting, monitoring, and documenting toxicities. Normally, there are team meetings at predefined intervals to review the status of all patients enrolled in the study. Patients are reviewed in the context of a data safety monitoring plan, which is set up to ensure the timely reporting of adverse events, to monitor the progress of the study, and to ensure data accuracy.

**Novel Agents**

The traditional paradigm of dose selection based on maximum tolerable toxicity may not apply to novel therapies that target cell signaling pathways or the cellular environment. Unlike cytotoxic agents, which act on DNA, these novel therapies have different targets such as membrane receptors, signaling pathways, and proteins or factors important in cell cycle regulation or in angiogenesis. As such, in laboratory models these agents may inhibit tumor progression rather than cause tumor regression. Novel agents also seem to be more selective and less toxic to normal tissue. Considering these points, the dose of the targeted agent needed to achieve tumor inhibition may not be the one that produces significant organ toxicity. Therefore, while the goal of Phase I trials of targeted agents remains the determination of the recommended Phase II dose, this dose is likely to be determined by biological endpoints and not necessarily by the MTD [16]. Biological endpoints are associated with a desired biological effect such as inhibition of an enzyme or immunological change, but not necessarily with a specific toxicity and may actually be reached below the MTD. Additionally, the toxic effects of molecular agents may be achieved through different mechanisms than the therapeutic effect and hence may not parallel one another at all.

An example of a biological endpoint as an alternative to toxicity is measurement of target inhibition. This approach requires a fixed understanding of the complexity of cellular pathways, and extensive laboratory data are needed to validate the mechanism of the new agent and its effect of inhibition on a specific target. After all, it is possible that the drug’s interaction with another cell pathway produces another effect at the cellular level that is responsible for the desired effect but has gone unmeasured. Another obstacle is that a reliable assay needs to be created to obtain tissue for evaluation. Pretreatment and post-treatment results could be obtained by multiple tumor biopsies, but this is invasive to the patient and prone to sampling errors, not to mention expensive and limited to those patients with accessible disease and to tumors that express the desired target. A possible solution is to use surrogate tissue like peripheral blood cells – provided that changes in the surrogate parallel those in the tumor. The chosen assay must also be performed in “real time” to allow decisions to be made regarding dose escalation.

Another possible alternative endpoint is functional imaging that quantifies the level of the target function in vivo. For example, enhanced magnetic resonance imaging (MRI) has been used to assess changes in tumor blood flow after treatment
with anti-angiogenic agents [19]. However, prior to using such changes as primary endpoints in a clinical trial, these surrogate endpoints need extensive preclinical evaluation correlating the effect of the new agent on the target in the tumor.

Until such alternative endpoints are validated, Phase I trials of novel agents incorporating multiple endpoints may be the most practical approach. For example, a useful design may be to define the recommended Phase II dose on the basis of the MTD and the maximum target inhibition dose. Taking into account that many targeted agents may require longer-term treatment than the relatively short-term treatment of cytotoxic agents, the definition of tolerable toxicity may need to be adjusted. In order to limit the intensity of daily toxicity there may be more impetus to discover a therapeutic dose below the MTD. In this vein, concurrent pharmacokinetic studies with molecularly targeted agents may prove important in assessing the time that inhibitory concentrations are sustained for a given schedule. Clearly, further work is needed to optimize strategies for dose selection for targeted therapies.

**Limitations**

The toxicity risk for patients on a Phase I study is high. As the goal of Phase I study is not patient benefit, practitioners may feel that patients are vulnerable to diminished quality of life due to toxic effects of new drugs. Additionally, Phase I studies often only accrue small numbers of patients and therefore may not detect all the toxic effects of a particular drug. Also, Phase I trials do not assess long-term toxicities (escalation measures are based on immediate toxicities), which may be especially problematic for cytotoxic agents given for repeated cycles or cytostatic agents that may require long-term administration.

**Phase II Trials**

**Cytotoxic Agents**

The primary objectives of conventional Phase II trials using a cytotoxic agent are to (1) determine the efficacy of the agent at a certain dose and schedule as identified in Phase I trials and (2) determine whether this level of efficacy warrants further testing in a Phase III trial. Phase II trials are restricted to patients with a specific tumor type, based on the mechanism of the drug and its observed activity in Phase I studies. To ensure detection of response and patient compliance, most patients also have a good performance status and little exposure to prior chemotherapy.

Most Phase II trials are conducted in a multi-stage design [20]. This design allows sequential treatment and evaluation of cohorts of patients with early stopping rules if the accumulated evidence for efficacy is poor or absent. The exact number of patients and number of responses required depend on the willingness to accept
specified probabilities of false-positive or false-negative results. Typically, Phase II cancer studies are open-label and single arm in design. However, if multiple agents are concurrently available for testing, or if various regimens of the same agent are under consideration, a randomized design may be used [20, 21]. The purpose of randomization is not to test which regimen is the “best” but to eliminate bias on the part of the investigator in assigning treatment [22, 23]. Because single arm trials use historical data to assess efficacy, in some instances an appropriate control population may not be available and a concurrent control group is required for some novel strategies, e.g., autologous vaccine use. It must be noted, however, that these trials estimate and do not prove potential differences in determining the likely usefulness of therapy. Biostatistical input is crucial for the appropriate planning of the study as well as the analysis and interpretation of the results [24].

Efficacy is commonly assessed in terms of antitumor activity, traditionally measured as decrease in tumor size after treatment. These measurements are commonly made with standardized criteria such as those of RECIST or in brain tumor trials the MacDonald criteria is used (radiographic response is discussed below) [25, 26]. However, any of these methods dictate that the patient has a measurable tumor and that you are confident that response is objectively identified.

Tumor response (regression) is not an appropriate endpoint for those patients who do not have measurable tumor. For example, those patients who undergo gross total resection do not have measurable tumor. Thus, surrogate endpoints such as time to tumor progression may be employed. This method requires prospective determination of the nature and frequency of evaluation methods used to assess tumor growth. Furthermore, such evaluation methods should be standardized in an effort to leave little to subjective interpretation. A difficulty inherent in the use of time to progression as a surrogate endpoint is the need for a prognostically similar historical control group. This historical control serves as a comparison by which one can detect whether the new agent prolongs time to progression. If a historical control is not available, the study will require a prospectively planned, concurrent control group.

The use of a set time at which the status of the patient and the tumor is assessed has also been employed as a surrogate endpoint, e.g., 6-month progression-free survival. Progression status at 6 months has been shown to be a strong predictor of survival in newly diagnosed or recurrent high-grade glioma and is a valid endpoint for trials of therapy for malignant glioma [27, 28]. Earlier assessments of progression status also predicted survival and may be incorporated in the design of clinical trials. This approach does not require that a certain event take place (progression) and allows for more timely completion of studies. Obviously, though, this approach also requires a similar historical control group.

**Novel Agents**

Molecular agents may prevent tumor growth without shrinking the tumor and thus not produce any radiographic change. Thus, response measured as tumor regression is not an appropriate endpoint for these agents. Possible endpoints for molecularly
targeted agents include time to tumor progression, change in tumor markers, measures of target inhibition, and metabolic imaging [29, 30]. Time to progression is a well-described endpoint in the literature, where benefit is measured by comparison with a historical cohort treated with the standard of care. Ideally, the only difference between the control and treatment group is the treatment itself. Selection bias may unduly make such comparison invalid as groups often differ in comparability of such factors as response assessment, ancillary care, and patient characteristics. One way to minimize selection bias is to use groups evaluated at the same institution.

Change in tumor markers is an appealing endpoint but the technique is unproven and not widely employed in brain tumor therapy for lack of a marker to measure [31, 32]. When a marker does exist, physicians must be certain that the drug does not directly lower the level by protein degradation independent of tumor burden.

Measures of target inhibition require a definitive cause and effect relationship between the novel agent, the targeted molecule, and tumor growth. As much understanding of these relationships is in its infancy, such targeting has yet to be shown to be clinically useful.

Metabolic imaging modalities like single-photon emission computed tomography (SPECT) and positron emission tomography (PET) can reveal the biochemical changes in tumors as they are treated or possibly measure the receptor density status – this usage is currently unproven and requires validation [33]. These imaging techniques may allow an assessment of clinical efficacy and play a role in the management and understanding of tumors [34]. Currently, these techniques are costly and still require study and validation.

**Secondary Evaluations**

Another objective of Phase II studies is a more thorough understanding of the toxicity associated with the agent being tested. Toxicity evaluation is an important secondary endpoint and can add to the knowledge gained in Phase I studies. Such evaluation is even more important when considering that molecular agents may be given long term and Phase II studies may require longer-term toxicity evaluation. An additional secondary endpoint is quality of life assessment. In patients with recurrent malignant glioma who have a poor median survival, quality of life is an important goal and needs to be assessed during a clinical trial. It is a difficult endpoint to assess because of understandable subjectivity and because as patients progress their quality of life tends to decrease; nevertheless, techniques for evaluation exist and should be used [35–37].

**Limitations**

The relatively small number of patients in Phase II trials raises the possibility of a false-positive or false-negative result. A false-negative result can eliminate further study of a potentially active agent while a false-positive study can commit further resources (patients, infrastructure, and finances) to evaluate an agent that
may be of marginal effect. Appropriate statistical considerations with attention to sample size, relevant and valid endpoints, and comparable historical controls and the determination a priori of what constitutes benefit can help minimize error.

**Phase III Clinical Trials**

The objective of a Phase III trial is to establish whether the efficacy of an experimental therapy is better than the standard therapy [38, 39]. These trials are usually large co-operative trials that randomize patients to new agents versus standard therapy. The goal of randomization is to prevent bias and usually leads to an equal distribution of measured and unmeasured (or even unknown) prognostic factors between treatment arms. Predefining risk groups (strata) and randomizing within strata further assure balance and can increase the power to detect treatment differences [39]. Ideally patients and doctors would be blinded to the treatment to reduce bias and any subjective “placebo” effect. However, blinding is often not possible in oncology trials. Typical endpoints are time to progression or survival, though quality of life should also be assessed. Biostatistical input in the design and planned analysis of these studies is crucial to determine the appropriate sample size for the study based on the assumptions of what is expected with standard therapy and the prestated effect size that would warrant declaring “success” of the experimental arm [39].

Whether the agent is cytotoxic or molecularly targeted should not change the design in a substantial way. However, eligibility should be restricted to patients with a specific tumor type or, in the case of molecularly based therapy, only patients with the target should be enrolled.

**Special Challenges of Brain Tumor Trials**

In addition to the principles of clinical trial design and conduct outlined above, there are special issues and challenges relevant to neuro-oncology clinical trials that call for closer examination. Several of these issues are described below.

**Drug Selection**

Many brain tumor patients take anti-epileptic drugs for seizure prophylaxis. Some anticonvulsants may induce the hepatic cytochrome P450 system and alter the metabolism of a treatment agent being studied [40]. Such drug interactions may alter the type and severity of toxicity that patients experience. For example, patients taking paclitaxel or CPT-11 while taking enzyme-inducing anti-epileptic drugs (EIAEDs) may have lower-than-expected plasma levels and higher-than-expected tolerated doses [41, 42]. Thus, Phase I studies of agents known to be metabolized by this enzyme system should stratify patients into two different dose escalation
cohorts of those on and off EIAEDs. A more recent approach in early-phase studies in neuro-oncology is to initiate a Phase II study in brain tumor patients using the established Phase II dose from other systemic cancer patients not taking EIAEDs. Only if some measure of activity is demonstrated will a Phase I study in patients taking EIAEDs be performed.

Additionally, study agents may cause neurological toxicity that may be difficult to distinguish from cerebral edema or effects of the tumor. Neurological toxicity assessments can be confounded by the disease process or concurrent medications. For instance, a seizure may be caused or influenced by the study drug, but could also be solely due to a pre-existing seizure disorder, tumor progression, or lack of adequate treatment with anticonvulsants. Consequently, in Phase I trials it is important to determine whether the patients may be experiencing neurological toxicity caused by the new agent or by pre-existing neurological status. If the toxicity is felt to be due to compromised neurological status and not the study agent, adverse events should be reported in the context of the patient’s pre-existing neurological condition. Of course, if the study agent is thought responsible, then this needs to be conveyed clearly. Taking such measures will assure that a study drug is not inappropriately blamed for adverse events and the study inappropriately halted.

Neuropathology

Histological confirmation of the diagnosis is necessary to predict clinical behavior and determine appropriate treatment. Unfortunately, multiple previously used grading systems exist for brain tumors. The WHO II classification is now accepted as the current system used to classify CNS tumors [43]. However, it remains difficult to compare historical controls that used older classification systems with studies using current histological classification. Additionally, vague terms are sometimes used to describe certain types of brain tumors. For instance, the term malignant glioma is commonly used but is not specific to one tumor type and includes anaplastic astrocytomas, anaplastic oligodendrogliomas, and glioblastomas. These histologies have different responses to therapy and corresponding prognoses. Thus, in an effort to allow for appropriate comparison between groups, use of vague terms should be avoided in any clinical trial.

Another difficulty is inter-observer variability and subjectivity in classifying brain tumors, especially with grades II and III gliomas [44]. It is recommended that brain tumor clinical trials incorporate central pathology review to guarantee statistical power. Also, patients are often included in trials on the basis of their original histological diagnosis even though there has been obvious tumor progression and possible change in the grade of the tumor. In these cases, a second surgery should be performed to check if pathology has changed and whether the patient qualifies for the trial. Ideally, Phase II studies should be performed with previously untreated patients, thereby avoiding the problems of acquired drug resistance and diminished tolerance associated with past treatment.
**Response Assessment and Endpoints**

In systemic cancers, one-dimensional tumor measurements have become the standard criteria to determine radiographic response [26]. The Response Evaluation Criteria in Solid Tumors (RECIST) instituted the use of one-dimensional measurements in 2000. Several retrospective studies compared the RECIST criteria, with two-dimensional and three-dimensional measurements and volumetric measurements in GBM. These studies suggest that there is good concordance between the different methods in determining radiographic response in patients with both newly diagnosed and recurrent GBMs. However, studies prospectively validating the RECIST criteria in gliomas have not been performed.

Instead, the most commonly used criteria, termed the Macdonald Criteria (Table 5.3), for assessing objective radiographic response rate (ORR) to therapy in GBM is based on guidelines written in 1990 by Macdonald et al. [25]. These guidelines are based on two-dimensional tumor measurements from computed tomography (CT) or magnetic resonance imaging (MRI) of the contrast-enhancing portion of the tumor, in conjunction with clinical assessment and corticosteroid dose – meaning that a significant increase in a contrast-enhancing lesion is used as an indicator of tumor progression or a decrease in enhancement is seen as a tumor response to treatment. Contrast enhancement on a CT or MRI, though, is a non-specific process which reveals the passage of contrast across a disrupted blood–tumor barrier or across an area of tumor with abnormal vascular architecture. Thus, decreased enhancement can be promoted by a number of things other than a tumor’s response to therapy including changes in corticosteroid doses, chemotherapy agents,

**Table 5.3** The Macdonald criteria

<table>
<thead>
<tr>
<th>Complete response:</th>
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<tr>
<td>(1) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks</td>
</tr>
<tr>
<td>(2) No new lesions</td>
</tr>
<tr>
<td>(3) No steroids</td>
</tr>
<tr>
<td>(4) Stable or improved clinically</td>
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<tr>
<th>Partial response:</th>
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<tbody>
<tr>
<td>(1) ≥50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks</td>
</tr>
<tr>
<td>(2) No new lesions</td>
</tr>
<tr>
<td>(3) Stable or reduced steroid dose</td>
</tr>
<tr>
<td>(4) Stable or improved clinically</td>
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<tr>
<th>Stable disease:</th>
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<tbody>
<tr>
<td>(1) Does not qualify for complete response, partial response, or progression</td>
</tr>
<tr>
<td>(2) Stable clinically</td>
</tr>
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<th>Tumor progression:</th>
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<tbody>
<tr>
<td>(1) ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions</td>
</tr>
<tr>
<td>(2) Any new lesion</td>
</tr>
<tr>
<td>(3) Clinical deterioration</td>
</tr>
</tbody>
</table>
and different radiological techniques. Increased enhancement can be produced by treatment-related inflammation, seizure activity, post-surgical changes, ischemia, radiation effects, and tumor growth.

Taking the above into consideration, there are evident limitations to the Macdonald criteria [45–47]. First and foremost among these limitations is that they only address the contrast-enhancing component of a GBM as seen on CT or MRI. Other confines include the difficulty in measuring irregularly shaped tumors, the lack of guidance for the assessment of multi-focal tumors, the difficulty in measuring enhancing lesions in the wall of cystic or surgical cavities as the cyst/cavity itself may be included in the tumor, and the inter-observer variability among those physicians interpreting the scans. These limitations also include evaluating pseudoprogression or the transient increase in tumor enhancement seen in 20–30% of patients with GBMs on their post-radiation MRI which is difficult to differentiate from genuine tumor progression [45–47]. In addition, a transient increase in enhancement that can be difficult to distinguish from recurrent disease can also occur following several additional therapies like chemotherapy wafers, therapies delivered by convection-enhanced delivery, regional immunotherapies, and radiosurgery.

In addition to the continued concern over the limitations of the Macdonald criteria in connecting changes in enhancement with changes in tumor growth arises the added challenge of how such changes in enhancement are made more difficult to evaluate appropriately when considering the introduction of therapies, such as bevacizumab, that affect the permeability of tumor vasculature [48]. Anti-angiogenic agents may produce decreased enhancement shortly after the initiation of therapy or long after its start indicating several possible biological mechanisms for such varied findings [49, 50]. Also, in all likelihood these “responses” are due in part to normalization of abnormally permeable tumor blood vessels and not to an antitumor effect [45, 46, 51, 52]. As a result, radiographic responses in studies with anti-angiogenic therapies should be interpreted with prudence that accounts for the apparent inconsistency between the high response rates produced in recurrent GBM and the modest survival benefit that has been reported [51, 53, 54].

Obviously, there exist substantial challenges in the radiologic evaluation of response during brain tumor clinical trials and its use as a surrogate for survival benefit [45]. Imaging measurement approaches, response criteria, selection of lesions for measurement, technical imaging factors, intervals between tumor measurements and response confirmation, and validity of imaging as a measure of efficacy are all continuing topics of debate in the neuro-oncology community [45, 46]. Added to these points and as discussed above, cytostatic agents are not expected to shrink a tumor and thus response as assessed by reduction in size of the tumor on imaging is not appropriate. Instead, these agents are evaluated by different endpoints such as progression-free survival or time to progression. Both these endpoints require historical controls, which pose several challenges (see below). Additionally, a longer time to progression does not necessarily correlate with longer survival.

Published proposals that account for such difficulties with radiographic response suggest that clinical studies report both radiographic and clinical response rates and use volumetric rather than cross-sectional area to measure lesion size [46].
Other studies suggested that techniques such as apparent diffusion coefficient (ADC) histogram analysis, diffusion-weighted imaging, or dynamic perfusion MRI measurements can assist in stratifying progression-free survival in patients with recurrent GBM [55–57].

These suggestions and the increased awareness that contrast enhancement is non-specific and not always a surrogate of tumor response together with the need to assess the non-enhancing component of GBM inspired the recent creation of The Response Assessment in Neuro-Oncology (RANO) Working Group [47 add JCO paper]. This group is charged with the development of new standardized response criteria for clinical trials for patients with brain tumors which accounts for both the known challenges of radiographic assessment of GBM and the emerging challenges associated with anti-angiogenic agents like bevacizumab. Unlike the Macdonald criteria which do not take into account progressive non-enhancing disease, the new response criteria will regard enlarging areas of non-enhancing tumor as evidence of tumor progression. However, the group cautions that the quantification of the increase in T2/FLAIR signal must be differentiated from other causes of increased T2/FLAIR signal including radiation effects, decreased corticosteroid dosing, demyelination, ischemic injury, infection, seizures, and post-operative changes. The RANO also advises that changes in T2/FLAIR signal that raises the possibility of infiltrating tumor include mass effect, infiltration of the cortical ribbon, and location outside of the radiation field.

Future, if not current, trials will likely combine therapies which inhibit angiogenesis with those which prevent invasion. Thus, in addition to the RANO group criteria it may also be wise to include, as a primary endpoint, the duration of response and the overall survival as a more accurate indicator of a true antitumor effect. It is also very important to incorporate novel imaging techniques such as perfusion and permeability imaging and diffusion imaging into clinical trials of these combination agents to develop better ways of measuring biologic effects. Such additional imaging techniques may help answer the critical questions which remain about how anti-angiogenic agents work and how to combine them with other therapies. Work is also left to be completed in understanding the progress relating to the identification of potential biomarkers for anti-angiogenic agent efficacy in humans [58]. Lastly, an ongoing area of interesting research involves examining whether MRI-based classifications of GBM may help predict tumor recurrence patterns of patients on bevacizumab or other novel agents [59, 60].

**Historical Controls**

Most Phase II neuro-oncology studies are open-label, single arm studies that necessitate the use of historical controls. These historical control groups must be chosen with great care, applying the same inclusion and exclusion criteria to controls that are applied to patients receiving the study agent. If this same rigor is not used in choosing a control group, an experimental agent can appear better than the standard
by virtue of the patient selection process. This type of error is evident in a recent intra-arterial chemotherapy study and in an interstitial brachytherapy study from the late 1980s [4]. On review, the apparent benefit in both studies was due to the patient selection process rather than the novel treatments [4]. To minimize this type of error, study populations should be compared to control groups that have been subjected to the same inclusion and exclusion criteria. Additionally, an appropriate historical control would have the same criteria for pathological assessment and the same endpoints used to assess efficacy.

**Conclusion**

Clinical trials are evolving scientific experiments with constant effort being made on the part of clinicians to develop more efficient designs that quickly identify and discontinue ineffective agents without discarding beneficial ones. Neuro-oncologists must continue to use resources well and implement data and reporting standards to foster advances on par with most other vital scientific endeavors. Quality control, endpoint evaluation, and data reporting techniques should be standardized and followed with the same rigor inherent in any scientific experiment. Additionally, to deal with the complexity of long-term follow up, new methods of chronically evaluating patients need to be devised. This is especially true not only for cytostatic agents, but is also evident when clinicians prescribe cytotoxic agents for longer periods of time than traditionally used, with unknown long-term risk or benefit. Also, as the molecular pathogenesis of brain tumors has not been linked to a single genetic defect or target, molecular agents may be used in tandem with cytotoxic agents, which will require a combination of clinical trial designs to properly determine patient benefit. Published guidelines specific to neuro-oncology are available to ensure standardized reporting of neuro-oncology trials [61, 62]. The guidelines also assist with accurate interpretation of results from these trials, facilitate the peer-review process, and expedite the publication of important and accurate manuscripts.

**References**

Chapter 6
Complications of Therapy

Derek R. Johnson, Jonathan B. Ashman, Paul D. Brown, Daniel H. Lachance, and Jan C. Buckner

Keywords  Chemotherapy · Targeted molecular therapy · Radiation therapy · Brain tumor · Complications

Primary brain tumors are typically treated with a combination of surgery, radiation, and chemotherapy. While currently available treatments can be combined in countless ways and many new potential treatments are in various stages of development, there are relatively few regimens with proven efficacy against primary brain tumors of any type. The widespread use of these treatments means that clinicians are likely to encounter even rare side effects, making the evaluation and management of therapy-related toxicities a vital part of clinical practice. Chemotherapy complications tend to be acute and range in severity from mild and self-limiting to life-threatening. While some of the acute complications of chemotherapy, such as neuropathy, can persist for years, it is rare for a new problem to arise long after discontinuing treatment. In contrast, the acute complications of radiation are often readily treatable, but delayed effects such as radiation necrosis, and encephalopathy can be devastating. This chapter will focus on the short-term and long-term sequelae of chemotherapeutic agents and radiation techniques currently in clinical use, with an emphasis on the treatment of glioblastoma multiforme, the most common primary brain tumor.

Pharmaceutical Therapy

Pharmaceutical therapies play an increasingly important role in the treatment of primary brain tumors. The past 5 years have seen a change in the standard-of-care regimens for both newly diagnosed and recurrent glioblastoma with the FDA approval of temozolomide (TMZ) and bevacizumab, and many other potentially promising agents are in various stages of development. The pharmaceutical agents

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currently used by neuro-oncologists can generally be divided into two categories: cytotoxic agents and targeted therapies. Temozolomide, the cytotoxic chemotherapy currently in widest use, is an alkylating agent which interferes with DNA replication and is conceptually similar to many other agents well known to neuro-oncologists and medical oncologists such as the nitrosoureas and the platins. Bevacizumab and similar agents represent a different approach to tumor therapy. They are molecularly targeted therapies aimed at specific signaling pathways thought to be important in tumor formation, growth, spread, and survival. We will examine the side-effect profiles of agents in widespread clinical use for the treatment of primary brain tumors, as well as monitoring and management of these complications.

**Systemic Therapies**

**Conventional Chemotherapeutic Agents**

**Temozolomide**

Temozolomide is a well-tolerated alkylating agent that is FDA-approved for use in combination with radiation therapy for patients with newly diagnosed glioblastoma or as a single agent for those with refractory anaplastic astrocytoma. The most commonly used TMZ regimen is 6 weeks of concurrent TMZ at 75 mg/m²/day along with radiation therapy followed by monthly adjuvant cycles of 5 days of therapy each 28 days. The first adjuvant cycle is typically given as 150 mg/m² daily for 5 days, and if no major myelosuppression is detected on day 22, the subsequent courses are increased to 200 mg/m² daily for 5 days. These doses were demonstrated to be well tolerated in Phase I trials [1, 2] and were used in the Phase II and Phase III trials that demonstrated the efficacy of TMZ in malignant glioma [3–5].

Temozolomide is generally well tolerated; in the EORTC/NCIC trial no decrease in health-related quality of life resulted from the addition of TMZ to standard radiotherapy [6]. Despite this fact, a variety of hematological and non-hematological toxicities are regularly seen. In the EORTC/NCIC Phase III trial of TMZ for newly diagnosed GBM, hematologic issues were the most common serious side effects, with 4% of patients experiencing severe or life-threatening neutropenia, as defined by the National Cancer Institute’s (NCI) *Common Toxicity Criteria*, and 3% of patients experiencing severe or life-threatening thrombocytopenia during the 6-week daily dosing radiation-concurrent phase of the trial. During the adjuvant phase, when TMZ was administered for the first 5 days of each 28-day cycle, 14% of patients experienced an NCI *Common Toxicity Criteria* 2.0 grade 3 or 4 hematologic toxic effect with thrombocytopenia occurring more frequently than neutropenia [3].

While acute side effects occur relatively frequently, their severity and clinical significance can be minimized through vigilant monitoring and prophylaxis. During the concurrent phase of TMZ chemotherapy, weekly complete blood count (CBC) is
recommended, along with monthly serum electrolyte panel and liver function tests. If significant hematologic toxicity occurs transfusion [7], growth factor administration [8], or TMZ dose reduction can be considered. During the adjuvant cycles of TMZ chemotherapy, a CBC should be checked before the beginning of each cycle. Treatment can be delayed or dose-reduced as needed if significant hematological toxicity occurs [4]. *Pneumocystis jirovecii pneumonia*, formerly referred to as *Pneumocystis carinii pneumonia* (PCP), has been seen in patients with TMZ-related neutropenia, and prophylaxis with trimethoprim and sulfamethoxazole should be considered [9]. In sulfa-allergic patients, other agents such as dapsone and pentamidine may be employed for PCP prophylaxis. Medication management can also minimize the non-hematologic toxicities of TMZ. Treatment-related nausea can be significantly reduced by pretreatment with an oral anti-emetic. Serotonin 5-HT3 receptor antagonists such as ondansetron are the most commonly used class, and they offer excellent efficacy and minimal side effects. Similarly, constipation occurs with enough frequency that stool softeners such as docusate are often prescribed on a prophylactic basis. Other complications, such as fatigue and rash, do not require prophylactic treatment but can be managed on a symptomatic basis (see Table 6.1).

Long-term complications of TMZ are not as well understood as the acute issues, owing to the relatively short median survival time of patients with glioblastoma. In patients treated with the standard regimen, TMZ-related myelosuppression is typically predictable and reversible, but there is emerging evidence of cumulative myelotoxicity with standard dosing. Chemotherapy-related

<table>
<thead>
<tr>
<th>Complication</th>
<th>Medication</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>Ondansetron 4–8 mg PO daily 1 h before TMZ or granisetron 1 mg PO daily 1 h before TMZ or prochlorperazine 10 mg PO Q6 h for N/V refractory to serotonin antagonists</td>
<td>Anti-emetics are recommended as premedication before each dose of TMZ</td>
</tr>
<tr>
<td>Constipation</td>
<td>Docusate sodium 100 mg PO BID and/or sennosides 2 tabs PO daily BID and/or bisacodyl 5–15 mg PO daily PRN and/or miralax 17 g PO Daily PRN</td>
<td>Docusate, senna, and a high-fiber diet can be used prophylactically. Other agents can be used for limited periods on an as-needed basis</td>
</tr>
<tr>
<td>PCP Prophylaxis</td>
<td>TMP–SMX 1 SS tab PO daily or TMP–SMX 1 DS tab PO 3 times a week or atovaquone 1,500 mg PO daily or dapsone 100 mg PO daily or pentamidine 300 mg INH every 4 weeks</td>
<td>PCP prophylaxis should continue until recovery from leukopenia. Some advocate treatment until several months after the completion of adjuvant TMZ therapy</td>
</tr>
<tr>
<td>CTCAE category</td>
<td>Adverse eventa</td>
<td>Recommended action</td>
</tr>
<tr>
<td>------------------------</td>
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<td>-----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Blood/bone marrow</td>
<td>ANC &lt; 1,500 but ≥ 1,000</td>
<td>Continue RT, but hold TMZ until ANC ≥ 1,500 and platelets ≥ 75,000, then decrease TMZ dose by 15%</td>
</tr>
<tr>
<td></td>
<td>ANC &lt; 1,000 but ≥ 5,000 or platelets &lt; 5,000 but &gt;25,000</td>
<td>Continue RT, but hold TMZ until ANC ≥ 1,500 and platelets ≥ 75,000, then decrease TMZ dose by 25%</td>
</tr>
<tr>
<td></td>
<td>ANC &lt; 500 or platelets &lt; 25,000</td>
<td>Hold RT and TMZ. Resume RT when ANC ≥ 500 and platelets ≥ 50,000. Resume TMZ when ANC ≥ 1,500 and platelets ≥ 100,000, then decrease TMZ dose by 50%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea/vomiting on optimal anti-emetic treatment Grade 2</td>
<td>May hold TMZ until recovery to grades 0–1, at investigators discretion</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Hold TMZ until Grades 0–2 (or within 1 grade of baseline) then decrease TMZ dose by 25%</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Hold TMZ until grades 0–2 (or within 1 grade of baseline) then decrease dose by 50%</td>
</tr>
<tr>
<td>Non-hematologic other, possibly, probably, or definitely related to treatment</td>
<td>Grade 2</td>
<td>For a symptomatic grade 2 adverse event, the dose may be held until recovery to grades 0–1, then decrease TMZ dose by 15% at investigators discretion</td>
</tr>
<tr>
<td></td>
<td>Grade 3</td>
<td>Hold TMZ until grades 0–2 (or within 1 grade of starting values for pre-existing abnormalities) then decrease dose by 25%</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Hold TMZ until grades 0–2 (or within 1 grade of starting values for pre-existing abnormalities) then decrease dose by 50%</td>
</tr>
</tbody>
</table>

aAdverse event grades per Common Terminology Criteria for Adverse Events (CTCAE) v4.0

myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are well-recognized consequences of long-term therapy with alkylating agents, and a number of cases have been reported in patients treated with TMZ [10, 11]. Temozolomide-related aplastic anemia is also a concern and over 50 cases have been reported [12]. Due to the success of TMZ in the treatment of GBM, it is now also frequently used for initial therapy in anaplastic astrocytoma, a condition with a significantly longer median survival. Small case-series report TMZ therapy for up to 8 years without
<table>
<thead>
<tr>
<th>CTCAE category</th>
<th>Adverse eventa</th>
<th>Recommended action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac general (hypertension)</td>
<td>Grade 2b</td>
<td>Initiate antihypotensive monotherapy (suggest dihydropyridine calcium channel blocker monotherapy), monitor BP every 2 days until stable</td>
</tr>
<tr>
<td></td>
<td>Grade 2b (symptomatic/persistent) or diastolic BP &gt; 110 mmHg or grade 3b</td>
<td>Add antihypertensive agents as needed. Hold bevacizumab until symptoms resolve AND diastolic BP ≤ 100 mmHg, then resume bevacizumab treatment at lower dose. If BP cannot be controlled to 150/100 with medication then discontinue bevacizumab</td>
</tr>
<tr>
<td>Cardiac general (CHF)</td>
<td>Grade 3</td>
<td>Discontinue bevacizumab therapy</td>
</tr>
<tr>
<td></td>
<td>Grade 4b</td>
<td>Hold bevacizumab until resolution to grade ≤ 1, then resume treatment. If CHR recurs, discontinue bevacizumab</td>
</tr>
<tr>
<td>Dermatology/skin</td>
<td>Grade &gt; 2 wound complication (non-infectious)</td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Any fistula, perforation, or leak</td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td></td>
<td>Grade 2 obstruction</td>
<td>Hold bevacizumab until resolution of obstruction</td>
</tr>
<tr>
<td></td>
<td>Grade 3 or 4 obstruction</td>
<td>Hold bevacizumab until resolution of obstruction. If surgery is necessary, patient may restart bevacizumab ≥ 28 days following surgery, at investigators discretion</td>
</tr>
<tr>
<td>CTCAE category</td>
<td>Adverse event</td>
<td>Recommended action</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Hemorrhage/bleeding – non-CNS,</td>
<td>Grade 3</td>
<td>Patients on full-dose anticoagulation should discontinue bevacizumab. All other subjects hold until all of the following criteria are met:</td>
</tr>
<tr>
<td>non-pulmonary</td>
<td></td>
<td>• The bleeding has resolved and hemoglobin is stable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• There is no bleeding diathesis that would increase the risk of therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence</td>
</tr>
<tr>
<td></td>
<td>Grade 4</td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>Hemorrhage/bleeding – CNS or</td>
<td>Grade 1</td>
<td>Patients on full-dose anticoagulation should discontinue bevacizumab. All other subjects hold until all of the following criteria are met:</td>
</tr>
<tr>
<td>pulmonary</td>
<td></td>
<td>• The bleeding has resolved and hemoglobin is stable</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• There is no bleeding diathesis that would increase the risk of therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• There is no anatomic or pathologic condition that significantly increases the risk of hemorrhage recurrence</td>
</tr>
<tr>
<td>Neurology</td>
<td>Grade ≥ 2</td>
<td>Discontinue bevacizumab</td>
</tr>
<tr>
<td>Any cerebrovascular ischemia</td>
<td></td>
<td>Subjects who experience a repeat grade 3 hemorrhagic event should discontinue bevacizumab</td>
</tr>
<tr>
<td>Leukoencephalopathy syndrome</td>
<td></td>
<td>Subjects who experience a repeat grade 3 hemorrhagic event should discontinue bevacizumab</td>
</tr>
<tr>
<td></td>
<td>Hold bevacizumab pending workup and management, including control of blood pressure. Discontinue if RPLS diagnosed. Resumption of bevacizumab may be considered in patients who have documented benefit from the agent, provided that RPLS was mild and has completely resolved clinically and radiographically</td>
<td></td>
</tr>
</tbody>
</table>
**Table 6.3 (continued)**

<table>
<thead>
<tr>
<th>CTCAE category</th>
<th>Adverse eventa</th>
<th>Recommended action</th>
</tr>
</thead>
</table>
| Vascular       | Thrombus/embolism grade 3 or asymptomatic grade 4 | If the planned duration of full-dose anticoagulation is <2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. If the planned duration of full-dose anticoagulation is ≥3 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation if all of the following criteria are met:  
  - The patient must have an in-range INR (usually between 2 and 3) if on warfarin; LMWH, warfarin, or other anticoagulant dosing must be stable prior to restarting bevacizumab treatment  
  - The patient must not have had a grade 3 or 4 hemorrhagic event while on anticoagulation |
|                | Grade 4 (symptomatic thrombosis) Any peripheral artery ischemia | Discontinue bevacizumab |

aAdverse event grades per common terminology criteria for adverse events (CTCAE) v4.0.

bCTCAE v4.0 hypertension definitions

*Grade 1:* Prehypertension (systolic BP 120–139 mmHg or diastolic BP 80–89 mmHg).

*Grade 2:* Stage 1 hypertension (systolic BP 140–159 mmHg or diastolic BP 90–99 mmHg); medical intervention indicated; recurrent or persistent (≥24 h); symptomatic increase by >20 mmHg (diastolic) or to >140/90 if previously WNL; monotherapy indicated.

*Grade 3:* Stage 2 hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated.

*Grade 4:* Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated.
significant side effects [13] but much more data will need to be collected before the implications of prolonged therapy are fully understood. Further, a variety of alternative adjuvant “dose-dense” dosing regimens that provide more TMZ in each cycle are currently being investigated. While the short-term adverse effects appear comparable to the standard regimen [14–16], these regimens could theoretically carry a higher risk of long-term marrow toxicity. A recent retrospective review of 680 malignant glioma patients identified several clinical factors and genetic polymorphisms associated with risk of myelotoxicity following temozolomide therapy [17]. A prospective study validating the risk factor formula developed in this report is planned. Another issue that will become more important as TMZ is used for tumors with longer median survival is that of gonadal toxicity. To date, the literature contains only a single case report of a male patient who successfully fathered a child after treatment with TMZ [18]. Options for preservation of fertility are expanding for both male and female patients, and patients should be aware of the available resources [19].

Nitrosoureas

The nitrosoureas are a lipid-soluble group of alkylating agents favored for their ability to cross the blood–brain barrier. Prior to the advent of TMZ, the nitrosoureas were the most widely used agents for the treatments of gliomas. BCNU (carmustine) is the prototypical nitrosourea and is the member of the family that is in the greatest use by neuro-oncologists. In the past, CCNU (lomustine) was commonly used in combination with procarbazine and vincristine to create the regimen known as PCV, but this has largely been supplanted by BCNU or CCNU monotherapy following a retrospective review that found no survival benefit to PCV over BCNU alone in the treatment of anaplastic astrocytoma [20]. Currently, PCV is most often used for treatment of anaplastic oligodendroglioma but recent data suggest that TMZ monotherapy achieves comparable results and is better tolerated [21].

In the dose range commonly used for the treatment of primary brain tumors, BCNU does not typically cause clinically significant neurotoxicity. At higher intravenous doses [22], or when delivered as an intra-arterial therapy [23], neurotoxicity can manifest as severe encephalopathy, focal deficits, or visual loss. The most common serious systemic toxicity of BCNU is myelosuppression, which led to a platelet nadir of less than or equal to 25,000/mm³ in 9% and a WBC nadir of less than 1,000/mm³ in 3% of the 137 patients treated with radiation plus concurrent and adjuvant BCNU for newly diagnosed high-grade glioma in a prospective trial [24]. Characteristically, nitrosourea-related myelosuppression is delayed 3–4 or more weeks after a single daily dose. In addition, myelosuppression is cumulative, with each subsequent dose increasing the risk. Consequently, most patients will be able to receive a limited number of cycles before myelosuppression limits further therapy. Moreover, the myelosuppression may be permanent, limiting the possibility of treatment with other myelosuppressive agents in the future. As with temozolomide, nitrosoureas may also cause myelodysplastic syndromes and acute leukemia, as well as gonadal toxicity. In a Phase II study of 40 patients who received at total of 100
cycles of BCNU for recurrent glioblastoma (mean 2.4 cycles per patient, range 1–6 cycles), grade 3 or 4 thrombocytopenia was seen following 10% of the cycles and grade 3 or 4 neutropenia followed 8% of cycles [25]. Other potentially serious side effects of BCNU include hepatic and pulmonary toxicities. Nausea, vomiting, and fatigue are often seen, but are frequently mild or responsive to medical management.

Patients treated with nitrosoureas should be monitored regularly with CBCs for hematologic toxicity and liver function tests for hepatic toxicity. Treatment delay and/or dose modification was recommended if leukocyte count was less than 3,000/μL, platelet counts was less than 100,000/μL, or AST or total bilirubin > 3 times the upper limit of normal [24]. Acute hepatic toxicity is usually asymptomatic, manifested by transaminasemia and hyperbilirubinemia. It usually resolves spontaneously with discontinuation of chemotherapy. Chest X-rays are often performed before every other cycle to monitor for pulmonary fibrosis, and carbon monoxide diffusing capacity can be assessed as clinically indicated. Acute pulmonary toxicity may be reversible with discontinuation of therapy and use of corticosteroids; however, frank pulmonary fibrosis is not reversible and must be treated symptomatically. It is occasionally fatal.

Procarbazine

Procarbazine, like temozolomide, is an orally administered alkylating agent. Prior to a Phase II study which demonstrated superior progression-free survival and 6-month overall survival with TMZ [4], procarbazine was widely employed and well tolerated in the setting of recurrent glioblastoma. In the above-mentioned trial, side-effect profiles were similar in the procarbazine and TMZ groups, with 76% of patients treated with procarbazine noting any treatment-related adverse event, compared to 77% treated with TMZ. Procarbazine did have a higher rate of grade 3 and 4 toxicities, which occurred in 25% of patients compared to 18% of TMZ-treated patients. The most common grade 3 or 4 toxicities in the procarbazine group were vomiting (5%), thrombocytopenia (4%), and neutropenia (3%). Neurological side effects of procarbazine are relatively rare, but peripheral neuropathy has been reported [26]. As temozolomide has become the first-line therapy for newly diagnosed glioblastoma, there has been renewed interest in procarbazine as a salvage therapy for recurrent glioblastoma. When given in combination with TMZ at time of tumor recurrence, procarbazine is well tolerated but only modestly effective [27].

Irinotecan

Irinotecan (CPT-11), is an intravenous topoisomerase-I inhibitor that has been evaluated for activity against glioma both as a monotherapy [28] and as part of various combination regimens [29–32]. Currently, irinotecan is used primarily in combination with bevacizumab (Avastin), but its efficacy in combination with bevacizumab versus bevacizumab alone is not clear [33].

When used as a monotherapy, the most frequent toxicities of irinotecan include neutropenia and severe diarrhea [34]. The diarrhea caused by irinotecan can be
delayed in onset and is due to a secretory mechanism [35]. Loperamide is a commonly employed symptomatic treatment for this issue. The utility of combining irinotecan with bevacizumab is currently a subject of active research, but the combination is relatively well tolerated. In both the original Phase II trial [36] and a subsequent series of 51 patients treated with this combination [37] the most frequent and significant toxicities were hypertension and venous thromboembolic events likely related to the bevacizumab component of therapy. In a more recent trial comparing bevacizumab alone to bevacizumab plus irinotecan, 46.4% of patients in the bevacizumab monotherapy group experienced any grade 3 or 4 toxicity, relative to 65.8% of the combination therapy group [33].

Etoposide

Etoposide, also known as VP-16, is an inhibitor of the enzyme topoisomerase II that can be administered orally or intravenously. Impairment of topoisomerase II activity leads to DNA strand breaks. Despite poor CSF penetration [38], etoposide has been shown to possess activity against primary brain tumors. Etoposide has been used by neuro-oncologists as part of multidrug regimens in the treatment of recurrent glioblastoma [39, 40], primary CNS lymphoma [41, 42], primary central nervous system germ cell tumors, medulloblastoma, and primary CNS primitive neuro-ectodermal tumors. Nervous system side effects are rare with oral and intravenous etoposide, although complications including neuropathy [43] and encephalopathy [44] have been reported.

Systemic side effects with prolonged oral administration of 50 mg/day of etoposide include minimal myelosuppression, fatigue, nausea, and alopecia [45]. Intravenous etoposide was similarly well tolerated, with only mild or moderate hematologic toxicity in patient treated between 50 and 100 mg/day in 5-day cycles repeated every 3 weeks [46]. Etoposide monotherapy for recurrent glioma is now rarely used as it has been replaced by other agents with superior efficacy. It is still in use for patients with CNS germ cell tumors and medulloblastoma.

Platinum Compounds

Platinum compounds are rarely used as treatments for glioma but remain an important compound in the treatment of tumors such as medulloblastoma and other primitive neuro-ectodermal tumors [47, 48], CNS germ cell tumors, and ependymoma [49, 50]. The two members of this class in greatest use by neuro-oncologists are cisplatin and carboplatin.

Cisplatin crosses the blood–brain barrier poorly and most of its associated neurotoxicity involves the peripheral nervous system. Cisplatin treatment predictably produces a large fiber sensory neuropathy with spared small fiber sensation and power. Symptoms typically begin with paresthesias of the hands and feet with proximal spread and early loss of distal reflexes. Neuropathy can develop at low doses and becomes frequent at doses in excess of 400 mg/m². In the setting of mild treatment-related neuropathy, retreatment is generally safe up to a total dose
of 800–900 mg/m² [51], however, the decision to treat is based upon symptomatic status rather than cumulative dose. Neuropathy symptoms can begin after treatment is completed and progress over a period of months. A slow and incomplete recovery is often seen, typically beginning months after therapy is discontinued. Another predictable cisplatin toxicity is high-frequency hearing loss, which is often subclinical but may occasionally be severe [52]. This is due to damage to the hair cells of the Organ of Corti and also damage to the spiral ganglion and stria vascularis. A variety of strategies have been utilized to minimize peripheral neuropathy and hearing loss due to cisplatin therapy, but to date no prophylactic measurements have proven successful. Other frequent cisplatin-related symptoms include muscle cramps which are thought to be related to the sensory neuropathy and a Lhermitte sign likely due to transient posterior column demyelination [53]. Central nervous system toxicity from intravenous administration is uncommon but can include posterior reversible leukoencephalopathy, visual loss, and seizures [54, 55]. Of historical interest, devastating CNS toxicity has been observed with intra-arterial administration.

Systemic side effects of cisplatin include nephrotoxicity, severe nausea and vomiting, and electrolyte disturbances. Cisplatin causes renal dysfunction through multiple different mechanisms [56]. Most patients experience a dose-dependent reversible decline in glomerular filtration rate, and some patients develop chronic kidney disease. Aggressive saline hydration is important in reducing the risk of cisplatin nephrotoxicity, and some evidence suggests that the use of mannitol or furosemide diuresis may further reduce risk [57]. Renal tubular injury is also common, resulting in electrolyte abnormalities, especially hypomagnesemia that can become symptomatic without aggressive magnesium replacement. Hyponatremia, hypokalemia, and hypocalcemia occur relatively frequently as well, particularly after multiple cycles of therapy.

Carboplatin is a second-generation platinum compound with less toxicity than cisplatin [58]. Neuromuscular complications are less frequent [58], and serious central nervous system toxicity is rare, except when administered intra-arterially, when retinal toxicity can be seen [59]. Carboplatin is used by neuro-oncologists to treat a number of conditions including medulloblastoma/PNET [60], recurrent glioblastoma [61], and low-grade glioma in children [62]. Unlike cisplatin, myelosuppression is the dose-limiting toxicity of carboplatin. In addition, repeated administration of carboplatin is associated with allergic reactions, including flushing, erythroderma, hives, dyspnea, and hypotension.

Methotrexate

Methotrexate is an antimetabolite and antifolate agent most frequently used by neuro-oncologists in the treatment of primary CNS lymphoma. Methotrexate crosses the blood–brain barrier poorly, so very high systemic doses are required to achieve adequate brain penetration. Folinic acid, a folic acid derivative that does not require dihydrofolate reductase for its conversion, is administered after MTX infusion to reduce systemic toxicity.
Central nervous system toxicity due to intravenous high-dose MTX infusion is more frequent when it is used in conjunction with radiation therapy, but CNS toxicity can occur with MTX alone. Both acute and delayed complications are seen. Acute toxicity can include a transient encephalopathy characterized by confusion, disorientation, somnolence, and seizures. Onset occurs within 24–48 h of treatment, and symptoms typically resolve spontaneously [63]. While the acute CNS toxicity of MTX is self-limited, delayed MTX toxicity is a significant cause of morbidity in long-term survivors of primary CNS lymphoma. In some trials, in excess of 80% of patients over the age of 60 treated with methotrexate-based chemotherapy regimens and radiation developed treatment-induced leukoencephalopathy [64]. The most frequent symptoms of this syndrome include cognitive decline, behavioral changes, gait abnormalities, and urinary incontinence [65, 66]. Due to this risk of leukoencephalopathy when MTX is combined with radiation, high-dose MTX without radiation therapy is often used in this population and is well tolerated, even by the elderly [67]. The most serious systemic side effects of high-dose methotrexate chemotherapy are renal dysfunction and myelosuppression. Methotrexate-induced renal toxicity is due to damage of the renal tubules, either by methotrexate precipitation or via a direct toxic effect [68]. Measures such as aggressive hydration, urine alkalinization, and use of leucovorin rescue reduce but do not eliminate the risk of renal toxicity. Reduced plasma clearance of methotrexate due to nephropathy also increases the risk of developing other systemic toxicities including bone marrow suppression, mucositis, and dermatitis. Hepatic toxicity is more common with chronic oral methotrexate use, as for rheumatic disease, than with periodic high-dose methotrexate chemotherapy. Finally, acute and chronic pulmonary toxicities can occur but are infrequent. In order to minimize toxicity, methotrexate levels should be monitored, and leucovorin administration continued until methotrexate levels are reduced to satisfactory levels.

Vincristine

Vincristine is a vinca alkaloid that blocks tubulin polymerization, thereby preventing the formation of microtubules necessary for cellular mitosis. It is primarily used as part of multidrug regimens to treat tumors such as pediatric low-grade gliomas, primitive neuro-ectodermal tumors, and atypical teratoid rhabdoid tumor. Vincristine was formerly widely used in combination with procarbazine and lomustine to treat recurrent malignant glioma, but this treatment has largely been replaced by other therapies, as previously discussed.

Microtubules are the backbone of the axonal transport system, and their disruption by vincristine results in a sensory and motor axonal neuropathy, the major nervous system toxicity of vincristine. Initial symptoms typically include paresthesias of the hands and feet as well as loss of distal reflexes. Unlike cisplatin-induced neuropathy, vincristine-induced neuropathy does often lead to clinically apparent weakness if dosing continues after symptoms appear. The weakness is usually most pronounced in ankle dorsiflexors and wrist extensors. Although weakness is typically mild, some patients, particularly those with pre-existing neuropathy,
can develop severe symptoms [69]. In particular, children with undiagnosed famil-
ial neuropathies such as Charcot–Marie–Tooth disease type 1a may experience a
devastating neuropathy, and a detailed family history should be obtained before
treatment is initiated [70]. In over a quarter of patients with vincristine-associated
neuropathy, symptoms worsen after discontinuation of treatment before beginning
to recover. Many patients with vincristine-associated neuropathy will experience
spontaneous recovery, but it is often incomplete and reflexes may never recover.
Vincristine can also cause focal neuropathy, including isolated cranial neuropathies
[71]. Autonomic neuropathy has also been noted, most commonly leading to consti-
pation [72], but other autonomic symptoms including heart rate abnormalities [73]
and orthostatic hypotension [74] have been reported and may be severe. Central ner-
vous system toxicity due to intravenous vincristine administration is rare, but acute
encephalopathy with seizures has been reported [75]. Inadvertent intrathecal vin-
cristine administration is devastating, leading to irreversible nervous system injury
or death [76].

The most frequent systemic side effects of vincristine are constipation, which is
thought to be a manifestation of the previously mentioned dysautonomia, and alope-
cia. Rarer, but potentially serious, issues include hyponatremia, which may be more
frequent in Asians [77], and hypersensitivity reactions. Bone marrow suppression is rare.

**Molecularly Targeted Agents**

**Bevacizumab**

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor
(VEGF). It is the only molecularly targeted agent that is FDA-approved for use in
primary brain tumors. Bevacizumab is commonly used either as a monotherapy or
in combination with irinotecan at recurrence but is currently in clinical trials with
other chemotherapeutic and targeted agents for recurrent glioma and as concurrent
and adjuvant therapy following initial diagnosis of newly diagnosed glioblastoma.
Bevacizumab has a number of common side effects including hypertension, pro-
teinuria, renal insufficiency, and fatigue [78]. Patients treated with bevacizumab
should have their blood pressure monitored at least every 2–3 weeks during therapy.
Patients who are hypertensive prior to therapy, or who become hypertensive during
therapy, require aggressive treatment with a goal of normotension. All patients on
bevacizumab should also be monitored closely for the development of proteinuria
and renal insufficiency. When severe hypertension refractory to medical treatment
occurs, bevacizumab therapy should be withheld until symptoms resolve and more
aggressive blood pressure management plan has been instituted. If hypertensive
urgency or encephalopathy occurs, treatment is discontinued indefinitely. Therapy is
also typically temporarily suspended in patients who develop significant proteinuria.

Rarer, but more serious, complications of bevacizumab include gastrointestinal
bleeding with or without perforation, hemorrhage into the tumor, arterial throm-
boembolic events such as stroke and myocardial infarction, and reversible posterior
leukoencephalopathy syndrome [78]. When these events occur, they are typically viewed as absolute contraindications to further treatment with bevacizumab. Given the risk of intratumoral hemorrhage with bevacizumab, the safety of initiating therapy in patients receiving anticoagulation has been questioned. In several small case series, the combination has not led to major hemorrhages, and pre-existing use of anticoagulation is not felt to be a contraindication to beginning bevacizumab therapy [79, 80]. An additional potentially serious complication of anti-angiogenic therapy is impaired wound healing. Whenever possible, bevacizumab therapy should be discontinued for several weeks before surgery and should not be resumed until wound healing is complete.

Anti-epileptic Therapy Issues

Seizures are a common manifestation of primary brain tumors, and many patients are treated with anti-epileptic medications concurrently with their chemotherapy. This is primarily of concern when using anti-epileptic medications that increase the hepatic metabolism of chemotherapeutic agents by inducing the cytochrome P450 system. There are a number of enzyme-inducing anti-epileptic drugs (EIAEDs) in clinical use, such as phenytoin, carbamazepine, oxcarbazepine, phenobarbital, and primidone, with phenytoin being the agent most commonly encountered by neuro-oncologists. Use of these agents may lead to increased clearance of the chemotherapy agent and less apparent efficacy. Both conventional chemotherapeutic agents such as irinotecan and targeted therapies such as imatinib and erlotinib can be affected by EIAEDs [81–83]. Conversely, chemotherapy can increase metabolism of anti-epileptic agents, leading to decreased serum drug levels and breakthrough seizures [84]. This issue can be dealt with at the clinical trial level, by stratifying patients to different doses of treatment on the basis of use of an EIAED, but in practice many clinicians simply prefer to avoid EIAEDs and use non-enzyme-inducing anti-epileptic drugs (Non-EIAEDs) such as levetiracetam [85].

Local/Regional Therapies

BCNU Wafers

BCNU-impregnated wafers, commonly known by the trade name Gliadel, are an FDA-approved treatment for newly diagnosed and recurrent malignant glioma. When combined with tumor resection and radiation, BCNU wafers also appear to be safe when used alongside temozolomide chemotherapy [86].

In the largest trial of Gliadel versus placebo wafer implantation, side effects were similar in the two groups, with the exception of an increased rates of late intracranial hypertension and CSF leak in the Gliadel group [87]. Reports have suggested an increased risk of wound healing issues and wound infection with Gliadel, and one series noted a wound infection rate in excess of 25% [88]. A retrospective review of 288 patients treated with Gliadel over a 10-year period showed no statistically significant difference in the occurrence of any side effect when compared to 725
patients who received craniotomies for tumor resection without Gliadel placement during the same period [89]. This study examined both early post-operative complications such as infection, CSF leak rates, and wound healing issues, as well as longer term complications such as seizure incidence. The patient group reported in this review had a remarkably low event rate of wound complications in both the craniotomy plus Gliadel and the craniotomy without Gliadel subgroups, limiting the ability to detect a difference in the risk of these events.

Intrathecal Therapy

*Methotrexate*

Neuro-oncologists most often use intrathecal methotrexate in combination with high-dose intravenous methotrexate and other systemic therapies as treatment for primary CNS lymphoma [90, 91]. In this setting it is difficult to differentiate adverse effects of IT MTX from those of the accompanying agents, but in a matched case–control study of patients with primary CNS lymphoma treated with and without intrathecal methotrexate, both approaches had similar side-effect profiles [92]. Rare cases of severe CNS complications following IT MTX administration have been reported, primarily in patients with bulky disease which may disrupt CSF flow [93]. Intrathecal methotrexate is also frequently used in patients with hematologic malignancies, both as prophylaxis in patients without known CNS involvement [94] and as treatment in patients with CNS involvement [95]. When used in combination with intrathecal Ara-C for this purpose, treatment is associated with a number of serious CNS toxicities including myelopathy and encephalopathy [96].

**Complications After Radiation Therapy for CNS Neoplasms**

*Introduction*

Complications of radiation therapy (RT) are subdivided into acute, subacute, and late toxicities. Acute side effects occur during treatment or within 3 months of treatment completion and are common, predictable, and transient. Subacute toxicities appear after RT within a few weeks to months. As with acute complications, the subacute toxicities are typically temporary. Appearing months or years after the completion of therapy, late effects are characteristically chronic and often progressive and irreversible. In contrast to acute toxicities, late effects are often unpredictable. Much of the knowledge of normal tissue tolerance to RT has been gained empirically over decades of shared clinical experience [97, 98]. When considering the potential risks of a course of RT, technical factors such as radiation dose, fraction size, and technique are undoubtedly central concerns. However, a variety of patient, treatment, and tumor factors must also be considered in the prospective or retrospective analysis of RT toxicity. For example, patient co-morbidities such as diabetes, multiple sclerosis, or collagen vascular disease, concurrent or sequential
chemotherapy (CT), and tumor histology and location all may modify the risks to a particular course of RT.

**Acute Toxicities**

**Fatigue**

With a prevalence of up to 99% in some studies, fatigue is a very common symptom in cancer patients generally [99]. The etiology of the fatigue most certainly is multifactorial. Most studies have focused on breast, prostate, or other common disease sites, and brain tumor patients comprise only a small minority of study subjects. Although fatigue is commonly recognized during and after RT for central nervous system (CNS) neoplasms, relatively limited data exist exploring the association between RT and fatigue in this setting. In patients with low-grade glioma on a randomized control trial of either 45 or 59.4 Gray (Gy), several quality of life factors were analyzed prospectively [100]. Suggesting a relationship between RT and fatigue, patients in the high-dose arm experienced significantly more fatigue both immediately following treatment and at 7–15 months post-RT. In addition, significant deficits in the realms of leisure time and emotional functioning were observed at the late time-point among the patients who had been treated with higher radiation doses. In a recent report, Struik and colleagues reported that 39% of long-term survivors with LGG experienced severe fatigue [101]. Significant associations were identified between fatigue and older age or anti-epileptic drug therapy, but, in contrast to the prior study, not with prior radiation therapy. Data are also limited with respect to quality of life (QOL) after RT for brain metastases. A small pilot study utilized modern self-assessment QOL instruments and found patient-reported fatigue and drowsiness to be significantly increased 3 months after whole brain radiotherapy (WBRT) compared to before RT [102]. Similarly, Wong et al. observed that 57% of patients experienced increased fatigue over the first 3 months after WBRT [103]. Unlike the trials in primary or metastatic brain tumors, the association between fatigue and WBRT can be studied in the context of prophylactic cranial irradiation (PCI) without the confounding variable of CNS disease. Prospective QOL data were collected as part of a Phase III randomized trial of PCI versus no PCI in extensive stage small cell lung cancer [104]. Increased fatigue was observed in PCI patients at the 6-week and 12-week post-RT time-points compared to non-irradiated patients.

**Local Symptoms**

Local symptoms after cranial RT can include skin changes, serous otitis, and alopecia. In WBRT, skin erythema and dryness often develop over the temples and forehead, but the severity is typically mild. Even with partial brain RT of superficial lesions, skin changes or desquamation are rarely significant clinical problems. Skin hyperpigmentation and desquamation should be monitored in patients undergoing
craniospinal axis irradiation (CSI). When photons are used for CSI, skin changes may develop on anterior chest or abdomen in addition to the back secondary to beam exit dose. Serous otitis occasionally occurs in patients undergoing WBRT but should be monitored in patients undergoing partial brain RT for temporal lobe lesions.

Alopecia is another common toxicity associated with cranial RT. Like fatigue, treatment-related alopecia is often a source of patient anxiety and decreased QOL. Damage to the hair follicles can be detected within the first 1–4 days of RT, and anagen phase follicles are more susceptible to damage [105, 106]. Clinically apparent epilation begins approximately 14–21 days after the initiation of therapy, and hair regrowth typically occurs within 2–3 months after cessation of RT. However, permanent hair loss with cicatricial (scarring) alopecia can occur in a dose-dependent fashion [107]. Because anagen follicles reside approximately 4 mm deep to the skin, Severs and colleagues suggested keeping the superficial dose to below 5 and 16 Gy to avoid temporary and permanent alopecia, respectively [107]. Modern treatment planning techniques can be used to monitor and limit scalp doses in partial brain RT. Even for palliative WBRT, the use of sophisticated technology such as intensity-modulated RT has been proposed to limit alopecia [108].

Acute complications from radiosurgery are relatively uncommon. Headache and pin site discomfort may occur when utilizing frame-based techniques. Acute neurologic complications are most likely related to treatment-related edema. In the Radiation Therapy Oncology Group (RTOG) radiosurgery dose escalation trial, only ten patients (6%) experienced acute toxicity [109]. However, a relationship could be demonstrated between risk of complications and increased dose and volume. Chin and colleagues reviewed 835 patients treated over a 6.5-year period with Gamma Knife radiosurgery (GKRS) in order to identify acute complications [110]. Seizures were observed in 12 patients (1.4%) and 1 patient died as a result of the seizure. Five patients (0.6%) developed transient neurologic deficits within 7 days of radiosurgery, but only two cases of diplopia appeared to be directly attributable to the procedure. Two cases of transient ischemic attacks and one case of altered mental status associated with a urinary tract infection were thought to be unrelated to the radiosurgery. In a review of 22 patients with 25 metastatic brainstem lesions treated with GKRS, Hussain et al. reported only 1 case of hemiparesis occurring 2 months post-treatment [111]. Even for larger volume tumors, acute complications of radiosurgery appear to be low. Linzer and colleagues reported a series of 35 patients treated with GKRS for tumors > 13.5 cm³ and observed acute toxicity in only 3 patients (8.5%) [112].

Craniospinal Axis Radiation

CSI is most commonly prescribed for both adult and pediatric patients with medulloblastoma. Hematologic toxicity is the most common acute effect observed in patients undergoing CSI. In a retrospective review of pediatric and adult patients treated with CSI at Royal Marsden, Jefferies and colleagues observed a 33% rate of
grades 3 and 4 hematologic toxicities in all patients [113]. Independent predictors of hematologic toxicity were young age and chemotherapy prior to CSI. The relative risk of leukopenia was 7.9 times higher in children compared to adults. The use of concurrent vincristine did not appear to impact acute hematologic toxicity. Chang et al. reviewed the MD Anderson Cancer Center experience using either electrons or photons for CSI in a pediatric population. When CT was followed by RT, the rates of leukopenia and thrombocytopenia during CSI were 76 and 90%, respectively [114]. Even when the RT was done prior to or without CT, the rate of leukopenia remained substantial at 49%. However, only two patients in each cohort required a treatment break of greater than 3 days. The risk of hematologic toxicity was found to be higher among the patients treated with electrons compared to photons and among patients younger than 6 years of age. No cases of grades 3–4 weight loss were observed as a surrogate for gastrointestinal toxicity. Dermatitis was also common but generally grade 1 and only one case of grade 3 dermatitis was observed among the patients treated with electron beam. In several single institution retrospective series involving only adult patients treated with CSI, relatively low rates of severe hematologic toxicity, nausea and vomiting, and esophagitis were reported [115–117]. Protons, because of their rapid fall-off in dose, appear to provide a significant dosimetric advantage compared to photons (due to the relatively high-exit dose of photons into the thorax and abdomen) [118, 119]. Clinical data documenting the clinical benefit of proton therapy in terms of reduced toxicity of CSI remain very limited [120].

**Subacute Toxicity**

**Pseudoprogression**

An increasing clinical challenge is distinguishing between tumor progression and treatment effect in the treatment of glioblastoma multiforme. Treatment-related change mimicking tumor progression at relatively early time-points after the completion of RT has been termed “pseudoprogression.” [121, 122] Several groups have attempted to determine the incidence of pseudoprogression. Hoffman et al. described a series of 51 patients treated with WBRT plus a boost together with carmustine in the pre-MRI era [123]. Within 18 weeks of RT, 25 patients (49%) met clinical or radiographic criteria for progression, but 7 patients (28% of the progression cohort, 13.7% of the entire cohort) subsequently improved. These patients then demonstrated a significantly longer time to ultimate progression. A second series analyzed patients treated with RT but without chemotherapy [124]. Nine patients from a cohort of 32 patients were found to have increased enhancement on the first post-RT MRI scan. Without additional treatment, three patients (33% of the progression cohort, 9.3% of the entire cohort) improved or stabilized. In the modern era using temozolomide (TMZ) concurrent with RT, three series have been reported addressing pseudoprogression. Chamberlain and colleagues observed that 26 of 51 patients (51%) treated with TMZ and radiation developed both clinical
and radiographic progression within 6 months of completing RT [125]. Fifteen patients underwent re-operation, and seven of these patients were found to have only treatment-related necrosis without evidence for tumor. Thus, the incidence of pseudoproggression was 13.7% of the entire patient cohort but 47% of patients undergoing re-operation. Taal et al. reported 36 of 85 patients who showed imaging progression at the first imaging study 1 month after completion of TMZ/RT [126]. Of these 36, 18 patients (50% of those showing progression; 21% of entire cohort) were diagnosed as pseudoproggression. In contrast to the Chamberlain study, only 1 of these patients underwent re-operation with pathological confirmation of necrosis and the remaining 17 patients were diagnosed with pseudoproggression based only upon stable or improved imaging findings over the subsequent 6 months. Using a similar methodology to identify cases of pseudoproggression, Brandes et al. found lesion enlargement in 53 of 103 patients at the time of the first post-RT MRI. Subsequently, 32 patients (64% of those showing progression; 31% of the entire cohort) were classified as exhibiting pseudoproggression. Again, the diagnosis of pseudoprogession was based on clinical and not pathologic evidence (Fig. 6.1).

In addition, both of these latter two studies examined only patients who showed imaging changes at the first post-RT MRI scan and thus did not account for possible cases of pseudoprogession at later time-points. However, these three studies taken together suggest that approximately half of patients demonstrating signs of progression in the early post-RT period may actually have only treatment-related effects.

![Fig. 6.1](image)

**Fig. 6.1** Imaging evidence of pseudoproggression at 4 weeks after radiation therapy and temozolomide. The patient was asymptomatic and temozolomide was continued with resolution of imaging changes 2 months later.
The risk factors for pseudoprogression are poorly understood at this time. It appears that chemotherapy in general and TMZ in particular are likely risk factors for pseudoprogression. In the study by Taal et al., pseudoprogression was more common among younger patients, while older patients were more likely to suffer real progression [126]. In contrast, the volume of radiation was not predictive of either pseudoprogression or real progression. Similarly, no significant differences in rate of pseudoprogression were observed with respect to initial performance status or extent of surgery. Brandes et al. identified MGMT promoter methylation status as a significant predictive factor pseudoprogression [127]. Methylation of the MGMT promoter was found in 66% of patients classified as pseudoprogression compared to only 11% of patients with early disease progression and 25% of patients with initial stable disease.

Surgical resection remains the gold standard for differentiating treatment effect from true progression if it is indicated in the context of the patient’s overall care. However, significant progress is being made in improved imaging techniques to diagnose pseudoprogression [128]. Sophisticated magnetic resonance imaging (MRI) techniques such as spectroscopy, diffusion-weighted and diffusion tensor imaging, and perfusion imaging continue to be refined. Single-photon emission computed tomography (SPECT) has been examined using a variety of radiotracers. Finally, positron emission tomography (PET) imaging has been evaluated again with a variety of radiotracers. The use of $^{11}$C-methionine appears to be superior to standard $^{18}$F-fluorodeoxyglucose (FDG) in differentiating tumor from necrosis, but several other radiotracers are also in the early stages of development.

The distinction between pseudoprogression and true progression has important implications in the management of patients [121, 122]. The relative risk of inadvertently abandoning an effective therapy if pseudoprogression is mistaken for progression must be balanced with the risk of continuing an ineffective therapy if suspected pseudoprogression is in fact rapid tumor growth. If early radiographic signs of progression are seen in a clinically stable patient, most clinicians continue with the current therapy, typically adjuvant temozolomide, for 1–2 additional months before repeating imaging. If the patient is symptomatic, then consideration should be given to surgical intervention, which may be both therapeutic and diagnostic. The institution of steroid therapy may be of benefit in controlling edema. Bevacizumab may be beneficial in the treatment of radiation necrosis [129]. These decisions also have significant implications for eligibility or exclusion from clinical trials. If patients are improperly determined to have progressed and removed from a clinical trial, the potential effectiveness of the therapy may be negatively biased. Likewise, if such patients with pseudoprogression are then entered into another trial, their subsequent improvement may improperly bias results toward the effectiveness of the new agent. Therefore, it has been recommended that imaging evidence of progression within the first 3 months is not sufficient to declare disease progression and treatment failure [121].
Somnolence Syndrome

Somnolence syndrome represents a subacute encephalopathy occurring between 1 and 4 months after cranial radiation. It was first described by Freeman et al. in the context of prophylactic cranial irradiation for pediatric acute lymphoblastic leukemia [130]. Somnolence was the central symptom and ranged from drowsiness to prolonged periods of sleep up to 20 h/day. Secondary symptoms included fever, nausea and vomiting, headache, anorexia, or irritability. Incidences in the setting of ALL range from 13 to 79% and prophylactic steroids may reduce the incidence [131–133]. Although it is typically observed in children who receive whole brain radiation, somnolence syndrome has been reported in adults and children receiving total body irradiation [134, 135]. Finally, Kelsey and Marks reported a case of somnolence syndrome in an adult patient after partial brain irradiation for a pineal region meningioma [136]. The etiology of somnolence syndrome is thought to be related to transient demyelination. Kelsey and Marks postulated additional mechanisms such as injury to the reticular activating system or alterations in cytokine levels [136]. Somnolence syndrome is self-limiting, and usually patient education and reassurance is all that is needed.

Lhermitte’s Sign

Lhermitte’s sign (LS) is a transient myelopathy characterized by shock-like sensations down the spine induced by neck flexion. It is has been described in the context of multiple sclerosis, vitamin B₁₂ deficiency, and head and neck trauma [137]. Radiotherapy-induced LS is typically encountered after treatment of head and neck or thoracic malignancies with an incidence ranging from 3.6 to 13%. After radiotherapy, LS develops within 6 months due to injury to myelin-producing oligodendroglial cells. Resolution occurs with the spontaneous recovery of the oligodendroglial cells. Primary or metastatic tumors of the spine can also be the primary etiology LS. Although steroids may play a role in management, patient education and reassurance is all that is usually necessary since this is a self-limiting process. Patients who experience transient LS are not at an increased risk for late, progressive spinal myelopathy.

Neurologic Late Toxicity

Etiologies such as fibrosis, neuropathy, vasculopathy, and tissue necrosis all contribute to late toxicity. The mechanisms of radiation injury are increasingly understood as a complex interaction between glial, neuronal, and endothelial cell deaths together with alterations in the microenvironment such as hypoxia and inflammation [138]. Fractional dose is a more important issue for late toxicity. The clinical consequences of late toxicity depend to a large extent on whether the functional subunits of a particular organ are organized in series or in parallel [139]. For example, the
kidney is an example of a parallel organ with multiple independent subunits, and the volume of the kidney receiving a dose above organ tolerance is more predictive of delayed toxicity. In contrast, the spinal cord is organized in series and damage to any volume along its length may have significant clinical consequences. Although volume of spinal cord exposed to radiation is important, maximum point doses may be more relevant to the risk of delayed myelopathy. Delayed brain toxicity other than cognitive changes is often related to the specific anatomic location within the brain.

**Brain Necrosis**

Radiation injury to brain is now recognized as a developing spectrum from transient edema to progressive necrosis. The TD 5/5 (tissue dose tolerance with 5% complication rate at 5 years) is 60 Gy for conventionally fractionated partial brain RT [98]. The latency of necrosis varies from 3 months to years after RT [140]. After treatment for glioma, the 3-year actuarial risk of developing necrosis has been reported as high as 13.3% [140]. In general, a relationship exists between increasing dose and volume of radiation and the risk of radiation necrosis [98, 121]. However, a recent study of dose escalation for glioblastoma using conformal radiotherapy did not identify a higher risk of late necrosis associated with larger target volumes or escalated doses [141]. The dose–volume relationship for late necrosis has been elegantly described by Flickinger and colleagues in the context of radiosurgery for arteriovenous malformations [142]. This multivariate model described the risk of late complications in relation to the volume of brain tissue exposed to 12 Gy or greater in combination with AVM location. The risk of necrosis also increases with dose and target volume in the context of radiosurgery for brain metastases [109].

**Spinal Cord Myelopathy**

Delayed spinal myelopathy is one of the most feared complications of radiation. Diagnosis must consider the time course after radiation, correlation of symptoms with region of cord irradiation, and exclusion of other pathology such as progressive disease [143]. Although the cord tolerance dose used in daily practice has been considered to be 47–50 Gy in 2-Gy fractions, this is understood to be a very conservative estimate [98]. Below this dose range, permanent myelopathy appears to be only a sporadic, extremely rare, event [144, 145]. Based on the combined data of multiple published reports, Schultheiss calculated the TD 5/5 for the cervical cord myelopathy to be 59.3 Gy and the risk for myelopathy at 50 Gy as 0.2% [146]. The risk for myelopathy does increase with large fraction sizes, especially with irradiation to large volumes of cord [147]. However, the dose–volume relationship for radiation injury of the spinal cord is complex. The risk of injury does not appear to be closely related to volume of irradiated cord when lengths of irradiated cord exceed 1 cm [148]. In contrast, at less than 1 cm of exposed cord length, there appears to be a marked volume effect with increasing tolerances over small
volumes [148]. This has important implications regarding the safety of overlapping external beam fields and for spinal radiosurgery. Multiple experiences with spinal radiosurgery suggest that the spinal cord can tolerate larger fraction sizes to small volumes. In a multicenter analysis of five cases of delayed myelopathy after spine radiosurgery, recommendations included limiting maximum point doses to <10 Gy in a single fraction and the 2-Gy normalized biological equivalent dose to less than 30–35 Gy in up to five fractions [149]. Risk for myelopathy after a second course of external beam RT appears low when the 2-Gy biologic equivalent dose is limited to <135 Gy cumulative and <98 Gy for each course with at least 6 months between courses [150, 151]. Delayed spinal myelopathy is related to white matter injury, and the etiology may be secondary to both microvascular damage and oligodendrogial cell injury [143]. This dual mechanism of injury may explain the bimodal latency period observed for spinal cord injury [152]. In addition, there appears to be differential risk of myelopathy between cervical and thoracic segments of cord. Schultheiss suggested that the thoracic cord may be less sensitive to RT injury than the cervical cord [146]. Using modeling from clinical data, Adamus-Gorka and colleagues found that the thoracic cord exhibited a high degree serial dose–response, but that the cervical cord displayed more volume effect and may therefore have more functional subunits operating in parallel [153].

**Optic Neuropathy**

Delayed cranial nerve injury can occur after either fractionated or stereotactic radiosurgery and can cause significant impairment in quality of life. The tolerance dose of the optic nerves and chiasm is 50 Gy in standard fractionation [98]. In an older series, Parsons et al. observed no cases of optic neuropathy with doses less than 59 Gy but the actuarial risk was 27% at 15 years for optic nerves exposed to 60 Gy or more [154]. Fraction size was important in this study. Injury developed in 8% of the optic nerves treated with daily doses of less than 1.9 Gy compared to 40% of the nerves treated with higher daily doses. Combined data from several series evaluating treatment of pituitary adenomas suggest approximately a 1.5% risk of optic nerve injury at doses of 45–50 Gy [155]. In a series of 30 patients with 33 optic nerve meningiomas treated to 50–54 Gy, Andrews et al. reported only 2 cases of late vision loss and 1 case of transient optic neuritis [156]. In single-fraction radiosurgery, maximum point doses of less than 10 Gy to the optic apparatus carry a low risk of clinically significant loss [157–159]. In the updated Mayo Clinic experience, the risk of developing optic neuropathy was 1.1% for patients receiving less than 12 Gy as maximum nerve dose, and additional EBRT was a significant risk factor for injury after radiosurgery [160]. Adler and colleagues reported their experience using hypofractionated regimens of 2–5 fractions for periopitic lesions [161]. A maximum dose to the optic apparatus was limited to 8 Gy/fraction when possible or 25 Gy in 5 fractions. Only 1 case out of 49 patients appeared to have visual deterioration attributable to radiation.
Ototoxicity

The TD 5/5 for sensorineural hearing loss has been reported as 60 Gy [98]. Much of the data with regards to hearing loss after radiation have been generated in the context of head and neck cancer where prescribed doses are approximately 70 Gy. However, several series have examined ototoxicity in the context of brain tumors. JohanneSEN et al. examined the Norwegian Radium Hospital experience of 1,841 patients aged 14 years or greater treated for supratentorial primary tumors and identified 33 participants who had received conventional RT involving the hemisphere or whole temporal bone [162]. Most of the patients were treated for glioma. The median time after RT was 13 years and the median dose was 53.1 Gy in 1.8 Gy fractions. Ten of 33 patients were found to have ipsilateral sensorineural hearing loss, and all cases had received doses >54 Gy. Other late complications identified included osteoradionecrosis, vestibular dysfunction, and loss of taste. Increased risk of hearing loss has also been observed with the combination of cisplatin and RT. In a study of 177 children and young adults with a variety of CNS and non-CNS neoplasms, cisplatin dose alone was correlated to the risk of hearing loss [163]. In addition, younger patient age, the presence of a CNS neoplasm, and RT prior to cisplatin all potentiated the hearing deficits at any given cisplatin dose level. Huang et al. have demonstrated that intensity-modulated RT can reduce the dose to the auditory apparatus compared to conventional RT techniques for pediatric medulloblastoma [164]. Moreover, this dosimetric improvement appeared to translate into less clinical hearing loss. For patients who survive medulloblastoma with hearing impairment, cochlear implant may be considered for improved quality of life [165].

The ototoxicity of RT has been intensely studied in the treatment of vestibular schwannoma (VS). Assessment of hearing preservation rates after either fractionated RT or radiosurgery is complicated by the probability that the natural history of these benign tumors is to cause hearing loss. Patient factors such as neurofibromatosis 2 (NF2) also increase the risk of ototoxicity. Early experience with single-fraction radiosurgery doses of 16–20 Gy led to hearing preservation rates of 50% or less [166, 167]. With reduction to the now standard doses of 12–13 Gy, hearing preservation rates improved at the University of Pittsburgh to 71–80% for maintaining the same hearing level [168, 169]. A critical review of the literature confirmed the relationship between dose and risk of hearing loss and reported an overall 60.5% hearing preservation rate at 3–4 years after radiosurgery doses of 13 Gy or less [170]. An early experience using a hypofractionated stereotactic radiosurgery regimen of 18–21 Gy in three fractions reported hearing preservation in 74% of patients [171]. Although radiosurgery has become widely used for treatment of VS, conventionally fractionated radiotherapy for VS may provide some improvement in reducing ototoxicity [172, 173].

Other Cranial Nerve Injury

Injury to other cranial nerves has been less well documented but would be considered at risk when treating base of skull tumors. Morita and colleagues reported a
10.6% rate of permanent injury to the trigeminal nerve after single-fraction radiosurgery for base of skull meningioma and a median dose of 19 Gy to Meckel’s cave [158]. This study also identified one case each of permanent oculomotor nerve and abducnt nerve injury after doses of 10 and 22 Gy to the cavernous sinus, respectively. However, the overall low rate of cranial nerve injury did not allow for analysis of a dose–response relationship. Early experience with radiosurgery for vestibular schwannomas demonstrated relatively high rates of cranial neuropathies. Using marginal single-fraction doses of 14–16 Gy, the University of Pittsburgh reported approximately a 20% rate of facial and trigeminal nerve dysfunction developing within 28 months of treatment, but these were typically mild in severity and most improved with time [167]. Since that time, dose for treated VS has been lowered to 12–13 Gy in a single fraction with decreased cranial neuropathy rates of less than 5% [174]. Davidson et al. reported a series of 112 patients treated for a mixture of benign and malignant lesions to a median dose of 16 Gy [175]. They found new cranial neuropathies in seven patients and multiple neuropathies in five of this group. In a study with long-term follow-up after single-fraction radiosurgery for petroclival meningiomas, Flannery et al. found a 2% risk of cranial neuropathy with a median marginal target dose of 13 Gy [176]. A multi-institutional review of complications after radiosurgery for AVM identified 12 patients out of 1,255 total who developed isolated cranial neuropathy [177]. In a series of 90 patients treated with radiosurgery for Cushing’s disease to a median marginal dose of 23 Gy, 5 patients (5.5%) developed third or sixth nerve palsy [178]. Interestingly, four of the five had prior radiosurgery or external RT.

The tolerance of cranial nerves other than the optic nerve to radiation injury is informed by the experience treating trigeminal neuralgia with radiosurgery. Multiple institutions with long follow-up have demonstrated pain improvement with a typical maximal point dose to the nerve of 80 Gy in a single fraction [179, 180]. Pollack found significant correlation between increasing dose and both improvement of facial pain and increasing facial numbness [181]. This suggests that the mechanism of pain relief is related to increasing nerve injury and that the dose to cause sufficient injury is over 70 Gy. Therefore, the cranial neuropathies, such as facial numbness observed at the low doses used to treat other base of skull lesions such as VS or meningioma, likely are a result of small areas of injury to the brainstem rather than to the nerve itself. Based on this mechanism of injury, Meeks and colleagues generated a normal tissue complication probability (NTCP) model to predict for cranial neuropathy after RS for VS [182].

**Stroke-Like Migraine Attacks**

A syndrome of episodic stroke-like migraine attacks after radiation therapy (SMART) has recently been recognized as an infrequent long-term sequelae of cranial irradiation [183–186]. Neurologic deficits are variables, depending on which brain region is affected, and may persist for weeks before ultimately resolving. These episodes are often accompanied by imaging abnormalities in the symptomatic region such as focal cortical gadolinium enhancement on MRI or hypermetabolism
Fig. 6.2  Axial and coronal T1 magnetic resonance images (MRI) with gadolinium demonstrating gyral enhancement in a patient with SMART syndrome. (a and b) Abnormal enhancement disappeared entirely after resolution of symptoms on FDG-PET. SMART has also been associated with seizures and focal EEG slowing over the area of abnormality (Fig. 6.2).

**Multiple Sclerosis-Related Toxicity**

The safety of external beam radiation therapy in patients with multiple sclerosis has long been questioned, in large part due to case reports of fulminant demyelination following treatment. Most of these reports concerned patients treated before the modern era of three-dimensional planning and conformal treatment, hence their applicability to current practice is not clear. In the largest published series of MS patients treated with radiation therapy, no significant acute complications were seen, but 6 of 15 patients (40%) developed delayed neurotoxicity related to demyelination within the radiation field [187]. Median time from treatment of occurrence of neurotoxicity was 1 year. Based on currently available data, multiple sclerosis is not an absolute contraindication to radiation therapy, but the risks must be carefully weighed against the potential benefits.

**Non-neurologic Late Toxicity**

While the focus has been on neurologic toxicities from radiation to the CNS, injuries may occur in other organ systems. For example, craniospinal irradiation has been associated with restrictive lung disease and loss of vertebral body height [188–190]. Ovarian transposition prior to CSI has been suggested as an option to minimize infertility risks [191].
Endocrinopathy

Endocrinopathy is a common complication after cranial irradiation, especially among children. Darzy provides two recent comprehensive reviews of this issue [192, 193]. Dysfunction is likely related to radiation injury to both the anterior pituitary and the hypothalamus. Growth hormone (GH) is the most sensitive with deficiencies noted only after 18 Gy TBI. More than half of patients may experience GH deficiency within 3–5 years after cranial RT doses of 30–50 Gy. In these moderate dose ranges of 30–50 Gy, deficiencies in thyroid-stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), or gonadotropins (GN) appear to be less than 10%. However, the risk increases substantially for doses higher than 60 Gy. While GH axis appears to be most sensitive to RT in childhood, TSH, ACTH, and GN may be more at risk after RT for adults. The risk for endocrinopathy after radiosurgery may not be significantly different than after conventional fractionation. Most studies have relatively short follow-up but Hoybe et al. did find a 66% incidence of endocrinopathy with a median follow-up of 17 years after radiosurgery [194].

Vasculopathy

Vasculopathy after radiation may manifest as ischemia, cerebral artery stenosis or occlusion, aneurysm, or moyamoya syndrome. Most of the literature is based on case reports mainly within the pediatric population. Omura et al. analyzed 32 pediatric patients with a variety of tumor types treated with RT fields encompassing the circle of Willis or major cerebral arteries [195]. All of the patients had at least 1 year of follow-up and had no evidence of tumor progression. They identified six cases of steno-occlusive disease resulting in either cerebral infarction or transient ischemic attack occurring between 2 and 12 years after RT. Only higher radiation doses of 61 Gy versus 50 Gy predicted for vasculopathy. Patients with optic pathway glioma and NF1 are at especially high risk [196]. Rudoltz and colleagues emphasize that risk factors for delayed vasculopathy are multifactorial beyond simply RT and NF1 [197]. Patient factors include younger age, genetic syndromes, and the cytokine and growth factor environment. Tumor factors such as encasement, compression, or displacement of vessels by the tumor or tumor recurrence may predispose for vascular events. Finally, surgical approach or vessel manipulation or RT variables such as dose, dose per fraction, volume, chemotherapy interactions must all be accounted for in determining a patient’s risk.

Secondary Neoplasm

The induction of secondary benign or malignant tumors after RT is a major concern in the setting of childhood cancer and the treatment of adult and pediatric
benign disease. The induction of meningioma after low-dose cranial RT for tinea capitis has been well documented [198]. With a mean latency of 36 years, the incidence of meningioma was 9.5-fold greater than the untreated population after a dose of 1–2 Gy and more than 18-fold greater for doses >2.6 Gy [199, 200]. In a study of 1,262 survivors of childhood medulloblastoma using 3 cancer registries, 20 cases of second neoplasms were identified at a median of 73 months post-treatment [201]. Since only 3.7 cases were expected, this represented a 5.4-fold greater risk of second neoplasms than a normal population. Nine of 15 evaluable cases were felt to be related to prior RT. A more recent study examined 2,821 adult, 5-year survivors of childhood CNS malignancies treated between 1970 and 1986 and who participated in the Childhood Cancer Survivor Study [202]. Cumulative mortality was 25.8% at 30 years, which was primarily due to disease recurrence. Among 1,877 evaluable survivors, the cumulative incidence of all subsequent neoplasms was 10.7%, with 4.1% of survivors developing malignant tumors including primary CNS neoplasms, soft tissue sarcomas, and thyroid cancer. The risk was significantly greater for patients who had received cranial RT. The 25-year cumulative risk was 7.1% for patients who had received 50 Gy or more compared to 5.2% for patients who had received less than 50 Gy and 1% for patients who had not received RT. The risk for second malignancies after radiosurgery appears to be far less than for external beam RT. Although several cases of second malignancies after radiosurgery have been reported, Lunsford notes that the risk is likely between 1 in 1,000 and 1 in 12,500 [203, 204]. In addition, risk may be further increased in some patients with cancer predisposition syndromes. For example, although short-term follow-up confirms safety and efficacy of radiotherapy among patients with neurofibromatosis-associated central nervous system tumors [205], secondary malignancy risk with longer follow-up remains a concern [206].

**Conclusion**

Treatment complications due to chemotherapy and radiation are a significant source of morbidity and mortality among patients with primary brain tumors. Clinicians must be aware of the possible side adverse effects of treatments so they can educate their patients, choose therapies with favorable side-effect profiles, and provide early intervention when complications arise. This task will only become more difficult in the future as new treatments, such as additional molecularly targeted therapies, immunomodulatory therapies, and newer radiation techniques, come into use. Further, as survival of glioblastoma improves and treatments initially evaluated in glioblastoma become more widely used in less-aggressive tumors, issues of long-term toxicities due to prolonged treatment will become more prominent.
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Chapter 7
Neuropsychological Function and Quality of Life

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Keywords  Neurocognitive function · Quality of life · Symptom measurement · Brain tumor

Aggressive therapy involving surgery, radiation, chemotherapy and immunotherapy has resulted in improvements in the treatment of cancer. Unfortunately, the non-specific nature of many cancer treatments often places normal tissues and organs, such as the central nervous system (CNS), at risk. In addition, direct involvement of the CNS by tumor as well as the many adjuvant medications (e.g., anti-epileptics) necessary for the treatment of medical complications can potentially affect CNS function. Malignant brain tumors often follow a relentless course associated with neurological deterioration and ultimately death. The tumor, the type of antineoplastic treatment the patient receives, adjuvant medications, and medical complications can all affect neurocognitive function and patient symptom burden.

Neurocognitive Function

When included in clinical trials for cancer patients, serial testing of neurocognitive function is a sensitive and important endpoint that measures the effect of a therapy on patient functioning. This information is not adequately captured by frequently used survival-based endpoints or performance status. Neurocognitive function is a sensitive predictor of survival [1], and decline in neurocognitive function often precedes magnetic resonance imaging (MRI) evidence of tumor spread.

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recurrence in glioma patients [2, 3]. Such findings have prompted the incorporation of neuropsychological evaluations into both the clinical care of cancer patients and clinical trials of therapeutic agents [3–5].

Impact of the Tumor on Neurocognitive Function

In adult patients with primary malignant brain cancer, neurocognitive deficits vary based on lesion type, rate of tumor growth, tumor location, and tumor-related epilepsy. Tucha et al. [6] assessed glioma patients with lesions in the temporal or frontal lobes before initiation of any treatment and reported neurocognitive dysfunction in 90% of patients. Impairment in executive function occurred in 78% and memory and attention were impaired in 60%.

Classic neuropsychological studies in populations with stroke and epilepsy have demonstrated that the nature of the cognitive impairments often relates to the location of a lesion. Left hemisphere lesions frequently cause difficulties with verbal learning and memory and language functions. Right hemisphere lesions cause difficulties with visuospatial and visuoperceptual functions. Anterior lesions may cause marked personality changes and impairments of executive function, including deficits in social judgment, divided attention, and the ability to plan and organize activities. While tumor patients have shown lateralizing patterns of cognitive impairment on some tests [7], the specificity and severity of neurobehavioral impairments related to lesion site are often less pronounced in tumor patients than are those observed in sudden-onset neurological conditions such as stroke [8]. This has been attributed to differences in the pathophysiology of these injuries; tumors diffusely infiltrate the brain, thereby disrupting normal brain function in networks that are proximal to the visible tumor as well as more distant from the site. Furthermore, studies using magnetoencephalography have demonstrated abnormal organization of widespread brain networks in cognitively impaired brain tumor patients [9]. Variability in the localization of brain behavior relationships can also be influenced by the neuropsychological tests used within studies. Some tests are less likely to detect lateralized neurocognitive deficits because they assess neurocognitive processes that are more distributed or because successful performance on the test requires multiple somewhat more localized neurocognitive processes. For example, verbal fluency tests have been associated with function in “eloquent” left frontal areas due to demands on expressive language abilities. However, due to the executive function demands of this test, patients with lesions outside of traditional language areas (e.g., right frontal tumors) also demonstrate impaired performances [10].

Therapies with promising activity against tumor growth continue to be actively investigated in clinical trials. These interventions may be associated with clinical benefit if they stabilize or improve patient function via tumor control and do not worsen patient function due to treatment toxicity. While it is clear that tumor progression is associated with adverse effects on neurocognitive function [11], treatments designed to control or kill the tumor cells may have adverse effects on normal tissue that also cause measurable neurocognitive decline [12]. It is thus
imperative to comprehensively understand the net clinical benefit associated with emerging treatments of brain tumors.

**Treatment Effects**

The adverse effects of chemotherapy are usually presumed to be acute and reversible. The neurobehavioral effects of most cancer therapy agents tend to be non-specific and diffuse, except for those that have a mechanism of action that is expected to affect focal brain regions [12] or immunologic agents that are known to affect particular inflammatory cytokines, neurotransmitters, and neuroendocrine hormones [13]. Agents such as temozolomide appear to increase survival without causing significant adverse symptoms [14, 15]. However, animal research has demonstrated that a number of antineoplastic agents can have adverse effects on behavior and have uncovered the brain substrate that may be responsible for these cognitive alterations [16]. It is hoped that the continued development of targeted therapies will also provide clinical benefit with reduced toxicity.

Neurological complications associated with a variety of chemotherapies include an acute encephalopathy characterized by a confusional state, insomnia, and often agitation, which is commonly believed to resolve off treatment; chronic encephalopathy characterized by cognitive dysfunction consistent with a “subcortical dementia,” incontinence, and gait disturbance; stroke-like episodes associated with transient motor impairments; a cerebellar syndrome with symptoms ranging from ataxia to a pancerebellar syndrome; and a variety of peripheral neuropathies. More subtle neurocognitive dysfunction has been described in patients including those without CNS disease and frequently manifests as diminished memory, executive function, attention, and information processing speed [16, 17]. Despite these potential adverse effects, treatment of primary central nervous system lymphoma involving intravenous, intra-arterial, or intraventricular multi-agent chemotherapy with blood–brain barrier disruption has been accomplished without induction of significant neurocognitive dysfunction in patients who achieve a durable remission 1 year after treatment [18, 19]. Unfortunately, there is limited research examining the neurocognitive effects of specific chemotherapy regimens in primary brain tumor patients. Hilverda et al. [15] serially evaluated 13 GBM patients after surgery but before concomitant chemoradiation with temozolomide, after completion of concurrent therapy but before adjuvant temozolomide, and again after three cycles of temozolomide. All patients were progression-free and 10 out of 13 had Karnofsky Performance Scores of 90–100. A battery of cognitive tests assessed the following domains: information processing speed, psychomotor function, attention, verbal memory, working memory, and executive function. Decline or improvement in a summary domain score of 1.5 SDs was used to define neurocognitive change. During the concomitant treatment phase, approximately 39% evidenced cognitive decline. In contrast, during the adjuvant temozolomide only phase 15% evidenced decline. In most cases, decline in neurocognitive function occurred in one domain – most frequently attention or psychomotor function. This small study suggests that non-progressed GBM patients with generally high performance status show
limited adverse neurocognitive effects from three cycles of adjuvant temozolomide completed after the concomitant treatment phase.

Pathological evidence supports adverse effects of radiation on white matter tracts and cerebral vasculature. Chronic radiation toxicity is also believed to involve alterations in neurogenesis as well as metabolic abnormalities and inflammatory responses [20–23]. Cognitive impairments consistent with frontal network system dysfunction are common including impaired processing speed, attention, learning and memory, executive function, and often bilateral decline in motor function (e.g., fine motor dexterity) [24–26].

Risk factors for developing radiation-induced cognitive dysfunction and radiation necrosis include age > 60 years old, >2 Gy dose per fraction, total dose, volume of brain irradiated, hyperfractionated schedules, shorter overall treatment time, concomitant or subsequent use of chemotherapy, and presence of comorbid vascular risk factors (e.g., diabetes) [26, 27]. Radiation encephalopathy has classically been separated into three stages: acute, early-delayed, and late-delayed reactions [28].

Acute reactions often develop within the first 2 weeks of treatment and include exacerbation of pre-existing neurologic deficits, fatigue, headache, seizure, nausea, and vomiting. Early-delayed effects occur 1–4 months after completion of radiation and include slowing, executive dysfunction, diminished memory, and motor deficits. These symptoms are believed to result from transient demyelination. Neuropsychological studies of patients before and after radiation treatment document neurocognitive impairments that are consistent with frontal network dysfunction, including slowing, inattention, decreased executive function, and memory as well as a decline in motor functioning, bilaterally, even in patients with no evidence of disease recurrence [29]. Unfortunately, some patients experience severe late-delayed encephalopathy that can involve progressive neurologic decline, dementia, leukoencephalopathy, and brain necrosis.

Studies of the neurocognitive functioning of patients surviving more than a year post-radiotherapy have yielded conflicting results. Meyers [24] reported that 80% of patients who received paranasal sinus radiation between 20 months and 20 years prior exhibited impaired memory and 33% manifested slowed visuomotor speed, executive dysfunction, and poor fine motor dexterity. Several studies have not found significant late-delayed neurocognitive dysfunction within 5 years of completion of radiotherapy [30, 31]. However, in low-grade glioma patients without progression who were treated with radiation between 6 and 28 years earlier, there was evidence for significantly greater declines in attention as well as increased slowing and executive dysfunction [32].

Effects of Adjuvant Medications and Medical Complications

Supportive medications are frequently required in brain tumor patients to control symptoms associated with the brain tumor or side effects of other therapies used to treat the tumor. Unfortunately, some supportive medications have side effects
that can result in deterioration of neurocognitive and neurobehavioral function. The use of glucocorticoids is ubiquitous and is associated with a 5–50% incidence of steroid-induced psychiatric syndromes including euphoria, mania, insomnia, restlessness, and increased motor activity. Glucocorticoids such as dexamethasone bind to corticosteroid receptors in the hippocampus and prefrontal cortex of the brain that are important for controlling emotions and memory. The impact of steroids on neurocognitive function is variable and is in part related to the dose and chronicity of treatment, with higher doses and longer duration of therapy associated with greater risks of neurocognitive and neurobehavioral dysfunction [33]. Steroids used to treat neurologic and neurocognitive symptoms associated with peritumoral edema often have initial beneficial effects. However, studies in healthy individuals have demonstrated that steroids may adversely affect memory and emotional lability over time [34].

Seizures have been reported to occur in over 60% of patients at some time during their illness [35] and can have a significant impact on neurocognitive and neurobehavioral functioning and quality of life (QOL). Persistent, poorly controlled seizures often decrease cognitive efficiency which is particularly apparent in the domain of processing speed [36]. Patients with seizures may become socially isolated due to the perceived stigma associated with having a seizure in a public area and/or around unfamiliar people. Many first-generation anticonvulsants (e.g., phenytoin, carbamazepine) have adverse constitutional and cognitive side effects including diminished attention, processing speed, and memory [37]. The newer anticonvulsant agents (including levetiracetam, lamotrigine, oxcarbazepine, and gabapentin) appear to have more favorable side-effect profiles and fewer neurocognitive side effects [38]. Levetiracetam is frequently used to control seizures in patients with brain tumors. Several studies have concluded that levetiracetam is generally not associated with cognitive dysfunction [39–41].

Patient Care and Management

Careful assessment of a brain tumor patient’s cognitive strengths and weaknesses, capabilities, limitations, available caregiver support, and treatment goals is crucial for rational patient management. A comprehensive neuropsychological evaluation forms the foundation for decisions regarding independence in self-care activities, ability to drive, returning to work, and the suitability of the patient for rehabilitation or other interventions.

Neurocognitive deficits and alterations in neurobehavioral function are associated with reduced ability to return to work (more often than physical disabilities) [42], decreased functional independence [43], increased caregiver burden and distress [42, 44], and reduced global quality of life [45]. Additionally, a decline in neurocognitive function has been demonstrated to occur in advance of decline in ratings of quality of life [45–47].
Neurocognitive Interventions and Pharmacotherapy

Despite the many challenges patients with malignant gliomas face, there are a number of strategies that can help maximize the patient’s ability to function at the highest level of independence possible for the longest duration of time. There has been considerably less work in the area of interventions to prevent or treat cognitive dysfunction due to cancer treatment (Table 7.1). Hence, both behavioral and pharmacologic treatment options for cognitive deficits in cancer survivors are borrowed from traditional rehabilitation populations as well as diverse diseases including attention-deficit hyperactivity disorder and neurodegenerative diseases such as Alzheimer’s disease.

**Neurocognitive Interventions**

With appropriate support, many patients can improve their function at home and in vocational and leisure pursuits and enjoy an improved level of independence and QOL. The intervention strategies used must be directed toward their specific disabilities and realistic future goals. For select patients, multidisciplinary rehabilitation including neurocognitive interventions can be very effective, with shorter stays, lower treatment costs, and better overall outcome in terms of independence and productivity compared with patients with traumatic brain injuries [48].

As in traditional rehabilitation, the goal of neurocognitive interventions is to increase skills, knowledge, use of compensatory strategies, and adaptive behaviors to improve functional independence [49]. Recent reviews of evidence-based compensatory interventions can be referenced for a more complete discussion of therapeutic approaches that may be helpful with brain tumor patients [50, 51]. Memory “prostheses” or external memory aids are one of the most common compensatory interventions with documented efficacy. These aids come in many forms (e.g., paper-based vs electronic) and must be individually tailored to each patient in the context of memory strategy training to optimize outcomes [50, 52, 53]. Several recent studies have extended earlier reports documenting the feasibility and effectiveness of neurocognitive interventions in both high-grade and low-grade glioma patients [54–56].

**Pharmacotherapy**

**Methylphenidate**

Methylphenidate is the most commonly prescribed psychostimulant and is indicated in the treatment of attention-deficit hyperactivity disorder. Methylphenidate is a potent CNS stimulant derived from amphetamine and is thought to exert its effect by increasing dopaminergic stimulation of the mesolimbic system in the brain and could help with improvement in neurocognitive function [57–60].
<table>
<thead>
<tr>
<th>Medication</th>
<th>Publication</th>
<th>N</th>
<th>Dosage</th>
<th>Patient population</th>
<th>Outcome</th>
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</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>Weitzner et al. [59]</td>
<td>3</td>
<td>15 or 20 mg/d</td>
<td>High-grade gliomas</td>
<td>Improved arousal, attention, initiation of speed, and mood</td>
</tr>
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<td></td>
<td>Meyers et al. [60]</td>
<td>26</td>
<td>10, 20, 30 mg in increasing doses – 4 weeks</td>
<td>High-grade gliomas</td>
<td>Doses between 10 and 30 mg twice daily improved cognition, mood, and subjective improvement</td>
</tr>
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<td></td>
<td>Lower et al. [62]</td>
<td>132</td>
<td>10–50 mg ≥ 2 weeks</td>
<td>Non-anemic cancer patients</td>
<td>Improvement of fatigue and impaired memory compared to placebo</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Kaleita et al. [71]</td>
<td>30</td>
<td>High dose and low dose</td>
<td>Primary brain cancer</td>
<td>Improvement seen in cognitive functioning, fatigue, and mood</td>
</tr>
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<td></td>
<td>Kohli et al. [72]</td>
<td>68</td>
<td>200 mg/d – 8 weeks</td>
<td>Breast cancer</td>
<td>Some improvements in memory and attention skills compared to placebo</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Shaw et al. [74]</td>
<td>35</td>
<td>5 mg/d – 6 weeks</td>
<td>Brain tumor</td>
<td>Improvement in attention/concentration, verbal memory, figural memory, and confused mood, QOL improved in emotional and social functioning</td>
</tr>
<tr>
<td>Alpha-tocopherol</td>
<td>Chan et al. [79]</td>
<td>19</td>
<td>2,000 IU/d for 1 year</td>
<td>Nasopharyngeal carcinoma</td>
<td>Improvement in global cognitive ability, attention, memory, language, and executive function after a 1-year medication period</td>
</tr>
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</table>

*Table 7.1 Clinical trials used in the treatment of cognitive deficits in patients with cancer*
Some adverse effects may emerge during chronic use of methylphenidate so a constant watch for adverse effects is recommended [61]. The most common side effects of taking methylphenidate are cardiac symptoms, nervousness, and insomnia.

In an early study, methylphenidate had been shown to improve neurobehavioral decline in three patients with brain tumors [62]. Methylphenidate was expected to act as an indirect agonist, causing release of catecholamines that would control attention and memory, and results confirmed that arousal, attention, initiation speed of tasks, and mood were all improved. A larger study that involved 26 patients with gliomas and evidence of neurocognitive deficits showed that methylphenidate at doses between 10 and 30 mg twice daily was able to improve cognition despite ongoing cranial radiation in a majority of the patients [63]. There were also improvements in subjective cognitive functioning and mood in those patients who had taken 30 mg. However, an important limitation of the study was the absence of a control group and hence, a placebo effect, or a practice effect due to repeated neuropsychological testing, might have accounted at least in part for the improvement in cognitive functioning and symptoms.

More recently in other tumor types, Mar Fan et al. [64] conducted a randomized, placebo-controlled, double-blind trial of the effects of \(d\)-methylphenidate on fatigue and cognitive dysfunction in women undergoing adjuvant chemotherapy for breast cancer. Women were randomized early during their chemotherapy to receive \(d\)-methylphenidate (\(d\)-MPH), a form of methylphenidate, or an identical appearing placebo. All participants took placebo for 1 cycle to ensure compliance and then study medication until completion of chemotherapy. Subjects were assessed at baseline, end of chemotherapy, and at approximately 6 months follow-up with the High Sensitivity Cognitive Screen (HSCS) and the Hopkins Verbal Learning Test-Revised (HVLT-R). They also completed the self-report Functional Assessment of Cancer Therapy-General (FACT-G) and FACT-F (\(F = \)fatigue) questionnaires, evaluating quality of life and fatigue. A total of 57 women were randomized (29 to \(d\)-MPH and 28 to placebo), the study did not meet its accrual goal of 170 patients, mainly because women were reluctant to take additional medication in general and methylphenidate in particular. There were no significant differences between the randomized groups in classification of cognitive function by HSCS or in summed FACT-F fatigue scores (the primary endpoints of the study) at any of the assessments. There were also no differences in HVLT-R scores or quality of life.

Another study conducted by Lower et al. investigated the safety and efficacy of \(d\)-MPH in the treatment of persistent fatigue and memory impairment after chemotherapy in non-anemic cancer patients [65]. Adult patients (primary or metastatic brain tumors excluded) treated with \(\geq 4\) cycles of cytotoxic chemotherapy (completed \(\geq 2\) months prior to entry) were eligible. Patients completing a single-blind placebo period with no symptomatic improvement were randomized to an 8-week double-blind phase. Dosing (\(d\)-MPH or placebo) was adjusted from 10 to 50 mg/d and maintained for \(\geq 2\) weeks. The HSCS was used to assess cognitive
function. The authors concluded that *d*-MPH was well tolerated and significantly more effective than placebo in improvement of fatigue and impaired memory after chemotherapy in adult cancer patients.

It is very important to understand the limitations of both studies. The Mar Fan and Lower studies did not establish a diagnosis of chemotherapy-associated cognitive decline prior to treating and used the HSCS as the primary outcome, which is insensitive to cognitive function [66]. The HSCS has a marked practice effect and it is possible that any improvement seen is a reflection of practice effect rather than true improvement in cognitive function. Therefore, methylphenidate could be considered in the management of neurocognitive deficits in patients with brain tumors, however, large, longitudinal studies with long-term follow-up are required and will need to account for practice effect.

**Modafinil**

Modafinil is a novel wake-promoting agent that is effective and well tolerated in the treatment of excessive sleepiness associated with narcolepsy and in persons with shift-work sleep disorder [67–71]. The precise mechanism through which modafinil promotes wakefulness is unknown. Modafinil has wake-promoting actions like those of sympathomimetic agents including amphetamine and methylphenidate, although the pharmacologic profile of modafinil is not identical to that of the sympathomimetic amines. The recommended single daily dose range for narcolepsy is 100–400 mg modafinil (Provigil®). These doses have wake-promoting efficacies comparable to 20–40 mg doses of methylphenidate [72], which has been used previously in cognitive studies in patients with advanced cancer [73].

Kaleita et al. [74] have reported preliminary data of a small, randomized study that compared high doses of modafinil with low doses in 30 patients with primary brain cancer. The authors concluded that cognitive functioning, fatigue and mood were all improved but no information regarding potential differences in doses was discussed. Another randomized, open-label study evaluated the effect of modafinil on cognitive function in breast cancer patients. However, fatigue was the primary endpoint of the study [75]. A secondary neurocognitive analysis was intended to evaluate whether modafinil improved cognitive function and to provide preliminary information upon which to design future trials. Results from this study did show that there were improvements in some memory and attention skills. Larger studies are needed to confirm these findings.

**Donepezil**

Donepezil, a cholinesterase inhibitor, is approved by the US Food and Drug Administration for use in Alzheimer’s disease [76]. As a result of its effectiveness in Alzheimer’s disease, Shaw et al. [77] conducted a phase II study of donepezil in irradiated brain tumor patients to investigate its effect on cognitive function, mood, and quality of life. Twenty-four patients received donepezil 5 mg/d for 6
weeks, then 10 mg/d for 18 weeks, followed by a washout period of 6 weeks off drug. Outcomes were assessed at baseline, 12, 24 (end of treatment), and 30 weeks (end of washout). All 24 patients had a primary brain tumor, mostly low-grade glioma. Scores significantly improved between baseline (pretreatment) and week 24 on measures of attention/concentration, verbal memory, and figural memory. Confused mood also improved from baseline to 24 weeks. Health-related QOL improved significantly from baseline to 24 weeks, particularly for brain specific concerns, with a trend for improvement in emotional and social functioning. Toxicities were minimal. Limitations included the lack of a control group, and practice effect may account for some of the change in test scores, as within a 7.5-month period of the study, participants took the test battery four times. Practice effect does not likely explain all of the observed improvement in scores, since robust changes on the Profile of Mood States (POMS) were observed; this instrument is not influenced by serial testing. Other possible explanations for the observed improvements include concurrent tumor shrinkage, resolution of radiation-induced fatigue, and/or repair/recovery from radiation-induced brain damage or even a placebo effect. The results of this initial phase II trial encourage continued investigation of donepezil and other acetylcholine inhibitors in this population. The authors are planning a double-blind, placebo-controlled, phase III trial of donepezil to confirm these favorable results.

**Alpha-Tocopherol (Vitamin E)**

Alpha-Tocopherol is the form of vitamin E that is preferentially absorbed and accumulated in humans [78]. With the discovery of the negative impacts of free radical generation on brain function, many studies have been conducted to explore the effectiveness of alpha-tocopherol (vitamin E) on brain function. The antioxidative function of vitamin E has been studied extensively in animals and humans over decades. In a neurobiologic experiment with hypoxic cultured neurons, vitamin E inhibited lipid peroxidation and reduced cell death [79]. It also decreased the degeneration of hippocampal cells after cerebral ischemia [80] and improved the recovery of motor function after spinal cord injury in animal studies [81]. Chan et al. [82] conducted a phase II study of alpha-tocopherol in patients with temporal lobe radionecrosis to determine its effect on cognitive function. Nineteen patients with temporal lobe necrosis after radiotherapy for nasopharyngeal carcinoma received 2,000 international units (IU) daily for 1 year, and 10 patients served as untreated controls. The study design did not incorporate randomization, placebo, or blinding. Patients in the treatment arm experienced improvements in global cognitive ability, attention, memory, language, and executive function after a 1-year treatment period. The findings suggest that vitamin E may be a promising complementary intervention, but more definitive data are required before the effectiveness of vitamin E for the cognitive deficits of patients with cerebral radionecrosis can be established.
Symptoms and Quality of Life in Brain Tumor Patients

**Overview of QOL and Symptoms**

The impact of both the disease and treatment on the patient and family is increasingly recognized in neuro-oncology. Efforts to determine the impact on patients frequently employ measures of patients’ health-related quality of life (HRQOL). Conceptually, HRQOL is defined as a multidimensional construct which frequently consists of physical, emotional, social, spiritual, and psychological well-being [83, 84]. HRQOL is influenced by the person’s experiences, expectations, perceptions, and beliefs and thus should be reported directly by the patient [85, 86]. In an effort to capture the patient’s perspectives about their current HRQOL, numerous questionnaires have been developed that attempt to measure the underlying HRQOL construct and are useful when evaluating global HRQOL. The application of these global measures to evaluate treatment effect and toxicity, or to specific domains such as neurocognitive dysfunction or physical symptoms, has led to confusion regarding the impact of HRQOL and limited the implementation of interventions that could target specific domains.

Primary brain tumor patients face multiple challenges to HRQOL including neurologic symptoms, symptoms related to medications and treatment, and the impact of a life-threatening diagnosis. Despite this, there are few well-powered studies evaluating HRQOL and even fewer interventions designed to improve HRQOL [87]. In studies completed to date, malignant glioma patients have been shown to score lower in all domains of functioning compared to matched healthy controls [88]. Patients with both low-grade and high-grade tumors report poor HRQOL, but studies have failed to show a difference between grade III and IV tumors [88–92]. Although earlier reports indicated that poor HRQOL at diagnosis was associated with more rapid decline and death, recent reports show that use of general HRQOL adds relatively little to traditional clinical factors in determining prognosis [93, 94]. This may result from the use of the broad content included in self-reported measures and insensitivity to obvious changes in clinical conditions in questionnaires designed to evaluate general HRQOL. In addition, it is recognized that patients may experience a “response shift” that influences how they appraise and report their HRQOL as the disease progresses [95]. During the course of the illness, patients may adapt to the diagnosis and existing deficits, establishing a new “normal,” thereby reporting less impact on general HRQOL. More recently, Gotay and colleagues published a meta-analysis in diverse cancer populations that examined the relationship between patient-reported outcomes and survival [96]. In brain tumor patients, they reported an association between measures of both cognitive function and symptoms, specifically fatigue, with survival but no such relationship between global HRQOL and survival. This supports the significance of HRQOL in brain tumor patients and the need for focused analysis to describe the impact and identify areas for interventions designed to improve HRQOL.
Recently, a relationship has been identified among symptoms and HRQOL in patients with primary brain tumors, with symptoms such as depression, fatigue, emotional issues, and existential concerns predicting HRQOL [97]. The development of symptoms is the primary reason patients seek health care. Management of general and neurologic symptoms is a critical component of patient care throughout the disease trajectory [98]. Several factors have been shown to impact the occurrence of symptoms in patients with cancer, including demographic characteristics such as gender [99], age [100, 101], marital status, ethnicity [102, 103], culture [104, 105], family role [104], education [106], disease, and health characteristics such as type and stage of cancer [107, 108], type of treatment [109, 110], type of care providers [111], comorbid medical and clinical factors [101, 112], and individual factors such as health knowledge, values, and past experiences [98]. More recently, health characteristics such as nutrition, sleep, and genetic predisposition have been shown to be related to the severity of symptoms in patients with other solid tumors [113, 114]. Symptoms are also recognized to be dynamic and seldom occur in isolation [95, 115]. Recently it has been identified that symptoms can occur in groups or clusters, and that these clusters may be manifestations of a broader syndrome with a common etiologic base [113, 116–119]. In patients with other solid tumors, the occurrence of multiple symptoms independently predicts changes in patients’ function, HRQOL, treatment failures, and poor therapeutic outcomes [106, 120, 121].

There are limited studies exploring the impact of symptoms and HRQOL in patients with primary brain tumors. In patients with malignant gliomas, depressive symptoms have been shown to be associated with worse overall survival and HRQOL [122]. Overall symptom severity has been reported to be predictive of recurrence in primary brain tumor patients [123]. Neurocognitive function, as discussed earlier in this chapter, is also predictive of survival, recurrence, functional independence, and HRQOL. Neurologic symptoms related to the disease and treatment were discussed in chapters 4 and 6. Following will be a discussion of the most common general symptoms, including fatigue, mood disturbance, and the emerging concept of symptom clusters and their impact on both the patient and the caregiver.

Overview of Common Symptoms

Fatigue

Similar to patients with other solid tumors, fatigue is one of the most common and most troublesome symptoms for primary brain tumor patients throughout the disease trajectory [89, 124]. In a survey evaluating HRQOL in a variety of primary brain tumor patients at various times in the trajectory of their illness, 42% reported “quite a bit low” or “very low” energy levels [125, 126].

Radiation therapy is the most common treatment modality for all tumor grades and has been the treatment evaluated in this patient population in relation to fatigue. Lovely and colleagues reported that over 80% of primary brain tumor patients report
fatigue during radiation therapy [127]. Fatigue has been reported to occur as early as within 1 week of the first radiation treatment and tends to increase with the number of radiation fractions [128]. Fatigue which occurs during radiation therapy may continue into the post-radiation period. Faithfull and Brada reported on the occurrence of a somnolence syndrome in the immediate post-radiation period [129]. This syndrome included fatigue, excessive drowsiness, feeling clumsy, and inability to concentrate. In this study, patients were followed during radiation and the immediate post-radiation period. Following completion of radiation therapy, the reported symptoms had a cyclical pattern, with increased severity between days 1–21 and then days 30–35 after treatment. This pattern has neither been further explored in subsequent studies, nor has the impact of concurrent chemotherapy with radiation on fatigue pattern and severity been explored. Fatigue has been reported to persist for 1–3 months after the completion of treatment but may be more chronic for some individuals [130].

Clinically, a variety of other factors may contribute to the frequency and intensity of the fatigue. These include concomitant medications such as chemotherapy, anticonvulsants and corticosteroids, metabolic disturbances, and psychosocial issues such as depression and anxiety. Most patients require corticosteroids to treat brain edema and anticonvulsants for seizure management. These medications have been reported to have a negative impact on fatigue in this patient population [128, 131]. Recently, poor performance status, female gender, and recurrent disease were found to be associated with moderate-to-severe fatigue in patients with primary brain tumors [132]. For males, antidepressant and opioid use also were associated with more severe fatigue.

Fatigue may also persist for years after diagnosis and completion of therapy. A recent report explored the occurrence of fatigue in patients with low-grade gliomas who were at least 3 years from completion of tumor therapy [133]. In this study, 39% of patients reported severe fatigue for more than 8 years after completion of therapy. The only variable found to predict fatigue was continued anticonvulsant use.

In summary, there are limited studies to date exploring the occurrence and correlates of fatigue in patients with primary brain tumors. In patients with other solid tumors, fatigue is often the most common and severe symptom associated with the disease and treatment [134, 135]. Fatigue has been demonstrated to cluster with other symptoms, including pain, distress, insomnia, and depression and influence outcomes such as perceived health and functional status [136, 137]. In the limited studies to date in patients with primary brain tumors, fatigue has been identified as a common symptom occurring in patients with both low-grade and high-grade tumors, to persist in long-term survivors of low-grade brain tumors, to be associated with both radiation and a variety of chemotherapies, and to be more severe in women and in those with progressive disease.

**Pathophysiology/Etiologic Contributors and Assessment**

Fatigue is a common complaint with multiple associated factors. It is recognized that fatigue can occur in relation to radiation, chemotherapy, and as a consequence
of concomitant medications such as corticosteroids and anticonvulsants. In addition, patients who are depressed or who have altered sleep–wake cycle can also complain of fatigue. If the patient has fatigue which occurs independently of the factors listed above or is severe or not resolving after treatment is completed, a search for other causes is warranted [138]. The work-up for fatigue includes evaluation of bloodwork, including a complete blood count, electrolytes, renal function screening, and evaluation for primary and secondary hypothyroidism. If any of these tests are abnormal, further evaluation may be in order. If the above tests are unrevealing and the patient also complains of dizziness and weight loss or has recently been tapered from corticosteroids, evaluation for Addison’s disease by performing an adrenocorticotropic hormone stimulation test should be considered. Additional tests which may be warranted based on patient assessment include evaluation for hypogonadism, pulmonary dysfunction, and cardiomyopathy [138]. If the patient has a history of a viral illness or previous Epstein–Barr virus infection, evaluation for reactivation of the virus may be indicated.

Interventions

Non-pharmacologic/Behavioral

The management of fatigue is dependent on the underlying etiology. If the evaluation reveals an underlying disease or an offending agent, treatment or removal of the offending agent may improve fatigue for the individual patient. In a systematic review of interventions for fatigue during and following cancer and its treatment, exercise was the only intervention supported with level 1 evidence in the literature. Two meta-analyses and five systematic reviews support the benefits of exercise in reducing fatigue [139–142, 143, 144]. Various modalities (walking, swimming, resistance) and various frequencies and intensities preclude a general recommendation as to the type and frequency for all patients [145]. Evaluation of the feasibility and benefit of exercise in the primary brain tumor patient population is warranted, as the impact of cognitive or functional limitations may limit the patients’ ability to participate.

Mitchell and colleagues [146] reviewed interventions for fatigue in the general oncology population and reported the following to be likely to be effective: energy conservation [147, 148], cognitive behavioral strategies (including relaxation training, sleep consolidation strategies, stimulus control therapy, and strategies to reduce cognitive-emotional arousal to optimize sleep quality) [149], and the provision of anticipatory guidance concerning fatigue during treatment [146].

Pharmacologic

Drug intervention trials have been completed with conflicting results depending on the cancer population studied. Minton et al. [150] completed a Cochrane Review and reported on 45 trials assessing drug therapy for the management of fatigue compared to placebo, usual care, or non-pharmacological intervention in a
randomized trial [150]. Drugs were evaluated by class (hematopoietic growth factors, antidepressants, progestational steroids, and psychostimulants). They reported that methylphenidate did show a small improvement in fatigue over placebo ($p = 0.02$). Erythropoietin showed improvement in fatigue in those patients with anemia ($p = 0.05$). Paroxetine and progestational steroids have not demonstrated superiority compared to placebo.

No studies to date have been performed exclusively in the primary brain tumor population. Meyers and colleagues evaluated the use of methylphenidate in the primary brain tumor population for impact on cognition and reported improvement in cognition and function, measured as improved stamina and motivation [63]. Modafinil is currently under investigation as a treatment of fatigue in patients with solid tumor malignancies, with a small pilot study reported in 2009 showing improvement in fatigue, mood, and overall quality of life [151]. Further investigation in the primary brain tumor population is warranted before recommendation for routine use can be made.

**Mood Disturbance**

Existential distress may include relationship-related concerns, loss of control, burden on others, loss of continuity, uncompleted life task, hope/hopelessness, and anxiety related to the diagnosis and death [97]. Existential concerns have rarely been evaluated in primary brain tumor patients, but one study reported that 50% of patients struggle with mild-to-moderate distress related to existential concerns [97]. However, patients may not express these concerns, reporting that they perceive staff to be too busy, stressed, or unskilled in providing guidance [152].

Mood disturbance and affective distress occur commonly throughout the cancer illness trajectory. The incidence of depression and anxiety that meets clinical criteria as defined by the *Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV)* is largely unknown owing to a paucity of studies using such rigorous criteria. Additionally, disproportionate effort has been directed to the study of depression while less attention has been directed to the spectrum of anxiety disorders that patients may manifest.

Major depressive disorder has a prevalence rate of 6% in females and 3% in men making it the most common psychiatric disorder among adults [153]. Criteria for a diagnosis of major depressive disorder include either depressed mood or loss of interest in activities that occur over a period of at least 2 weeks, most of the day, nearly every day and cause marked distress or impairment in social, occupational, or other functioning [154]. Four additional symptoms must also be present and may include feelings of worthlessness or guilt, diminished ability to concentrate, suicidal ideation, weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, or fatigue [155].

Two studies reported using DSM-IV criteria to establish the prevalence of major depression in newly diagnosed adult brain tumor patients. In these studies the prevalence rates of depression ranged from 15 [122] to 28% [156] after surgery. Litofsky
et al. [122], as part of the Glioma Outcomes Project, compared DSM-IV-guided physician rates of major depression with patient-reported depressive symptoms and examined differences in rates of depression at 3 and 6 months after surgery. At all time points, patients reported much higher rates of depressive symptomatology (70–94%) than physicians (15–22%), indicating that mood disturbance may be underdiagnosed by clinicians [122]. Wellisch et al. [156] found that at least 50% of patients reported experiencing the following symptoms of depression: fatigue, inattention, weight change, sadness, sleep disturbance, psychomotor slowing, and anhedonia. The incidence of elevated symptoms of depression based on psychometric scales such as the Beck Depression Inventory has ranged from rates as low as 10 [11, 45] to as high as 80% of patients [122, 157]. Unfortunately, all too often these symptoms are not discussed either by physicians or by patients, with patients reporting that they perceive staff to be too busy, stressed, or unskilled in providing guidance [152].

**Pathophysiology/Etiology and Assessment**

Depression has been hypothesized to arise due to alterations in cortical-limbic pathways, brain monoamine levels, maladaptive cognitive styles (i.e., schemas), and decreased engagement in positively reinforcing behaviors among other possible contributors [158]. These same factors as well as the understandable distress associated with a cancer diagnosis and the all too frequent loss of functional independence are thought to be associated with depression in brain tumor patients [159]. In patients with cancer, several additional risk factors for the development of depression have been delineated. These include younger age [160, 161]; individual or family history of depression or history of substance abuse [162]; advanced stage, relapse, or progression [163–167]; large space-occupying lesions that result in greater cortical-limbic disconnection and possibly greater neurotransmitter alterations [122], concomitant medications [155, 163], and unrelieved symptoms such as pain [168].

Personality changes frequently occur with frontal tumors; and depressive symptoms have been reported to be associated with frontal, diencephalic, and temporal lesions [97, 169]. The impact of lesion laterality on mood is controversial [90, 91, 97, 122, 169, 170]. Left frontal lesions have been associated with what has been termed a “catastrophic reaction” including depression, anxiety, and agitation, while right frontal lesions are more commonly associated with indifference or even euphoria. Recent work on this topic has suggested that relative inactivity in left frontal regions may be associated with increased symptoms of depression in individuals with low reassurance seeking behavioral styles, while relative right frontal hypoactivity is associated with increased depressive symptoms in individuals with high reassurance seeking behavioral styles [171]. Particular tumor types are associated with depression, with those patients with pituitary tumors [169], meningiomas [169], and high-grade gliomas [122] having a high incidence of depression.
There are a variety of screening questionnaires to evaluate depression, with the most widely used being the Hospital Anxiety and Depression Scale (HADS), the Beck Depression Inventory, and the Center for Epidemiologic Studies Depression Scale. Several studies have reported that a single question, “Are you depressed most of the day nearly every day?” identified all depressed individuals (100% sensitivity) and all non-depressed individuals (100% specificity) [155, 172]. The gold standard is for the patient to be seen and evaluated by a mental health professional (i.e., psychiatrist or psychologist) who uses the DSM-IV criteria to make a diagnosis [159]. This should be done urgently in any patient with depressive symptoms with suicidal ideation. If a patient has depressive symptoms, evaluation for contributing factors should be undertaken and managed if present. These include evaluation of concomitant medication which may be contributing and substitution if possible; evaluation for hypothyroidism; and altered sleep–wake cycle. Aggressive intervention against mood disturbance is very important not only to improve patient quality of life but also because mounting evidence suggests that depressed brain tumor patients have decreased survival times [173].

Interventions

Non-pharmacologic/Behavioral

Empirically supported interventions for major depressive disorder in individuals without cancer include behavior therapy, cognitive behavior therapy, interpersonal therapy, and pharmacotherapy with selective serotonin reuptake inhibitors (SSRI) due to their generally preferred safety profile [153]. There is supportive evidence that the use of psychotherapeutic interventions including behavior therapy and cognitive behavior therapy is helpful in the management of depressive symptoms in patients undergoing cancer therapy for a variety of solid tumors [148, 174–180].

Pharmacologic

Although support exists for the use of antidepressants to manage depression in the general population, few randomized controlled trials have examined the efficacy of these agents in patients with cancer, and none have focused specifically in the primary brain tumor patient population.

Studies in patients with other solid tumors have reported efficacy of SSRIs, tricyclic antidepressants (TCAs), and others for treatment of depression [175, 181–184]. In these studies, greater benefit was demonstrated when evaluated after more than 5 weeks of therapy, due to the time needed to reach therapeutic effect. No study showed a difference among classes of agents, and choice of treatment should consider other factors, such as cost and side-effect profile. In general, fewer side effects seen with the SSRIs often lead them to be preferable in cancer patients [184].
New Paradigms: Sleep–Wake Cycle Disturbance and Symptom Clusters

It is recognized that symptoms can occur concurrently in groups or clusters. In patients with brain tumors, the constellation of symptoms associated with increased intracranial pressure (headache, vomiting, and reduced level of consciousness) and those related to focal deficits based on lesion location are recognized and often used in clinical care [116]. Two additional clusters have been identified in patients with newly-diagnosed brain tumor: a language cluster which includes difficulty reading, writing, and finding the right words; and a mood cluster including feelings of sadness, anxiety, and depressed mood [185]. A common cluster of symptoms that has been recognized in other solid tumor malignancies is the association among fatigue, depression, pain, and sleep disturbances. This cluster has also been reported to occur in patients with high-grade glioma [157]. Altered physiology related to the cancer process has been postulated to play a role in the occurrence of this cluster by causing disruption of sleep, circadian rhythms, and hypothalamic–pituitary–adrenal (HPA) axis regulatory processes. These then may result in production of cytokines and hormones and result in disturbed sleep, depression, fatigue, and pain [186–189].

Impact on the Patient and Family

The impact of the diagnosis and treatment is significant not only for the patient, but also for their families. The uniqueness of providing care to someone who experiences neurological and neuropsychiatric sequelae as well as the impact of a short, terminal trajectory of the disease is significant [190, 191]. Caregivers also experience anxiety, depression, and worse overall quality of life if the patient has more neuropsychiatric deficits or a high-grade tumor [192, 193]. The need for assistance with activities of daily living also has been shown to impact caregiver health and stress [193].

Studies addressing the psychosocial needs of both patients and caregivers have been limited. A recent report identified that both patients and caregivers identified similar unmet supportive care needs, including interventions to overcome fatigue, improve physical activity, and manage stress and fear [194]. A recent pilot study indicates that both patients and caregivers would be interested in stress reduction programs and most would be willing to participate in home or clinic-based programs [195]. In addition, caregivers have reported interest in education on providing safe care in the home, balancing other roles and responsibilities, managing difficult behavior, and improving communication with health care professionals [196]. Research priorities should target the investigation of service provision and education of caregivers.

Conclusions

The progressive decline in brain tumor patients’ neurologic and neurocognitive function makes brain cancer as much a progressive neurodegenerative disorder
as it is a neoplastic illness. Assessments of neurocognitive function, functional independence, symptom burden, and other patient-reported outcomes are indispensable in providing the best interventions for patients and salient information for therapeutic clinical trials. Selection and evaluation of a specific therapy needs to consider toxic side effects and effect on patient QOL to truly appraise the net clinical benefit of a therapy for a patient. The assessment of the neurocognitive, neurobehavioral, and emotional function of brain tumor patients as well as their reports of diverse symptoms also helps guide the institution of appropriate adjuvant interventions. As primary therapy leads to longer survival, interventions for and assessment of neurocognitive function, symptoms, and QOL will gain even greater importance.

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Part II
Gliomas
Chapter 8
Low-Grade Gliomas

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Keywords  Low-grade glioma · Astrocytoma · Oligodendroglioma · Oligoastrocytoma

Abbreviations
DTI  Diffusion tensor imaging
ECOG  Eastern Cooperative Oncology Group
EORTC  European Organization for Research and Treatment of Cancer
fMRI  functional MRI
GBM  Glioblastoma multiforme
GKSR  Gamma Knife stereotactic radiosurgery
iMRI  Intraoperative MRI
IDH  Isocitrate dehydrogenase
LGG  Low-grade glioma
LOH  Loss of heterozygosity
MSI  Magnetic source imaging
PET  Positron emission tomography
rCBV  Relative cerebral blood volume
RTOG  Radiation Therapy Oncology Group
SBT  Stereotactic brachytherapy

Epidemiology

Low-grade gliomas (LGGs) comprise approximately 10–20% of all primary brain tumors and include a compilation of WHO grade I and II tumors [1]. Such tumors as pilocytic astrocytomas, subependymal giant cell astrocytomas, and pleomorphic xanthoastrocytomas are included in this category. However, this chapter will be
limited to a discussion on diffuse astrocytomas, oligodendrogliomas, and oligoastrocytomas. Approximately 2,000–3,000 low-grade gliomas are diagnosed annually in the United States for these tumor subtypes [2]. The incidence is reported as 2.28/1,000,000 persons/year for astrocytomas, 2.45/1,000,000 persons/year for oligodendrogliomas, and 0.89/1,000,000 persons/year for oligoastrocytomas [3].

Diffuse astrocytomas are thought to comprise 10–15% of primary astrocytic neoplasms. These tumors display a peak incidence between 30 and 40 years, with a mean of 34 years. In addition, there is a slight male predominance of these tumors with a rate of 1.18:1 [4]. Oligodendrogliomas, on the other hand, represent 5–6% of glial neoplasms and 2.5% of all primary brain tumors [4, 5]. These tumors display a peak incidence between 40 and 45 years, with a slight male predominance of 1.1:1 [4–6]. The incidence of oligoastrocytomas has been slowly climbing over the last decade secondary to changing pathological criteria as well as increased recognition [7]. The incidence of oligoastrocytomas ranges from 1.8 of brain tumors according to the Central Brain Tumor Registry to 9.2% in the Norwegian Cancer Registry [4, 8, 9]. Peak incidence for these tumors is between 35 and 45 years [4, 5, 10]. There is also slight male predominance with a ratio of 1.3:1 [4, 8]. Diagnosis of LGG in the elderly has increased over recent years. This rising incidence has been partly attributed to the willingness of physicians to evaluate and subsequently treat these patients [2, 11, 12].

Pathology and Pathogenesis

Low-grade gliomas are one of the most challenging categories of brain tumors for neuropathologists to provide a precise histopathological diagnosis. Pathological criteria for distinguishing astrocytoma, oligodendroglioma, and oligoastrocytoma are controversial. In fact, many LGGs lack classic features of “astrocytic” or “oligodendroglial” differentiation and exhibit considerable morphologic overlap. Furthermore, LGGs share many histological features. Most are infiltrative tumors, with microscopic invasion of normal brain including neuronal satellitosis and subpial spread of the tumor cells. Mitotic activity is minimal and proliferative index assessed by MIB-1 (Ki-67) labeling is generally low. Features of anaplasia including microvascular endothelial proliferation and necrosis are absent.

Astrocytic Tumors

The category of low-grade astrocytic tumors includes tumors with diffusely infiltrating growth (diffuse astrocytoma) and pathologically circumscribed lesions including the pleomorphic xanthoastrocytoma, the pilocytic astrocytoma, and the subependymal giant cell astrocytoma. As previously noted, the latter category will not be discussed in this chapter. Aside from the capacity to diffusely invade gray or white matter, diffuse astrocytomas have a distinct tendency to undergo anaplastic transformation over time.
Astrocytomas have been traditionally subclassified into three variants – fibrillary, protoplasmic, and gemistocytic astrocytomas – representing morphologic subtypes of astrocytes in normal and reactive brain. However, the majority of the tumors have a mixed population of the different subtypes. Among these variants, fibrillary astrocytomas are the most common tumors and are composed of cells with multipolar cytoplasmic processes that form a rich fibrillary glial stroma. Gemistocytic astrocytomas are the second most frequent variant and are composed of cells with abundant eosinophilic, round to slightly angulated cytoplasm, and eccentric nuclei. Gemistocytic astrocytomas are rare as a pure histological variant, but the presence of significant numbers of gemistocytes implies a significantly shorter time to progression than other low-grade astrocytomas [5]. Protoplasmic astrocytomas are the least common variant and are composed of large numbers of stellate-shaped cells with small cytoplasmic processes embedded in a microcystic or loose matrix.

Histologically, diffuse astrocytomas exhibit mild-to-moderate cytologic atypia and cellularity (Fig. 8.1). Mitotic activity is low and MIB-1 labeling indices are usually less than 4% [4]. Astrocytomas are recognized by immunoreactivity for glial fibrillary acidic protein (GFAP), vimentin, and S-100 protein. The proportions of tumor cells staining with these markers vary among diffuse astrocytomas; tumors with more prominent fibrillary and gemistocytic components show stronger GFAP immunoreactivity than protoplasmic variants. Anaplastic progression is anticipated in 50–70% of the diffuse astrocytomas, but the latent period to progression is quite variable with a mean time interval of 4–5 years [5, 13].

Over the last decade, oligodendroglial tumors, either pure or mixed with an astrocytic component, have been diagnosed with increasing frequency. Diagnostic criteria for oligodendroglial tumors have become somehow “less rigid,” maybe in part due to neuropathologists’ awareness of the need for distinguishing oligodendroglial tumors from other gliomas due to the implications of new therapeutic options and potentially in response to pressure from clinicians.

![Fig. 8.1](image)

**Fig. 8.1** Histopathological features of low-grade gliomas. (a) Diffuse astrocytomas (WHO grade II) displaying low cellularity and cellular atypia. Most tumors show mixed populations of fibrillary and gemistocytic astrocytes within a fibrillary matrix. (b) Oligodendroglioma (WHO grade II) displaying classic appearance of uniform cell population with round nuclei and perinuclear halos. Delicate blood vessels are conspicuously present. Hematoxylin and eosin; a: 40×; b: 100×
Oligodendrogliomas are soft, gelatinous masses that extend from the white to gray matter obliterating the gray–white junction. Areas of cystic degeneration and calcification are common. The “classic” oligodendroglioma is histologically distinctive and composed of a uniform population of cells with round nuclei, with a delicate particulate chromatin pattern, and scant cytoplasm (Fig. 8.1). Artifactual clearing of the cytoplasm gives the cell a characteristic “fried egg” appearance. The tumor cells are dispersed in a poor fibrillary matrix intersected by delicate, branching vessels referred as a “chicken wire” vascular pattern. Oligodendrogliomas diffusely infiltrate the cerebral cortex, forming characteristic secondary structures such as perineuronal satellitosis, perivascular accumulations, and subpial infiltration. Often, neoplastic oligodendrocytes have a small rim of eosinophilic cytoplasm and eccentric nuclei, so-called mini-gemistocytes.

Reliable immunocytochemical markers that distinguish neoplastic oligodendrocytes are not presently available. Most markers expressed by developing and mature oligodendrocytes are inconstantly expressed by neoplastic oligodendrocytes [14]. Therefore, the diagnosis of oligodendrogliomas is primarily based on observations on hematoxylin and eosin (H&E) stained sections and the absence of reactivity for markers associated with astroglial differentiation. The majority of oligodendrogliomas do not express GFAP and vimentin, although minigemistocytes commonly show intense GFAP immunoreactivity. Although the basic helix-loop-helix (bHLH) transcription factors, OLIG1, and OLIG2 are associated with oligodendroglial differentiation in development, neither is expressed exclusively in oligodendrogliomas [15–17]. These transcription factors are present in high levels in infiltrating astrocytomas (low grade and high grade) and pilocytic astrocytomas. Low-grade oligodendrogliomas (WHO grade II) lack immunexpression of nuclear p53 protein, an observation in keeping with their low incidence of TP53 mutation [14].

Mixed oligoastrocytomas are gliomas with areas that resemble both oligodendrogloma and astrocytoma. The diagnosis of oligoastrocytoma is quite problematic since there are no definitive histological criteria for confirming this diagnosis. The two glial elements may be distributed in distinct areas (biphasic pattern) or in an intermingled pattern, the latter being more common [18]. Frequently, the predominant cell component is oligodendroglial. Some investigators have defined mixed glioma as a tumor in which a second minor glial component is present in at least one 100× field [19]. Others avoid diagnosing mixed gliomas or oligoastrocytomas, choosing to classify the tumor according to predominant glial morphology [20]. At present, the combination of light microscopy, immunohistochemical studies, and molecular genetic analysis appears to be the best approach for identification of these gliomas [18].

**Molecular Genetics of Low-Grade Gliomas**

Key steps in the tumorigenesis of astrocytomas involve the progressive loss of cell cycle regulation in the setting of increased growth signaling pathways stimuli.
Inactivating mutations of the TP53 gene represent an early detectable genetic alteration in astrocytic tumors, occurring in about 50% of diffuse astrocytomas (WHO grade II) [21–23]. In the absence of a mutation, p53 function may be disrupted by other mechanisms such as promoter hypermethylation and the resulting inhibition of the tumor suppressor gene p14ARF [24]. Promoter methylation of the DNA repair gene MGMT has also been detected in about 50% of diffuse astrocytomas and is associated with TP53 mutations [25].

Platelet-derived growth factor (PDGF) receptor and ligand are frequently overexpressed in low-grade astrocytomas resulting in autocrine activation of downstream pathways to which they are linked. PDGF ligands and receptors are expressed approximately equally in all grades of astrocytomas, suggesting that this pathway is important in the initial steps of astrocytoma pathogenesis [26]. Other chromosomal abnormalities present in low-grade astrocytomas include gains of chromosomes 7q, 5p, 9, and 19p and losses of 19q, 1p, and Xp [4].

The recent Cancer Genome Atlas report has confirmed that deregulation of Rb, p53, and phosphatidyl inositol-3 kinase-Akt-mammalian target of rapamycin (PI3K-Akt-mTOR) pathways are obligatory events in almost all glioblastomas [27]. PTEN mutations that activate the PI3K-Akt-mTOR pathway do not occur in low-grade astrocytomas, though a majority of these tumors epigenetically silence PTEN via hypermethylation [28].

Oligodendroglial tumors have a distinct molecular genetic profile from that of diffuse astrocytomas. About 60–90% of oligodendrogliomas in adults have genetic losses on chromosomes 1p and 19q as the result of the translocation t(1;19)(q10;p10) [29, 30]. Conversely, the presence of 1p/19q codeletions in a glioma is significantly associated with an oligodendroglial phenotype [31]. Oligodendrogliomas in the pediatric population, however, only rarely harbor these deletions [32, 33]. Chromosome 1p/19q codeletions have been associated with longer survival and a better response to therapy in both low-grade and anaplastic oligodendrogliomas [31, 34–37].

Oligoastrocytomas are genetically heterogeneous [18]. Thirty to seventy percent of oligoastrocytomas appear genetically related to oligodendrogliomas and have 1p/19q codeletions [18, 38–40] while another 30% have genetic aberrations frequently found in diffuse astrocytomas, including mutations of the TP53 gene and/or loss of heterozygosity (LOH) on chromosome 17p [39, 40]. Identical genetic alterations have been identified in both astrocytic and oligodendroglial elements in a given tumor, indicating a clonal origin for mixed gliomas. It appears that the subsets of oligoastrocytomas with 1p/19q codeletions are often oligodendroglial-dominant, while those with TP53 mutations and/or 17p loss are more often astrocytic-dominant [39].

While it seems that there are two distinct pathways of LGG pathogenesis, i.e., TP53 mutations and 1P/19P codeletion, recent studies have shown a common genetic link between astrocytomas and oligodendroglial tumors. Isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2) are ubiquitous enzymes that catalyze the conversion of isocitrate to alpha-ketoglutarate in the Krebs cycle. Acquired point mutations in gliomas have been described at codon 132 of IDH1, producing an arginine substitution (predominantly not only Arg132his, but also Arg132cys, Arg132ser,
Arg132leu, and Arg132gly). An analogous codon 172 is present on IDH2 inducing similar amino acid substitution (Arg172gly, Arg172lys, and Arg172met). IDH1 mutations at codon 132 have been demonstrated in 54–90% of diffuse astrocytomas and 65–85% of oligodendrogliarial tumors [41–46]. IDH2 is also mutated in these tumors, although at much lower frequencies. IDH1 and IDH2 mutations are common in secondary glioblastomas, but are rarely found in primary adult or pediatric glioblastomas [43, 46].

IDH1 mutations are strongly correlated with TP53 mutations and 1p/19 codeletions [47, 48, 49] and, in some instances, have been demonstrated to occur concomitantly with these genetic abnormalities, suggesting that the combination of IDH1 mutation and either TP53 mutation or loss of heterozygosity of 1p/19q is the earliest common genetic abnormality identified in LGG [43, 46].

Clinical Presentations

Patients with LGG present with a variety of signs and symptoms. As these tumors often grow slowly, presentation can be delayed. However, with advances in imaging, the time from initial symptom onset to diagnosis has decreased [4]. For supratentorial brain tumors in general, approximately 35–40% of patients present with seizures. Of patients with LGG, seizures are characteristically the presenting symptom and are seen in up to two-thirds of patients [47]. Seizures are most commonly generalized followed by an equal distribution of simple partial and complex partial seizures [50]. Seizures are more common in patients with tumors in either the frontal or temporal lobes [51]. The majority of diffuse astrocytomas are present in this location. Oligodendrogliomas and oligoastrocytomas present most commonly in the frontal lobe (50–65% of cases), followed by the temporal lobe [4, 48, 52].

Tumor location dictates the patient’s presenting signs and symptoms. Large tumors, particularly in non-eloquent areas, often present with signs and symptoms of increased intracranial pressure such as headaches or papilledema [4, 49, 53]. In addition, patients with frontal lobe lesions may display alterations in behavior or personality [4].

Imaging

Following initial presentation, various imaging modalities can be utilized to assist in the diagnosis of LGG. The CT scan is typically the initial imaging modality used in diagnosis. Low-grade gliomas are usually ill-defined and hypodense to normal brain. Contrast enhancement is typically absent. Calcifications within the lesion are common in oligodendrogial tumors [4].

MRI usually displays hypointensity on T1-weighted images and hyperintensity on T2-weighted images (Fig. 8.2). As seen with CT scans, LGGs usually do not display contrast enhancement. Calcifications can present as hypointense areas on
Fig. 8.2 Sagittal T1-weighted image (a) and axial FLAIR image (b) demonstrating a large infiltrative tumor involving the left frontal and temporal lobes as well as the insula. The histopathology displayed a low-grade glioma; specifically an oligodendroglioma, grade II, chromosomes 1p/19q intact.

T1-weighted images. In addition, these lesions rarely display peritumoral edema. However, on MRI the distinction between tumor, edema, and normal brain can be challenging to make with certainty [49, 54]. MRI features may help to predict molecular characteristics of LGG. For example, there is a correlation between an ill-defined margin on T1-weighted MR images ($p = 0.005$) and 1p/19q codeletion [55].

Dynamic contrast-enhanced perfusion MRI (DCE-MRI) is a research technique that may differentiate between low-grade and high-grade glial neoplasms. This imaging modality is used to assess relative cerebral blood volume (rCBV). In one study, the rCBV was 7.32, 5.84, and 1.26 for glioblastoma, anaplastic astrocytoma, and LGG, respectively [56]. A significant difference between low-grade oligodendrogliomas and astrocytomas was also identified with values of 3.68 ± 2.39 in the former and 0.92 ± 0.27 in the latter. This difference is thought to relate to the difference in vascularity between these tumor subtypes. Proposed hypotheses include capillary neovascularization seen in oligodendrogliomas and a lack of vascular proliferation in astrocytomas. Alternatively, oligodendrogliomas are typically located in the cortex as compared to the white matter as seen in astrocytomas. The higher number of blood vessels in the cortex could correlate with a higher vascular density in oligodendrogliomas and consequently a higher rCBV [57]. MR spectroscopy (MRS) may also help to differentiate between low-grade and high-grade lesions. In one study, a choline:N-acetylaspartate (Cho:NAA) ratio of 2.60 was more indicative of the former, while a Cho:NAA ratio of 0.90 was more indicative of the latter [58]. Promising as DCE-MRI and MRS are, these techniques have not been rigorously
validated. Therefore, a histological diagnosis is always required before treatment should be initiated.

Prognostic Factors

Numerous factors may assist clinicians in assessing the prognosis of patients with LGG. Age is a strong independent prognostic factor. The 5-year survival rate for low-grade astrocytomas is estimated at 80% for patients less than 20 years, 50% for patients 20–40 years, and approximately 30% for patients greater than 40 years [59]. The European Organization for the Research and Treatment of Cancer (EORTC) studies 22,844 and 22,845 identified such poor prognostic signs as a neurologic deficit at presentation, tumor size greater than 6 cm, non-oligodendrogial histology, age greater than 40 years, and bihemispheric tumor involvement [60, 61]. The trials were designed to investigate the timing and dosage of post-operative radiotherapy in LGG. In these trials, 322 patients were randomized to EORTC study 22,844 and 288 patients were randomized to EORTC study 22,845. Using Cox regression, patients in the former study were used as a construction set to identify the aforementioned prognostic variables. Patients in the latter study were then used to validate these prognostic factors [60].

In addition to histology and age, an analysis of the National Cancer Institute’s Surveillance Epidemiology and End Results (SEER) data identified female gender and Caucasian race as positive predictive markers [62]. A separate study identified age less than 40 years, oligodendrogial subtype, extent of surgical resection, and a preoperative Karnofsky Performance Status (KPS) score between 80 and 100 as statistically significant positive prognostic markers [63]. Additional imaging modalities currently under investigation to assist clinicians in assessing prognosis include positron emission tomography (PET), MRS, and thallium-201 single-photon emission computed tomography (SPECT) [61, 64].

As noted above, patients with anaplastic oligodendrogliomas with 1p/19q codeletion display increased chemosensitivity and progression-free survival as compared to non-codeleted tumors. Low-grade gliomas have recently been analyzed in order to investigate if this correlation holds for the more benign tumor subtypes. In pure oligodendrogliomas, 1p/19q codeletion was identified as an independent predictor of improved overall survival in both univariate and multivariate analyses. This association was not identified in either astrocytomas or oligoastrocytomas [37].

*IDH* mutations have recently been identified in a high percentage of grade II and III gliomas as well as secondary glioblastoma [46]. Patients with high-grade astrocytomas with *IDH1* or *IDH2* mutations were reported to have a better survival [49]. Likewise, the presence of *IDH1* mutations in low-grade astrocytomas identifies a subgroup of tumors with an improved overall and progression-free survival [49, 52, 65].

Recently, there has been an increase in the diagnosis of LGG among older patients. In a study of LGG patients older than 60 years of age, increasing age was a poor prognostic factor. Presentation with seizures indicated a favorable prognosis, as tumors were more commonly unilateral ($p < 0.05$) and smaller in diameter.
A separate study in LGG patients older than 54 years of age concluded that older patients have poorer outcomes and suggested that LGG may follow a more malignant course in this patient population [66]. As an alternative explanation, data collected by the EORTC suggest that younger patients may have a higher proportion of oligodendrogial pathology as compared to older patients, with a rate of 21–25% in the former group and 9% in the latter group [66–68].

In an effort to summarize these prognostic factors, a preoperative prognostic classification system was recently developed. Using a multivariate Cox proportional hazards model, four factors were associated with a decreased overall survival: tumor location in eloquent cortex, KPS \( \leq 80 \), age > 50 years, and tumor diameter > 4 cm. While the latter three factors were previously identified as negative prognostic factors, location in eloquent cortex was a new prognostic marker. This factor’s significance was presumed to reflect increased neurological deficit and decreased degree of tumor resection. Patients were assigned one point for each factor. A significant difference was noted in both overall survival and progression-free survival in comparing low (scores 0–1), intermediate (score 2), and high-risk (scores 3–4) groups (\( p < 0.001 \)) [69]. This scoring system was later validated using a large, multi-institutional cohort [70].

**Surgical Management**

Surgery is curative for most grade I gliomas such as pilocytic astrocytomas or gangliogliomas. However, the vast majority of grade II gliomas will eventually recur and progress despite an apparent gross total surgical resection [71]. Surgery plays an essential role in the management of LGG, and appropriate adjuvant therapy demands a tissue diagnosis in almost all cases [63].

The first question one must address in the management of LGG is whether immediate intervention is necessary or whether these tumors may be observed. Some have argued that the slow growth of these tumors and the potential harm caused by surgical intervention warrant a “watch and wait” approach [72]. Indeed, some retrospective studies have demonstrated that early versus delayed surgery does not yield benefit in terms of prolonged survival or risk of malignant degeneration [59, 65]. In a study of prognostic factors in 90 patients with low-grade astrocytomas, extent of resection did not predict survival after accounting for age and presenting symptoms. In the same study, the subset of 30 patients with seizures as the sole symptom was examined. In this group, 5-year survival was identical (63%) in the group that had immediate surgery compared with the group that received an operation only after radiological or clinical progression [59]. Similarly, in comparing 26 patients with suspected LGG and deferred resection to 20 patients with immediate resection, another analysis found no significant difference in the time from diagnosis to malignant progression, overall survival, or quality of life [65]. The retrospective nature of these studies limits their applicability. Furthermore, the “watch and wait” approach is only tenable in cases where the suspected LGG is not causing symptoms due to mass effect, obstructive hydrocephalus, or seizures refractory to medication.
Observation of suspected LGG without tissue diagnosis risks the substantial possibility of failing to treat a higher grade tumor [73, 74]. In 20 consecutive patients with suspected LGG who underwent stereotactic biopsy, nearly half of patients harbored an anaplastic astrocytoma and one patient had encephalitis instead of a neoplasm [73]. The classic radiographic distinction between a suspected low-grade and high-grade glioma is contrast enhancement. However, in some series, one-third of histologically confirmed malignant gliomas failed to enhance [74]. Observing a suspected LGG without tissue diagnosis deprives the patient of the benefit of therapy tailored to the tumor cytogenetics and other prognostic information, as discussed above [63].

Once the decision has been made to pursue a tissue diagnosis, the next management question concerns the choice of stereotactic biopsy versus open surgery. One factor that supports stereotactic biopsy is that these operations yield a diagnosis in greater than 90% of cases with low morbidity and mortality [75]. The diagnosis appears to be sufficiently accurate that the correct treatment decision is made in 96% of cases [76]. However, several studies have raised concern about the accuracy of these diagnoses by examining pathological specimens taken from resections performed within a close time period after stereotactic biopsy. When specimens from stereotactic biopsy are compared with those from subsequent resection, the diagnosis may differ in 30% of patients. Although the difference is often considered minor (e.g., a change from pure to mixed glioma), it may be clinically significant more than half of the time (e.g., a change in category or grade of neoplasm) [77]. Another group examined the accuracy of stereotactic biopsy in suspected gliomas in or near eloquent cortex. This study demonstrated a difference between stereotactic biopsy and open resection of gliomas that resulted in a difference in prognosis in 49% of cases and that would have led to a difference in treatment in 33% of cases [78]. Such rates of misdiagnosis are unacceptable given the differences in prognosis, treatment options and responsiveness, and possible enrollment in clinical trials. Therefore, it may be argued that stereotactic biopsy for LGG should be reserved for cases where craniotomy and resection with biopsy pose an unacceptable risk of impairment or mortality. As will be discussed below, advances in surgical technology now allow for greater resection with less morbidity, thus limiting the role of stereotactic biopsy for suspected LGG.

The next consideration in the surgical treatment of LGG is whether there is a benefit of maximal resection versus craniotomy and subtotal resection for diagnosis alone. There are currently no class I data demonstrating a benefit of increased resection in terms of overall survival, progression-free survival, malignant degeneration, or quality of life. Many have noted that a randomized controlled trial assessing the benefit of resection for LGG would be very difficult to perform. This difficulty stems from both the relatively long survival time for patients with LGG and the perception that resection in general and maximal resection in particular provides some benefit. Nonetheless, retrospective studies have demonstrated a survival advantage with increased extent of resection. A recent publication reviewed ten studies published between 1990 and 2008 in which the extent of resection of LGG was evaluated in terms of its relationship with overall survival and progression-free survival [79]. The
authors distinguished the studies that evaluated extent of resection volumetrically from those that limited the evaluation to the surgeon’s assessment of completeness of resection. All three of the volumetric studies [59, 80, 81] and six of the seven non-volumetric studies reviewed demonstrated a survival advantage to increased extent of resection.

Another study recently demonstrated a strong positive relationship between extent of resection and outcome in LGG [81]. Medical records were reviewed from a cohort of adult patients with LGG treated between 1989 and 2005 who underwent resection with preoperative and immediate post-operative MRI. The median time to progression was 5.5 years and the median time to malignant progression was 10.1 years. In multivariate analysis, extent of resection was a significant predictor of overall survival ($p < 0.001$) and malignant progression-free survival ($p < 0.001$) and demonstrated a positive trend for progression-free survival ($p = 0.088$). The predictive value of extent of resection on overall survival remained significant even when analysis was confined to patients with >80% resection ($p = 0.016$). In patients with 100% resection, 8-year overall survival was 98%, progression-free survival was 48%, and malignant progression-free survival was 79%. In addition to extent of resection, preoperative tumor volume and post-operative tumor volume were predictors of progression-free survival and malignant progression-free survival. Involvement in eloquent cortex was a negative predictor for overall survival and progression-free survival ($p = 0.028$). Importantly, there was no association between extent of resection and new post-operative deficit [81].

**Innovations in Surgical Management of Gliomas**

Over the past two decades, advances in preoperative and intraoperative imaging and mapping have enabled surgeons to resect LGGs more extensively with lower morbidity. The tools of cortical and subcortical stimulation, functional MRI (fMRI), magnetic source imaging (MSI), diffusion tensor imaging, intraoperative MRI, and neuronavigation have allowed for maximal resection in some cases that would have been limited to subtotal resection or biopsy in the past.

Direct cortical stimulation, which was the first method of definitive intraoperative identification of eloquent cortex, was implemented in 1930 and is considered the gold standard for the detection of motor and language cortex [82, 83]. In current practice, biphasic square wave pulses are transmitted across 1-mm bipolar electrodes separated by 5 mm. This stimulation causes depolarization of a small area of cortex, which results in local excitation or inhibition. This depolarization is used to identify the cortical areas involved in speech and language and motor response through the generation of either speech arrest or motor stimulation. For language mapping, an area can be considered positively mapped if stimulation causes speech arrest. In recent years, the use of cortical stimulation for language mapping during tumor resection has evolved from this positive mapping technique to a negative mapping protocol, whereby an area of cortex is considered safe to resect if stimulation at that site fails to produce speech arrest [82]. This negative mapping
allows for smaller craniotomies and minimizes the time and size of cortex necessary for mapping. These techniques have resulted in significant improvements both in terms of incidence of neurological deficits, probability of gross total resection, and overall survival. In a comparison of patients with LGG who were resected without (between 1985 and 1996) and with (between 1996 and 2003) intraoperative cortical stimulation, major neurological deficits occurred with one-third of the frequency (6.5% vs. 17%) and MRI confirmed gross total resections were more than four times more likely (25.4% vs. 6%) during the latter period. These improvements occurred despite operating on tumors located in eloquent cortex nearly twice as frequently after the implementation of intraoperative mapping (62% of cases vs. 35%) [84]. A second analysis showed that when resections are carried through subcortical areas that are identified through stimulation as part of the corticospinal tract, permanent motor deficits are more than twice as common (27.5% vs. 13%, \( p < 0.001 \)) [85].

Both fMRI and MSI are preoperative imaging tools that are based on task-specific neuronal activity. One early study of fMRI using a 1.5-T magnet in patients with dominant hemisphere lesions demonstrated relatively high sensitivity but low specificity for essential language cortex detection [86]. This study suggested that fMRI might be valuable as a tool to help identify areas for intraoperative cortical stimulation but insufficient to replace cortical stimulation. More recently, 100% of intraoperatively demonstrable motor cortex locations were verified by preoperative fMRI using a 3-T magnet [87]. MSI is a functional imaging method that combines magnetoencephalography with MRI. In one study, this technology was used to stratify the risk of neurological deterioration from resection and guide operative planning in patients with lesions near eloquent cortex. Patients with eloquent cortex greater than 5 mm from the lesion site, identified via MSI, were offered resection. Gross total resection was only attempted in cases when the distance was greater than 10 mm. In these operative groups, only 6% of patients experienced neurological deterioration, suggesting that the preoperative planning correctly identified patients in which surgery was relatively safe [88].

DTI is another preoperative imaging tool that maps white matter tracts through the orderly patterns of water distributed in axons. This imaging modality accurately identifies white matter tracts as confirmed by intraoperative stimulation and recording [89, 90]. This technology can assist clinicians in predicting if a tumor is displacing white matter tracts or in fact infiltrating and damaging these tracts (Fig. 8.3). DTI has not yet been demonstrated to result in decreased operative morbidity. However, the preoperative knowledge of the tumor’s relationship to these tracts can potentially allow for better assessment of operative risks and provide the surgeon the freedom to more extensively resect a lesion with lower morbidity.

In addition to the preoperative imaging discussed above, two intraoperative imaging tools have entered the surgical armamentarium and allowed for improved operative planning and increased resection. The neuronavigation systems use a preoperatively obtained image that is registered with external anatomical landmarks. This allows for detailed planning of the craniotomy and enables to some degree the identification of tumor borders that might otherwise be difficult to discern, especially in LGG. The combination of neuronavigation with cortical mapping
Fig. 8.3 T1 post-contrast MRI (a) and DTI (b) in 27-year-old woman who presented with seizures. The mass measured approximately $4 \times 4 \times 6$ cm and did not enhance with contrast, suggesting low-grade glioma. The DTI demonstrates superior displacement of the arcuate fasciculus. This imaging allows for surgical planning to maximize resection and minimize injury to language pathways.

has yielded impressive results in terms of completeness of resection with minimal deficits. In one study, the use of a neuronavigation system in combination with electrocorticography allowed for complete resection of greater than 90% of deep lesions [91]. Still, the neuronavigation systems are limited by the fact that they fail to account for intraoperative changes, including brain shift due to movements that occur when the dura is opened as well as conformational changes of the tumor mass during resection.

iMRI, on the other hand, is a tool that allows for repeated assessment of the surgical target and the identification of residual tumor during resection. In an early study of this technology, iMRI demonstrated residual tumor in one-third of cases in which the surgeon had assessed the operation as a gross total resection. The use of iMRI therefore allowed more extensive resection in some cases [92]. Indeed, one series found nearly double the rate of gross total resection using iMRI for both low-grade and high-grade gliomas (56% vs. 27% for high grade, $p = 0.002$, 48% vs. 24% for low grade, $p = 0.024$) [93]. Prolonged survival was seen in this study and a subsequent one [89].

**Radiation Therapy**

Whereas surgery remains the standard first-line treatment for LGG, numerous studies have demonstrated the benefit of radiation therapy when gross total resection is not achieved [94–98]. This benefit exists for both astrocytomas and
oligodendrogliomas. In low-grade astrocytoma patients with apparent complete resection, no radiation was given and 10-year survival was 100%. For patients with incompletely resected low-grade astrocytomas, the choice of whether or not to add radiation therapy was based on the neurosurgeon’s preference. For patients with incompletely resected low-grade astrocytomas, 5-year and 10-year survival in patients receiving radiation was 46 and 35%, respectively, versus 19 and 11%, respectively, in patients who were not irradiated [95]. A separate study reported a similar survival benefit of radiation for incompletely resected oligodendrogliomas; patients receiving radiation for incompletely resected oligodendrogliomas survived a median 37 months versus 26 months for those not receiving radiation ($p = 0.008$) [96]. Importantly, both of the above studies suggested that there was little if any benefit to irradiating patients where gross total resection was achieved. The low survival rates seen in these studies suggest that these incompletely resected tumors, despite being low grade, were nonetheless quite advanced at the time of treatment.

Given radiation therapy’s apparent benefit, timing and dosage of radiation are important questions, particularly since this treatment is associated with cognitive impairment, white matter changes, and radiation necrosis. Two large multicenter randomized trials, by the Radiation Therapy Oncology Group (RTOG) and EORTC, investigated the dose–response of radiation for LGG. Both studies failed to demonstrate an overall survival benefit of high-dose (59.4, 64.8 Gy) versus low-dose (45, 50.4 Gy) radiotherapies [67, 99]. In fact, the RTOG study demonstrated slightly lower survival and higher rates of radiation necrosis in the high-dose group [99]. A follow-up study by the EORTC evaluated the benefit of early post-operative radiation for low-grade gliomas versus delayed radiation at the time of tumor recurrence or progression. This study found that while progression-free survival was significantly longer when radiation was given post-operatively (5.3 years vs. 3.4 years, $p < 0.0001$), overall mean survival was similar in both groups (7.4 years for early radiation vs. 7.2 years for delayed, $p = 0.872$) [100].

The benefit of radiation in terms of prolonged progression-free survival must be weighed against the potential adverse cognitive effects and white matter changes associated with this treatment. In one study, patients who underwent radiation therapy in addition to surgery were significantly more likely to experience cognitive deficits and white matter changes than those receiving surgery alone [101]. Similarly, higher dose radiation may be associated with increased radiation necrosis compared to low-dose radiation [99]. Still, other studies have questioned this impact of radiotherapy. A study by Taphoorn et al. demonstrated that while all patients with low-grade gliomas had significantly more cognitive impairment and fatigue than patients with systemic hematologic cancers, radiation therapy compared to surgery or biopsy alone did not add to that cognitive deficit [102]. However, this same group recently demonstrated that when patients are later evaluated, the prevalence of cognitive deficits in patients who had undergone radiation therapy was nearly double the rate in radiotherapy-naïve patients (53% vs. 27% for attentional functioning deficit, $p = 0.003$) [103].
In an attempt to avoid the toxicity of external beam radiation therapy to the brain, stereotactic brachytherapy (SBT) and radiosurgery (SRS) have been tested for use in patients with LGG. In a study of SBT along with microsurgery for newly diagnosed LGGs greater than 4 cm in diameter and SBT alone for small recurrences, 5-year progression-free survival was 72% for the large de novo tumors and 62% for the smaller recurrences. In the 5-year study period, only 18% of the patients in this study required adjuvant external beam radiation therapy or chemotherapy \[104\]. SRS may also be useful for LGGs located in eloquent cortex, for patients with residual tumor burden after surgery, and for tumor progression. Studying one series, the 5-year clinical progression-free survival rate was 41% and complete radiologic remission rate was 29% \[105\]. While neither SBT nor SRS is capable of completely treating LGGs that are often large and infiltrative, the modalities represent compromises between the focal nature of surgery and the systemic effect of radiation or chemotherapy. Their purported benefit requires confirmation in prospective controlled clinical trials.

**Chemotherapy**

Whereas surgical treatment is generally the primary therapy for LGG and radiotherapy is a frequent adjunct, chemotherapy has historically played a more limited role in the treatment of these lesions. To help clarify the role of chemotherapy, numerous studies have investigated the use of combination procarbazine, lomustine (CCNU), and vincristine (PCV) or temozolomide at various doses and schedules for LGG \[61, 106–111\]. One study retrospectively reviewed cases of recurrent oligodendroglioma treated with PCV chemotherapy. While the rate of complete radiographic response was 17% and partial response was 46%, the median time to progression was only 10 months \[110\]. Recently the RTOG reported initial results of a phase II study comparing the addition of PCV to radiation versus treatment with radiation alone in patients with LGG who were considered high risk. These initial results demonstrate that the addition of PCV prolongs progression-free survival, though overall survival between the groups did not differ significantly \[112\].

Over the past several years, there has been increasing interest in the use of chemotherapy as an adjunct or even an alternative to radiation. This interest is largely focused on the use of temozolomide on the basis of its use in high-grade gliomas, oral bioavailability, CNS penetration, and favorable side-effect profile. A phase II study examining the first-line use of temozolomide in recurrent oligodendrogliomas demonstrated complete response in 30% of patients and partial response in an additional 25%. However, median time to progression was still only 10 months overall and only 13 months in patients with complete or partial response \[109\]. A phase II trial of temozolomide after resection of LGG demonstrated a 3-year progression-free survival of 66%. This time course for progression is similar to that achieved with early radiation therapy. Radiographically, no patients were complete
responders to temozolomide, 10% were partial responders, and 50% were minimal responders [106].

The results of the various phase II trials investigating the use of chemotherapy in addition to radiation have led to the launch of an EORTC/NCIC phase III trial comparing the use of temozolomide versus radiation therapy as primary post-surgical treatment. Similarly, the ECOG has launched a prospective phase III trial evaluating the adjunctive benefit of temozolomide with radiation in LGG. These large, randomized, multicenter trials will help clarify the relative benefits of radiation and chemotherapy. Furthermore, these studies will incorporate cytogenetic prognostic features into the analysis of the benefits of these treatment modalities. While results are not yet available, the launch of these trials demonstrates the significant interest in the use of temozolomide for LGG [1].

One experimental use of chemotherapy for LGG that has yielded positive results has been a neoadjuvant therapy prior to surgical resection. This approach has only been demonstrated in isolated case reports of oligodendrogliomas [113, 114]. In one case, a grade II oligodendroglioma was incompletely resected due to the bilateral invasion of the tumor. After treatment with six cycles of temozolomide, the tumor regressed to involve only the left frontal lobe. When the mass failed to regress further with chemotherapy, it was re-resected with resultant radiographic gross total resection [113]. This use of neoadjuvant chemotherapy demonstrates the potential to use the various treatment modalities creatively to individualize LGG treatment.

**Conclusions**

The diagnosis of LGG includes a variety of pathological diagnoses with variable prognoses. Patients are presenting earlier in the course of their disease as imaging modalities are becoming more advanced and more readily available. In addition, elderly patients are more often being diagnosed with these lesions and the prognosis for this patient population has yet to be delineated. Surgery remains the core treatment and diagnostic modality. Numerous preoperative and intraoperative tools are currently being used to assist the surgeon in treating these lesions and allowing for increased extent of resection with lower morbidity. However, there exists no class I evidence demonstrating the benefit of surgery versus conservative management. Radiation therapy serves as the primary adjunctive treatment, though there has been increasing interest in the use of chemotherapy in conjunction with or even instead of radiation. With clinical trials of various treatment modalities and regimens underway, future research will address the many still unanswered questions regarding the management of LGG.

**References**


Chapter 9
High-Grade Astrocytomas

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Keywords  High-grade glioma · Anaplastic astrocytoma · Glioblastoma · Malignant glioma

Introduction

High-grade astrocytomas (HGAs) are the most common adult primary malignant brain tumor, which include anaplastic astrocytoma (AA; World Health Organization [WHO] grade III) and glioblastoma multiforme (GBM; WHO grade IV). Although HGAs represent an overall uncommon cancer, they are associated with morbidity and high mortality. Despite state-of-the-art multimodality treatments, the median survival of GBM patients is 12–15 months, whereas that of AA is 2–3 years [1]. Current treatments for HGA include surgery, radiation, and chemotherapy. Temozolomide, an oral alkylating chemotherapy, has been approved for newly diagnosed GBM and recurrent AA. It offers significant, albeit modest, survival benefit for unselected HGA patients. Recent elucidation of molecular abnormalities underlying glioma pathogenesis has led to several novel therapeutic approaches, which include molecularly targeted therapy, immunotherapy, gene/viral therapy, and new delivery systems. Among these novel treatments, anti-angiogenic agents represent a promising therapeutic approach. Bevacizumab, a neutralizing monoclonal antibody of vascular endothelial growth factor (VEGF), received accelerated approval by the US Food and Drug Administration (FDA) in 2009 for progressive GBM. In this chapter, we discuss the current management and new therapeutic strategies for HGA.
Epidemiology

Gliomas account for 34% of all primary brain tumors with an annual incidence rate of 5.97 per 100,000 person-years [2]. GBM is the most common and malignant form of glioma with an incidence rate of 3.17 per 100,000 person-years [2]. AA accounts for 6.7% of all gliomas with an incidence rate of 0.4 per 100,000 person-years [2]. The incidence of HGA has slightly increased over the past two decades probably due to the improvement of imaging technology. These tumors affect men more than women and white more than black [2]. The median age of diagnosis for GBM is 64 years and that for AA is approximately 40 years. The prognosis of HGA has remained dismal despite multimodality treatments. The Survival, Epidemiology, and End Results (SEER) registry demonstrated 5-year survival rates of 4.5 and 27.4% for GBM and AA patients, respectively, diagnosed between 1995 and 2006 [2]. The only well-established environmental risk factor for HGA is cranial exposure to ionizing radiation [3]. Several inconclusive risk factors need further studies that include dietary calcium, cured foods, and anti-oxidants [4]. Various factors have been identified as potential protective factors for gliomas such as allergic or atopic conditions, caffeine consumption, non-steroidal anti-inflammatory drugs (NSAIDs) intake, and history of varicella zoster infection [4]. Some hereditary syndromes that predispose patients to develop HGA include Li–Fraumeni syndrome, neurofibromatosis, tuberous sclerosis, and Turcot syndrome. Genetic causes apart from hereditary syndromes are unclear. An international study on linkage analyses in familial gliomas (GLIOGENE) is ongoing. Another ongoing effort by epidemiologists is to search for genetic susceptibility for brain tumors. Few genome-wide association studies have demonstrated several risk loci for glioma susceptibility such as TERT rs2736100, CCDC26 rs4295627, CDKN2A/CDKN2B rs4977756, RTEL1 rs6010620, PHLDB1 rs498872, CDKN2B rs1412829, and RTEL1 rs6010620 [5]. Identification of the specific roles of these single-nucleotide polymorphisms in gliomagenesis will require functional and biological network analyses.

Although there has been increasing concern over the risk of brain tumors from mobile phone use, most studies have failed to show a definite association [5]. One meta-analysis study demonstrated a possible link between mobile phone use and development of brain tumors [6]. However, another recent study in Scandinavian countries did not show an increase in incidence trends of gliomas between 1998 and 2003, when the effect of mobile phone use on induction of brain tumors should be evident [7]. The use of mobile phone has become more common in children and adolescents in the past 5–10 years. Therefore, effects of early-onset, long-term, and heavy use in these young generations may not be seen at present. Unbiased, long-term, prospective cohort studies are needed to resolve this controversy.

Pathology and Pathogenesis

According to the 2007 WHO pathological classification, AA displays increased cellularity with pleomorphism, nuclear atypia, and mitoses, whereas GBM is defined by vascular proliferation and/or necrosis with frequent pseudopalisading features
(Fig. 9.1) [8]. Uncommon variants of GBM include gliosarcoma, which has sarcomatous component; giant cell glioblastoma, which contains multinucleated giant cells; small-cell glioblastoma, which contains tumor cells with small nuclei associated with epidermal growth factor receptor (EGFR) gene amplification; and glioblastoma with oligodendroglial features, which contain oligodendroglial components, thus associated with better treatment response and prognosis. Current pathological classification of gliomas may not be sufficient as it is based on only histological findings. Therefore, molecular and genetic classification may be more important in prognosis determination and treatment decision for each patient in the future [9].

Fig. 9.1 Pathologic findings of high-grade astrocytomas. (a) Anaplastic astrocytoma (WHO grade III) displays increased cellularity and nuclear pleomorphism and mitoses (arrows); (b) glioblastoma multiforme (WHO grade IV) is characterized by necrosis (*) and/or vascular proliferation (arrows). Courtesy of Jantima Tanboon, MD and Tumtip Saengruchi, MD, Department of Pathology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand

HGAs, as other cancers, exhibit malignant characteristics including unlimited proliferation, resistance to apoptosis, evasion of antigrowth signals and immune surveillance, tissue invasion, and ability to form and sustain new blood vessels (angiogenesis) [10, 11]. HGAs contain both tumor cells and stromal elements with pathological heterogeneities among patients. Advances in genomic technology have facilitated molecular and genetic characterization of these tumors in the past 5 years. A gene expression profiling of 76 HGAs classified these tumors into 3 categories including proneural, proliferative, and mesenchymal types [12]. Proneural type resembling neurogenesis was associated with younger age, intact chromosomes, and better prognosis, whereas proliferative and mesenchymal types were associated with older age, genetic aberrations such as EGFR amplification or phosphatase and tensin homolog (PTEN) loss, and poor prognosis [12]. A recent study using reverse engineering and unbiased interrogation of a glioma-specific regulatory network revealed two transcription factors, C/EBP-β and signal transducer and activator of transcription 3 (STAT3), as synergistic initiators and critical regulators of mesenchymal transformation of neural stem cells [13].

Despite the notorious genetic heterogeneity, common genomic alterations that maintain malignant phenotypes of these tumors are found (Fig. 9.2). An integrated
Neural stem cells or glial progenitor cells or mature astrocytes

Glioblastoma Multiforme (WHO grade IV)

Fig. 9.2 Molecular alterations in astrocytomas. Secondary glioblastoma (GBM) develops from malignant transformation of lower-grade astrocytomas (low-grade astrocytoma [WHO grade II] or anaplastic astrocytoma [WHO grade III]), whereas the more common type, primary GBM, develops without antecedent lower-grade tumors. Genetic analyses reveal common and differential molecular aberrations between primary and secondary GBMs. Data from Parson et al. [14], TGCA research network [15], and Wen and Kesari [1]

genome-wide evaluation, which included DNA copy number, gene mutation, and expression analyses of GBM, demonstrated alterations in **CDKN2A (50%)**, **TP53 (40%)**, **EGFR (37%)**, **PTEN (30%)**, neurofibromatosis (**NF1 (15%)**, **CDK4 (14%)**, retinoblastoma (**RB1 (12%)**, and isocitrate dehydrogenase (**IDH1 (11%)** [14].

Another large collaborative study by The Cancer Genome Atlas (TCGA) research network using integrated multidimensional analyses including gene sequencing, DNA copy number, methylation, transcriptome, and miRNA analyses also found similar genetic abnormalities and established common deregulated pathways including receptor tyrosine kinase/RAS/PI3K (88%), **P53 (87%)**, and **RB (78%)** [15]. Furthermore, these studies also revealed unexpected therapeutic relevant findings, which include mutations of **PI3K (15%)** or **ERBB2 (8%)**. Integrating TCGA genomic data with a robust gene expression-based molecular classification of GBM demonstrates that alteration of **EGFR, NF1**, and **PDGFRA/IDH1** each define the classical (proliferative), mesenchymal, and proneural subtypes, respectively [16]. In addition, proteomic analyses revealed that **EGFR** alteration was associated with notch pathway activation, whereas **NF-1** deletion was associated with lower
mitogen-activated protein kinase (MAPK) activity with PI3K activation and over-expression of a mesenchymal marker, YKL40 [17]. Patients with classical (EGFR) and mesenchymal (NF1) subtypes had survival benefit from aggressive chemoradiotherapy, whereas patients with proneural (PDGFRA) subtype derived no benefit from such treatment [16]. Another recent multidimensional genomic profiling of 501 patients with gliomas from several independent genome databases revealed 7 landscape genes (POLD2, CYCS, MYC, AKR1C3, YME1L1, ANXA7, and PDCD3) altered by recurrent chromosomal aberrations, which deregulate critical signaling pathways through complex mechanisms [18]. These genetic mutations are likely from non-random selection of a distinct genetic landscape during gliomagenesis and are associated with patient prognosis [18]. Other genomic and system biology techniques have been exploited to study the complexity of genetic abnormalities, which may shed some light on pathogenesis and identify new therapeutic targets in HGA.

Most GBM tumors (90%) are diagnosed without antecedent lower-grade tumor—termed primary or de novo GBM, whereas secondary GBM has clinical evidence of transformation from lower-grade gliomas (WHO grades II–III) (Fig. 9.2). Low-grade astrocytoma (WHO grade II) usually has tumor suppressor gene TP53 mutation and/or overexpression of platelet-derived growth factor (PDGF) ligands or receptors [19]. Transformation to AA involves accumulation of other genetic alterations of cell cycle regulatory pathways, including loss of 11p and/or 19q, amplification or overexpression of cyclin-dependent kinase (CDK)4/6 and human double minute 2 (HDM2), loss of cyclin-dependent kinase inhibitor p16INK4A/CDKN2A, and mutations of the retinoblastoma (RB1) gene. Transformation to GBM (i.e., secondary GBM) is associated with deletion of chromosome 10, mutation of PTEN, loss of deletion in colorectal cancer (DCC) gene, and amplification or mutation of PI3K. Secondary GBMs tend to occur in younger patients than primary GBMs and share a subset of genetic abnormalities with primary GBMs such as loss of PTEN, deletion or mutation of cyclin-dependent kinase inhibitors p16INK4A (which shares a locus with p14ARF on chromosome 9) and amplification of HDM2 or CDK4 [20]. However, some genetic abnormalities distinguish primary and secondary GBMs such as EGFR amplification, which is more common in primary GBMs. A recent gene sequencing study of 445 CNS tumors demonstrated that most WHO grade II and III gliomas and secondary GBMs display mutations of IDH1 or IDH2 [21]. These mutations not only distinguish secondary from primary GBM, but also represent an early genetic event that serves as a robust prognostic factor and may present novel targets for therapeutic development for HGA [21].

Some of these genetic abnormalities lead to deregulation of signal transduction pathways, a communication network of regulatory molecules within the cell, controlling cellular processes contributing to normal homeostasis and malignancy (Figs. 9.2 and 9.3) [22]. For example, mutations of EGFR or NF1 can increase activity in the RAS-mitogen-activated protein kinase (MAPK) pathway. PI3K overactivity may result from loss of PTEN, a negative regulator of PI3K function, PI3K mutations, or AKT amplification. Understanding these molecular and genetic
Fig. 9.3 Signal transduction pathways in high-grade astrocytomas and targeted therapeutics. Malignant astrocytoma cells and associated endothelial cells often have activation of the pathways of several growth factor receptor tyrosine kinases (RTK) such as epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGF), hepatocyte growth factor/c-MET receptor, fibroblast growth factor receptor (FGFR), and insulin-like growth factor receptor (IGF). Ligand binding to receptors induces receptor dimerization and phosphorylation ($P$). This permits activation of numerous intracellular signal transduction pathways that regulate gene transcription of essential cellular proteins contributing to malignancy. Several points in these cascades are the targets of therapies in development for malignant astrocytoma, some of which are shown. Signaling molecules might include RAS, RAF, mitogen-activated protein extracellular regulated kinase (MEK), extracellular-regulated kinase (ERK; also termed mitogen-activated protein kinase, MAPK), phosphatidylinositide-3-kinase (PI3K), AKT, mammalian target of rapamycin (mTOR), and protein kinase C (PKC). AMPA-R, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BMP, bone morphogenetic proteins; CHK, checkpoint kinases; GDP, guanine diphosphate; GTP, guanine triphosphate; HDAC, histone deacetylase; HIF, hypoxia-inducible factors; NF1, neurofibromin; PIP$_2$, phosphatidylinositol-(4,5)-bisphosphate; PIP$_3$, phosphatidylinositol-(3,4,5)-trisphosphate; PLC, phospholipase C; PTEN, phosphatase and tensin homolog; STAT3, signal transducer and activator of transcription-3.

Abnormalities will lead to a rational development of molecular-targeted therapies in HGA. For example, patients with NF1 mutations might benefit from RAF or MEK inhibitors. Patients with PTEN loss or PI3K-activating mutations might benefit from PI3K inhibitors, while patients with amplification of AKT (downstream molecule from PI3K) might not respond to these agents. Other cellular and stromal elements...
such as ubiquitin–proteasome system, microRNA, endothelial cells, pericytes and bone marrow-derived, and immune cells are also important in gliomagenesis and may have therapeutic implication (Fig. 9.3) [23–25]. Finally, the recent elucidation of cancer stem cells in GBM has led to greater understanding of glioma pathogenesis, which may lead to a novel therapeutic approach [26]. The details of cancer stem cell hypothesis and its therapeutic implications are discussed in an earlier chapter.

Management of Newly Diagnosed High-Grade Astrocytomas

Surgical Management

Patients with radiographically suspected HGA (Fig. 9.4) usually undergo either biopsy or surgical resection for histological diagnosis. If tumor is located in eloquent brain areas, resection is usually performed while the patient is awake to preserve neurological function. Maximum safe resection is recommended as several retrospective studies show that gross total resection appears to improve survival outcomes for HGA [27, 28]. A multicentered, randomized, prospective study using standard surgery versus fluorescence-guided resection with 5-aminolevulinic acid (ALA) to enable maximum resection confirmed that complete resection defined by absence of enhancing tumor in early post-operative MRI (within 72 h) was better achieved in the 5-ALA group [29]. Complete resection with or without 5-ALA was associated with significantly longer survival [30]. Although surgery offers a survival advantage, the degree of benefit seems modest. Other advances to assist surgery include preoperative planning with MRI neuronavigation and functional and intraoperative MRI. Locoregional therapy given surgically may offer promise as it bypasses the blood–brain barrier, thus improving delivery of therapeutics and minimizing systemic toxicity. In addition, because the majority of malignant astrocytomas recur within 2 cm from the primary tumor site, locoregional treatments such as chemotherapy wafer and conjugated biological toxins may improve local tumor control [31].

Carmustine Wafers

Polifeprosan 20 with carmustine, also known as BCNU [1,3-bis(2-chloroethyl)-1-nitrosourea], implant (Gliadel; Eisai, NJ, USA) is approved for the treatment of GBM. Carmustine wafer placement after resection followed by radiation therapy (RT) was associated with a 2.3-month survival advantage compared to placebo in a randomized Phase III trial [32]. Furthermore, the survival benefit appears to sustain after 3 years following treatment [33]. Healing abnormalities, increased intracranial pressure and seizures were more common in the carmustine wafer-treated group.
Fig. 9.4 Radiographic findings of high-grade astrocytomas. MRI of glioblastoma multiforme (WHO grade IV) demonstrates (a) large, heterogeneous, and irregular ring-nodular gadolinium (Gd)-enhancing lesion with central hypointensity at the left fronto-parietal area on T1-weighted image with (b) extensive surrounding hyperintense signal abnormalities on FLAIR (fluid-attenuated inversion recovery) sequence predominantly involving cerebral white matter, consistent with vasogenic edema. MRI of anaplastic astrocytoma (WHO grade III) demonstrates (c) hypointense T1-weighted lesion at the left thalamus with minimal intratumoral enhancement after gadolinium administration and (d) corresponding hyperintense FLAIR abnormality. Enlarged lateral ventricles with periventricular hyperintense FLAIR abnormalities (transsependymal migration of cerebrospinal fluid) indicate obstructive hydrocephalus from third ventricle compression by the thalamic tumor

[32]. Carmustine wafer can be safely used in conjunction with concurrent chemoradiotherapy with temozolomide in newly diagnosed GBM with promising survival outcome [34, 35].

**Radiation Therapy**

RT has been the mainstay treatment for HGA, unless patients opt to have supportive care [36]. It is administered in the early post-operative phase (approximately 2–4 weeks following resection). However, a short delay of radiation therapy up to 6
weeks post-operatively is not associated with poor outcome [37, 38]. Radiotherapy is generally given to a focal field including the tumor bed or resection cavity with a 2- to 3-cm margin at a total dose of 58–60 Gy divided into 1.8–2 Gy fraction/day; 5 days/week for 6–6.5 weeks. Whole brain radiotherapy is not associated with improved survival. Similarly, strategies to deliver locally high-dose radiation such as stereotactic radiosurgery or brachytherapy have not demonstrated significant survival benefit in unselected HGA patients [39]. Other RT techniques such as proton beam therapy and boron neutron capture therapy have also been investigated in HGA.

Chemotherapy

Adjuvant chemotherapy with nitrosoureas had not provided significant clinical benefit in patients with HGA with <10% increase in 1-year survival rate [40]. However, this has changed since 2005, when the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) reported in a pivotal Phase III trial that addition of temozolomide (TMZ; Temodar®; Merck, NJ, USA) to standard RT improved survival of GBM patients without degradation in quality of life, when compared to RT alone [41, 42]. Therefore, TMZ has become a new standard-of-care treatment for newly diagnosed GBM.

There is no standard treatment following resection for AA. Both radiotherapy and chemotherapy seem to have activities against AA. A recent Phase III study in Germany (NOA-04) with a unique and complex design randomized anaplastic glioma patients to first receive either radiotherapy or chemotherapy (PCV; procarbazine, CCNU and vincristine, or TMZ) and subsequently receive the other treatment upon progression [43]. This study showed that initial radiotherapy or chemotherapy offered similar survival outcomes [43]. The role of concurrent followed by adjuvant TMZ (i.e., standard GBM regimen) in newly diagnosed AA is less clear. Multicentered clinical trials such as CATNON and CO-DEL are ongoing to address this question [44].

Temozolomide

TMZ is an orally available, imidazotetrazine-derived, alkylating agent [45]. TMZ methylates specific DNA sites—N [7] position of guanine, O [3] position of adenine, and O [6] position of guanine. The O [6] position of guanine is a critical site to mediate TMZ toxicity, although it accounts only for 5–10% of DNA lesions. TMZ induces DNA double-strand breaks and apoptosis by causing nucleotide mismatch between complementary strands in tumors. TMZ has almost 100% oral availability and good blood–brain barrier penetration. The level of TMZ in CSF is approximately 40% of that in serum [45].

TMZ exhibits broad antitumor activity in various types of CNS tumors including gliomas in subcutaneous and orthotopic xenograft models [46]. Based on the
promising initial clinical trial results in recurrent AA, TMZ was granted an accelerated approval from the US Food and Drug Administration (FDA) in 1999 for treatment of nitrosourea-resistant recurrent AA and from the European Medicines Evaluation Agency (EMEA) for treatment of recurrent AA and GBM [47, 48]. Neoadjuvant TMZ therapy was associated with a 51% radiographic response rate in newly diagnosed GBM [49]. Subsequent studies evaluated the efficacy of TMZ in a concurrent daily dose with RT, followed by monthly cycles of adjuvant TMZ in newly diagnosed GBM patients [41, 50, 51]. A Phase III study by the EORTC and the NCIC, which equally randomized 573 patients to receive either RT alone or RT plus temozolomide, demonstrated a 2-year survival rate of 24% for RT–TMZ (75 mg/m²/day for 42 consecutive days)/TMZ (150–200 mg/m²/day for 5 days every 28-day cycle for six cycles) group compared to 10% for the RT group [41]. The median survival was 14.6 months for the RT–TMZ/TMZ group compared to 12.1 months for the RT group [41]. Long-term follow-up demonstrated the durable benefit of TMZ with a 5-year survival rates of 9.8% for the RT–TMZ/TMZ group and 1.9% for the RT group [52]. Common adverse effects of TMZ are hematologic toxicity (neutropenia and thrombocytopenia). Grade 3 or 4 hematologic toxicities were found in 7% during concomitant phase with RT and in 14% during adjuvant phase [41]. Severe infections are uncommon and other non-hematologic toxicities such as nausea, vomiting, constipation, and fatigue are mild to moderate. Another similar study that evaluated 110 patients with a more intensive post-RT adjuvant TMZ regimen (150 mg/m²/day on days 1–5 and days 14–19 of each 28-day cycle) confirmed the efficacy of TMZ with the median survival of 13.4 months for RT–TMZ/TMZ group compared to 7.7 months for RT-alone group [51].

The survival benefit from addition of TMZ to RT, albeit significant, is modest. However, a subset of patients (10%) achieved long-term survival (at least 5 years) following combined treatment [52]. Identification of biomarkers of response to TMZ is critical to select patients who will derive most benefit from TMZ. O⁶-methylguanine-DNA methyltransferase (MGMT) (also termed O⁶-alkylguanine-DNA alkyltransferase [AGT]) is a DNA repair enzyme that removes methyl groups from the O⁶ position of guanine, a critical site for DNA methylation [53]. MGMT functions as a suicidal protein: the reversion of O⁶-methylguanine to an unmethylated state leads to irreversible inactivation of the enzyme. If MGMT is deficient (usually by epigenetic silencing (e.g., methylation) of CpG islands within the MGMT promoter), temozolomide-induced O⁶-methylguanine will be left unrepaired and cells will undergo futile DNA replication with subsequent apoptosis. MGMT activity in tumors can be assayed either by immunohistochemistry of MGMT protein or by PCR to assess the methylation of MGMT gene promoter. Using immunohistochemical detection of MGMT, newly diagnosed GBM patients with low level of MGMT had a 60% response rate to TMZ, compared to only 9% among patients with high level of MGMT [49]. Although immunohistochemistry is more readily available, scoring and interpretation of results require expertise and may be subject to interobserver variation. Hegi et al. exploited a methylation-specific PCR to study tumor MGMT promoter status of newly diagnosed GBM patients from the aforementioned EORTC/NCIC trial [54]. In this retrospective study patients
with a methylated \textit{MGMT} gene had a longer survival regardless of their treatments (RT alone or RT–TMZ), when compared with patients with unmethylated \textit{MGMT}. Combined treatment (RT–TMZ) was associated with significant survival benefit regardless of methylation status of \textit{MGMT}, although the benefit in the methylated \textit{MGMT} group (hazard ratio (HR) = 0.51; \( p = 0.004 \)) is more prominent than in the unmethylated \textit{MGMT} group (HR = 0.66; \( p = 0.035 \)) [54]. Another recent study demonstrated that \textit{MGMT} methylation is a prognostic factor as well as a predictive marker of survival benefit to RT without alkylating agents including TMZ [55].

Taken together, these data suggest that tumor \textit{MGMT} status is an independent prognostic factor and may also serve as a predictive marker for RT and/or TMZ benefit in GBM patients. Prospective validation of \textit{MGMT} status as a predictive marker for TMZ benefit is needed before it is routinely used to select patients to receive TMZ. The Radiation Therapy Oncology Group (RTOG)-0525 stratified patients based on \textit{MGMT} status in a large prospective study which completed accrual in 2009. If \textit{MGMT} status is prospectively validated to predict TMZ benefit, there is still an urgent need for (1) standardization of \textit{MGMT} assays and validation of cutoff values as there is technical heterogeneity reflected by difference in percentage of \textit{MGMT} methylation across several laboratories and (2) identification of alternative therapy for patients with unmethylated \textit{MGMT} [56].

Other strategies to improve the efficacy of TMZ are clearly needed. Alternative dosing schedules, extended length of therapy, addition of agents to prevent or rescue TMZ resistance, and combination with other treatments such as other chemotherapies, targeted therapeutics, gene therapy, or immunotherapy may improve treatment efficacy. Dose-dense, intensified, and metronomic TMZ schedules may be more effective in depleting MGMT in tumor. A recent trial of standard concurrent RT–TMZ followed by six adjuvant cycles of either dose-dense (150 mg/m\(^2\)/day on days 1–7 and days 15–21; \( n = 42 \)) or metronomic (50 mg/m\(^2\) daily; \( n = 43 \)) TMZ also included maintenance with 13-\textit{cis}-retinoic acid after completion of TMZ until disease progression [57]. Both regimens were tolerated with common toxicities of myelosuppression and elevated liver transaminases. The survival benefit was more prominent in the dose-dense arm with the 1-year survival rate of 80%, whereas it was 69% for the metronomic arm [57]. Of note, the 1-year survival rate was 61% in the landmark EORTC/NCIC trial [41]. Combination of TMZ and lomustine (CCNU) administered concomitantly with radiation followed by adjuvant TMZ/lomustine for 6 months demonstrated promising survival outcome in a study of 39 newly diagnosed GBM patients. However, grade 4 hematologic toxicities are significantly higher, when compared with standard RT–TMZ/TMZ regimen [58].

\textit{O}\textsubscript{6}-benzylguanine (\textit{O}\textsubscript{6}-BG) is an MGMT substrate that inhibits MGMT by suicidal inactivation. Preclinical studies demonstrate that the antitumor activity of TMZ is enhanced by \textit{O}\textsubscript{6}-BG in an animal model [59]. A Phase I trial of intravenous \textit{O}\textsubscript{6}-BG in combination with TMZ confirmed that MGMT was depleted following \textit{O}\textsubscript{6}-BG administration [60]. A Phase II trial of single dose of TMZ (472 mg/m\(^2\)) plus 48-h infusion of \textit{O}\textsubscript{6}-BG demonstrated that TMZ sensitivity was restored in 16% of anaplastic glioma patients and only 3% of GBM patients [61]. Grade 4 hematologic toxicities were found in 48% of patients [61]. To increase efficacy
and decrease toxicities, a 5-day regimen of TMZ and O\textsuperscript{6}-BG was evaluated in a Phase I trial of recurrent malignant glioma [62]. Another potent MGMT inhibitor that has the advantage of being an oral formulation, O\textsuperscript{6}-(4-bromothenyl)-guanine (PaTrin-2), is currently in preclinical development [63]. Resistance of TMZ has also been demonstrated in tumor cells deficient in the DNA mismatch repair system, independent from the MGMT level. A recent study using TCGA data demonstrated that mutations of \textit{MSH6} mismatch repair gene develop during TMZ treatment and may be responsible for TMZ resistance [64]. Another strategy to overcome resistance conferred by mismatch repair deficiency is to block base excision repair, which differentially repairs the methyl adducts at the N\textsuperscript{3} adenine and N\textsuperscript{7} guanine positions rather than at the O\textsuperscript{6} guanine [65]. Base excision repair can be inhibited by blocking a key enzyme, poly(ADP-ribose) polymerase (PARP). Phase I/II study of a PARP inhibitor, BSI-201 (BiPar Sciences, South San Francisco, CA, USA), in newly diagnosed malignant gliomas is ongoing.

Recently, a stem cell-related “self-renewal” signature by expression of \textit{HOX} cluster genes, which contain CD133 (prominin-1), an enrichment marker glioma stem cells, has been shown to predict poor survival to the RT–TMZ/TMZ regimen [66]. Targeting glioma stem cells may therefore improve efficacy of TMZ in GBM.

\textbf{HGA in the Elderly}

As the aging populations are growing, a number of elderly patients affected by HGA may increase. Older age is an independent poor prognostic factor for survival in HGA [67]. Treatment for this patient population (age ≥ 70 years) is often challenging as many elderly patients have poor functional status and high risk to develop systemic and neurological toxicities from therapies. By using the Surveillance, Epidemiology, and End Results (SEER) database, elderly patients with HGA were not likely to have multimodal treatment and hence worse prognosis. Elderly patients who received surgical resection only or biopsy plus radiation had worse survival outcomes than those who had resection plus radiation [68]. A randomized trial of RT plus supportive care versus supportive care only in elderly HGA patients with good performance status (KPS ≥ 70) demonstrated significant, albeit modest, improvement of survival in RT group (median survival 29.1 vs. 16.9 weeks) with similar quality of life and cognitive functions in both treatment groups [69]. Hypofractionated RT (40 Gy) that may limit length of treatment and treatment-related morbidity seems to have similar survival outcomes to conventional focal RT (60 Gy) [70]. Upfront TMZ treatment may represent an alternative option. A retrospective analysis from three US institutions demonstrated no survival difference between RT and TMZ treatments in elderly patients with malignant gliomas [71]. In another study of 39 elderly GBM patients, upfront TMZ was associated with 28% radiographic response rate, PFS of 20 weeks, and the median survival of 27.4 weeks for the 27 patients who did not receive salvage treatment following TMZ progression [72]. Grade 3 and 4 toxicities were found in 21% of patients with no
treatment-related death [72]. Concurrent RT-TMZ seems to be safe and well tolerated in a few series of elderly GBM patients without major co-morbidities [73–75]. Although the survival outcomes seem better than those with RT alone, significant mental deterioration was observed in 25% of patients in one study [75]. Further studies are needed to identify treatment regimens with optimal efficacy and acceptable toxicities for this elderly population. Several randomized trials evaluating hypofractionated RT regimens, RT in comparison with TMZ and hypofractionated RT in comparison with the same RT plus TMZ are ongoing in elderly patients with newly diagnosed GBM.

Management of Recurrent HGA

**Diagnosis of Recurrence**

Most patients with HGA eventually recur or progress following multimodality treatment. Interpretation of MRI upon recurrence or progression can be challenging. Although increased contrast enhancement and edema on MRI often indicated tumor progression, various treatments such as RT alone (especially high dose), concurrent chemoradiation (such as RT + TMZ or carmustine wafer and RT +/- TMZ), or brachytherapy may induce similar radiographic changes that represent diagnostic challenge. This phenomenon of treatment-related effects is termed “pseudoprogression,” which occurs more commonly in the first 3 months following RT +/- TMZ [76]. Approximately 30% of malignant glioma patients treated with RT alone had early radiographic progression and one-third of these had pseudoprogression, i.e., MRI lesions improved at 3–6 months later [77]. At 1 month post-RT-TMZ, patients have radiographic worsening in about 40–50% and approximately half of these have pseudoprogression [78–80]. Therefore, the incidence of pseudoprogression of all patients treated with RT–TMZ is 20–30%. Interestingly, patients with early pseudoprogression had better survival than patients with no early radiographic progression [78, 79]. In addition, pseudoprogression is more common in patients with methylated MGMT, which may indicate more treatment-induced tumor damage from RT + TMZ [79]. Several imaging modalities such as advanced MRI techniques and positron-emission tomography (PET) may be helpful to distinguish tumor progression from treatment-related effects and may also direct a biopsy to the site of optimal yield. However, prospective studies of correlation between neuroimaging and pathological findings are required. MR spectroscopy (MRS) presents an analysis of the presence and ratio of tissue metabolites such as N-acetylaspartate (NAA), choline, creatine, lipid, and lactate [81]. Elevated choline-to-creatine and/or lactate-to-creatine ratios are usually signatures for tumor metabolites, whereas generalized suppression of all metabolites is consistent with treatment effects. However, MRS cannot accurately determine an area of mixed necrosis and tumor. Diffusion-weighted MRI measures the apparent diffusion coefficient (ADC), which indicates
mobility of extracellular water. Diffusion of water may be greater for necrotic tissues in the treatment-related effects than for recurrent tumor. Therefore, ADC ratios of recurrent tumors are generally lower than those of treated brain tissue [82]. However, corticosteroids such as dexamethasone can affect water diffusion in the peritumoral area, which can pose additional interpretation difficulties [83]. Other MRI techniques such as diffusion tensor imaging and perfusion MRI may also be helpful but require further prospective investigation.

\(^{18}\)F-fluorodeoxyglucose (FDG)-PET is another imaging technique to identify anaplastic transformation of tumor and has been utilized for differentiating tumor recurrence/progression from treatment effects. High uptake of FDG (hypermetabolic or “hot”) is usually consistent with tumor progression. However, false-positive results can occur with accumulation of macrophages as a result of treatment effect or high background activity from adjacent cerebral cortices [84]. Co-registration with MRI and a 3- to 8-h delay in acquisition of PET images may improve sensitivity and specificity [84]. Amino acid tracers such as \(^{11}\)C-methionine may be more sensitive than FDG in distinguishing treatment-related effects from tumor recurrence but additional evaluation in further studies is required.

Most patients with pseudoprogression are asymptomatic, therefore continuing TMZ and re-evaluation at 3 months is recommended. In patients with mild symptoms, corticosteroids may be used in conjunction with TMZ. In patients with severe symptoms or worsening of symptoms despite optimal corticosteroid use, surgery may be indicated.

Most patients with HGA inevitably develop tumor progression. The median time-to-progression after RT–TMZ/TMZ regimen is 6.9 months for GBM patients [41]. There is no standard treatment for recurrent HGA. However, therapeutic options may include repeat resection, focal re-irradiation, salvage chemotherapy, and novel-targeted therapeutics. Unfortunately, most salvage systemic therapies following progression are ineffective with 6-month progression-free survival (PFS-6) rates of 15–16% for GBM and 28–31% for AA [85–87]. Of note, PFS-6 has been demonstrated as an acceptable endpoint in clinical trials for recurrent HGA and also appears to predict OS among newly diagnosed GBM [86–88].

**Surgical Resection**

Repeat resection in recurrent HGA may be considered for diagnostic confirmation, symptomatic relief for mass effect/edema, and cytoreduction [89]. Surgical resection often improves symptoms in recurrent HGA patients with large mass effect and may increase survival in selected patients [90, 91]. However, survival benefit from repeated resection in unselected populations with recurrent HGA has not been evaluated in prospective studies. One retrospective study demonstrated better response to chemotherapy in recurrent HGA patients who had smaller pretreatment tumor volume [92]. In addition, repeat resection may be included in clinical trials using locoregional therapeutics or systemic agents with pharmacodynamic studies in patients with recurrent HGA.
Locoregional Therapy

Most HGAs have local treatment failure. Locoregional therapeutics may represent reasonable options to improve local control of tumor while limiting systemic toxicities [93]. Carmustine wafers have been evaluated in recurrent GBM with a modest increase (8 weeks) in median survival [94]. MGMT methylation may also serve as an independent prognostic factor of survival in GBM patients treated with resection and carmustine wafer implants [95]. Most recurrent GBM patients already failed on TMZ treatment; therefore an attempt to increase sensitivity of tumor to carmustine, which is also an alkylating agent, has been explored. Systemic O6-BG administration was evaluated in a Phase II trial with carmustine wafer implants in patients with recurrent GBM. The survival was improved when compared to carmustine wafer implants alone but treatment-related toxicities including hydrocephalus (9.6%), CSF leak (19.2%), and CNS infections (13.4%) were also increased [96, 97]. In addition to local polymer delivery system, convection-enhanced delivery (CED) is another mode of locoregional delivery that has been developed for HGA treatment. Increased interstitial pressure in glial tumors may limit drug delivery from systemic vasculature and local infusion, particularly in the infiltrative edges of tumor. CED delivers a small volume of therapeutic continuously at positive pressure over time via stereotactically placed catheters [98]. Various therapeutic agents delivered by CED have been evaluated including chemotherapies, gene/virus therapy, and ligand–toxin conjugates. A randomized Phase III study of cintredekin besudotox (IL-13 conjugated with Pseudomonas exotoxin; IL13-PE38QQR, NeoPharm, IL, USA) versus carmustine wafer (PRECISE trial) in patients with recurrent malignant gliomas failed to demonstrate significant difference in survival benefit, which might be partly explained by poor drug distribution and variable expertise of surgeons in catheter placement [99, 100].

Re-irradiation

Most patients with recurrent HGA have undergone a full course of conventional external beam RT. Re-irradiation with conventional RT is not generally recommended due to the lack of clear survival benefit and the high incidence of radiation necrosis [101]. Stereotactic radiotherapy (SRT) is highly focused radiation, which can be administered as a single fraction (stereotactic radiosurgery; SRS) or multiple fractions (fractionated stereotactic radiotherapy; FSRT). SRT is usually suitable for brain lesions up to 3–4 cm in size. In recurrent GBM, several small studies have demonstrated promising activity of SRT with the median survival of 10–12 months after SRS and 7–12 months after FSRT [102–105]. Large prospective studies are required to further evaluate the efficacy and toxicity of SRT without selection bias [106]. Furthermore, SRT is also evaluated in combination with other treatments such as targeted therapies. A recent study of bevacizumab administration followed by FSRT in 20 patients with recurrent GBM demonstrated a promising response rate of 50%, the PFS-6 rate of 65%, and the median OS of 12.5 months [107].
Radiotoxin and radioimmunotherapy are novel local approaches in the treatment of HGA by using radiolabeled toxins and monoclonal antibodies, respectively, to enhance peritumoral radiation delivery. A number of tumor targets and antigens have been identified and led to the synthesis of therapeutic radiotoxin conjugate and radioimmunoconjugates. One of the prominent targets in HGA is tenascin, an extracellular matrix protein commonly expressed in tumors but not in normal brain (Fig. 9.3). Intracavitary administration of $^{131}$I-labeled monoclonal antibody against tenascin ($^{131}$I-m81C6; Neuradiab®️, Bradmer Pharmaceuticals, Canada) was evaluated in a Phase II trial of patients with recurrent HGA. With a median follow-up of 172 weeks, 63 and 59% of patients with GBM and AA tumors, respectively, were alive at 1 year. Median overall survival for patients with GBM and AA tumors was 64 and 99 weeks, respectively [108]. In a Phase II trial for newly diagnosed GBM, $^{131}$I-m81C6 was administered after resection, followed by conventional RT and a year of alkylator-based chemotherapy with the median survival of 79.4 weeks [109]. This therapy was well tolerated, however, 27% developed reversible hematologic toxicity and 15% developed histologically confirmed, treatment-related, mostly reversible, neurologic toxicities [108, 109]. A randomized Phase III study of $^{131}$I-m81C6 in combination with RT–TMZ versus RT–TMZ in newly diagnosed GBM has initiated. Another radioimmunoconjugate in clinical trials, $^{131}$I-TM-601 (TransMolecular, Cambridge, MA, USA), a radiolabeled chlorotoxin targeting tumor and associated vasculature via annexin A2, demonstrated safety and promising antitumor activity following intracavitary administration in a Phase I trial of recurrent HGA [110, 111]. A Phase II trial of $^{131}$I-TM-601 is in progress.

**Salvage Chemotherapy**

In recurrent AA and anaplastic oligoastrocytoma, TMZ was associated with 52% response rate, PFS-6 of 46%, and median survival of 13.6 months [47]. As TMZ has become a standard-of-care treatment for newly diagnosed GBM, the role of TMZ monotherapy in recurrent GBM is decreasing. Prior to routine TMZ use in newly diagnosed GBM, salvage therapy with TMZ (150–200 mg/m$^2$/day × 5 days every 28 days) following progression with RT was associated with a radiographic response rate of 6% and PFS-6 of 21% [48]. In another Phase II trial of TMZ-naïve recurrent GBM patients, TMZ administered at 75 mg/m$^2$/day for 21 consecutive days each 28-day cycle was associated with a 9% overall response rate with a PFS-6 rate of 30% [112]. In addition, TMZ rechallenge may be effective in HGA patients, who are not currently on TMZ but had a prior response to TMZ [113, 114]. In GBM patients who fail on RT–TMZ/TMZ, alternative TMZ dosing regimens such as dose-dense or metronomic fashions that can deplete MGMT level may have antitumor activity [115]. Alternative dosing regimens include 10/28 days (days 1–5 and days 15–19 every 28 days), 14/28 days (7 days on/7 days off), and 21/28 days (21 days on/7 days off) with relative dose intensities that are 1.5- to 2.1-fold higher than standard 5-day TMZ (5/28 days) dosing [116]. Alternative TMZ regimens were associated
High-Grade Astrocytomas

with PFS-6 rates of 30–48% for recurrent GBM and 43–56% for recurrent MG [116]. TMZ can be administered in a low-dose daily (metronomic) fashion as a “rescue” approach in prior TMZ failure [117]. In recurrent GBM, metronomic TMZ was associated with PFS-6 rates of 27.3% in patients who recurred during months 3–6 of adjuvant TMZ (group 1), 7.4% in patients who recurred while on adjuvant TMZ for more than 6 months (group 2), and 35.7% in patients who had completed 6 months of TMZ and were no longer receiving TMZ (group 3) [117]. The efficacy of TMZ for group 1 may reflect the potential inclusion of patients with pseudoprogression following RT–TMZ and that for group 3 supports the antiglioma activity of TMZ rechallenge in prior TMZ responders. Metronomic TMZ was associated with PFS-6 of 42% in recurrent anaplastic gliomas patients who failed on standard TMZ regimen. In addition, TMZ has been evaluated with other chemotherapies such as procarbazine, BCNU, irinotecan, etoposide, and topotecan with modest combinatorial benefit [118–122].

Nitrosoureas have long been used for treatment in HGA with modest activity in recurrent GBM. The PFS-6 rates were 20% for nimustine [123], 19% for lomustine [124], and 21% for fotemustine [125].

Irinotecan (Camptosar®, CPT-11; Pfizer, NY, USA) is a camptothecin derivative that acts as a prodrug that undergoes hydrolysis to an active metabolite SN-38, a potent topoisomerase-I inhibitor [126]. Irinotecan displayed robust antitumor activity against human glioma xenografts [127]. Although it demonstrated encouraging clinical activity in an early clinical trial [128], two subsequent trials have not shown a survival benefit in patients with recurrent malignant glioma [129, 130]. Combinations of irinotecan with other chemotherapies or targeted agents have been explored.

Other chemotherapeutic agents such as gemcitabine [131] and ifosfamide, carboplatin, and etoposide (ICE) have been investigated in HGA. Gemcitabine can function as a radiosensitizer in GBM [131]. A small Phase II study of gemcitabine plus radiotherapy in newly diagnosed GBM demonstrated feasibility and comparable efficacy with TMZ [132]. In a Japanese Phase II study of ICE in recurrent alkylator-refractory GBM, the radiographic response rate was 25% and the PFS-6 was 35% [133]. The regimen was tolerated with alopecia as a main side effect. High-dose chemotherapy with stem cell rescue [134] and intraarterial chemotherapy [135] have demonstrated activity in selected patients with recurrent HGA. However, these modalities are not widely available and prospective randomized trials are required to confirm efficacy and further evaluate toxicity.

Novel Treatment Approaches

Molecularly Targeted Therapy

During the past decade, treatment paradigm for cancers has shifted from traditional cytotoxic agents to molecularly targeted therapies with the aims to increase tumor
specificity and decrease toxicities. Selection of targeted agents in HGA is based on underlying frequent genetic and molecular abnormalities that are important in glioma initiation and maintenance. In addition, such agents should readily cross the blood–brain barrier. Recent advances in genomic studies have elucidated several potential new targets, which lead to development of novel therapeutics (Figs. 9.2 and 9.3). Antiglioma efficacy in preclinical glioma models and/or promising activity with adequate safety and tolerability in other cancers is usually required before clinical trial evaluation of each targeted agent in HGA. Molecularly targeted therapies encompass growth factor signal transduction pathway inhibitors, anti-angiogenic agents, epigenetic modulators, and proteasome inhibitors. The two most common modes of targeted therapies include small molecule kinase inhibitors and monoclonal antibodies. Monoclonal antibodies are multivalent proteins engineered to have high selectivity and affinity to epitopes of target antigens. In brain tumors, most monoclonal antibodies are delivered locally to tumor or resection cavity because systemic administration may not achieve adequate delivery owing to restriction by the blood–brain barrier. However, monoclonal antibodies that can function on the abluminal side of blood vessels (such as a neutralizing VEGF antibody, bevacizumab) without a need to traverse the blood–brain barrier may be effective in the treatment of brain tumors. Low molecular weight kinase inhibitors are frequently adenosine triphosphate (ATP) mimetics that display affinity for the ATP binding site in the kinase domains of growth factor receptors and intracellular signaling elements. The specific targeting of single kinases has proven challenging as the ATP site is highly conserved in kinase genes. Because of their small size, these low molecular weight inhibitors might have advantage for central nervous system (CNS) delivery. However, several other factors such as physiological variables, polarity of drugs, and active efflux transporter (such as P-glycoprotein and breast cancer resistance protein (BCRP); also known as ABCG2) at the blood–brain, the blood–cerebrospinal fluid (CSF), or the blood–tumor barriers might limit CNS and subsequent tumor delivery. Some tumor cell subpopulations, for instance, cancer stem cells, may also express these efflux transporter proteins, thus further limiting efficacy of targeted agents [136].

Most receptors for growth factor pathways (such as EGF, PDGF, vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and insulin-like growth factor (IGF)) are associated with tyrosine kinases and they therefore activate common downstream effectors in growth signaling pathways. Overexpression or mutations of receptors and intracellular downstream effectors have been identified in HGA, leading to constitutive activation of signaling pathways, resulting in uncontrolled cellular proliferation, survival, invasion, and secretion of angiogenic factors (Fig. 9.3).

First-generation kinase inhibitors were designed to be selective to single targets. Among most evaluated are kinase inhibitors of EGFR, PDGFR, or mTOR [137]. These single-targeted kinase inhibitors produced radiographic response rate of 0–15% with no or only modest survival benefit as measured by PFS-6 in unselected GBM patient populations (Table 9.1). Of note, PFS-6 rates associated with TMZ in first recurrent HGA (21% for GBM and 46% for AG) were used as historical
### Table 9.1 Selected Phase II and III trials of molecularly targeted agents in HGA

<table>
<thead>
<tr>
<th>Targets</th>
<th>Agents</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Gefitinib</td>
<td>Recurrent MG: no radiographic response, PFS-6: 14–17%</td>
<td>[138,139]</td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td>Recurrent AG: PFS-6: 27%</td>
<td>[140,141]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent GBM: 0–4% PR, PFS-6: 3–11.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-progressive GBM: 1-year survival: 57%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erlotinib plus carboplatin</td>
<td>Recurrent GBM: 2% PR, PFS-6: 14%</td>
<td>[142]</td>
</tr>
<tr>
<td></td>
<td>Erlotinib plus RT–TMZ</td>
<td>Newly diagnosed GBM: median OS: 15.3–19.3 months</td>
<td>[143–145]</td>
</tr>
<tr>
<td></td>
<td>Cetuximab</td>
<td>Recurrent HGA: 5% PR, PFS-6: 9%</td>
<td>[146]</td>
</tr>
<tr>
<td>Farnesyltransferase</td>
<td>Tipifarnib</td>
<td>Recurrent GBM: PFS-6: 12%</td>
<td>[147]</td>
</tr>
<tr>
<td>PDGFR</td>
<td>Imatinib mesylate (NABTC)</td>
<td>Recurrent GBM: PFS-6: 3%</td>
<td>[148]</td>
</tr>
<tr>
<td></td>
<td>Imatinib mesylate (EORTC)</td>
<td>Recurrent GBM: PFS-6: 16%</td>
<td>[149]</td>
</tr>
<tr>
<td></td>
<td>Imatinib mesylate plus hydroxyurea (Duke)</td>
<td>Recurrent grade 2–3 astrocytoma: PFS-6: 9%</td>
<td>[150]</td>
</tr>
<tr>
<td></td>
<td>Imatinib mesylate plus hydroxyurea (multicentre)</td>
<td>Recurrent GBM: 3.4% PR, PFS-6: 10.6%</td>
<td>[152]</td>
</tr>
<tr>
<td></td>
<td>Rilotumumab</td>
<td>Recurrent MG: ongoing</td>
<td>–</td>
</tr>
<tr>
<td>mTOR</td>
<td>Temsirolimus</td>
<td>Recurrent MG: 6-month PFS: 2.5–7.8%</td>
<td>[153,154]</td>
</tr>
<tr>
<td>PKC-β</td>
<td>Enzastaurin (NCI)</td>
<td>Recurrent GBM: PFS-6: 7%</td>
<td>[155]</td>
</tr>
<tr>
<td></td>
<td>Enzastaurin vs. lomustine</td>
<td>Recurrent GBM: no benefit in interim analysis</td>
<td>[124]</td>
</tr>
<tr>
<td></td>
<td>(multicentre Phase III)</td>
<td>3% PR, PFS-6, median OS 6.6 months</td>
<td></td>
</tr>
<tr>
<td>Integrins</td>
<td>Cilengitide</td>
<td>Recurrent GBM: PFS-6: 15%, median OS 9.9 months</td>
<td>[156]</td>
</tr>
<tr>
<td>HDAC</td>
<td>Vorinostat</td>
<td>Recurrent GBM: PFS-6: 17%; median OS 5.7 months</td>
<td>[157]</td>
</tr>
</tbody>
</table>

**Abbreviations:** AA, anaplastic astrocytoma; AG, anaplastic gliomas; EGFR, epidermal growth factor receptor; EORTC, European Organization for Research and Treatment of Cancer; GBM, glioblastoma multiforme; HDAC, histone deacetylase; HGF, hepatocyte growth factor; mTOR, mammalian target of rapamycin; NABTC, North American Brain Tumor Consortium; OS, overall survival; PDGFR, platelet-derived growth factor receptor (PDGFR); PFS-6, progression-free survival at 6 months; PKC, protein kinase C; PR, partial radiographic response; RT, radiotherapy; TMZ, temozolomide
comparators to define whether novel agents have meaningful antiglioma activity in these studies.

The failures of first-generation kinase inhibitors may result from genetic heterogeneity and the existence of multiple parallel or compensatory pathways. Recent evidence demonstrated concomitant activation of multiple tyrosine kinases in glioma cell lines, xenografts, and primary glial tumors [158]. Furthermore, the redundancy and crosstalk between pathways allow for compensatory effects by alternative pathways when one pathway is targeted, reducing the efficacy of targeted monotherapies. Unlike the success of imatinib mesylate in chronic myelogenous leukemia, which has a single genetic abnormality that is “druggable” by imatinib mesylate [159], treatment of HGA with agents disrupting only single targets may not be sufficient to eradicate the tumor [160]. Therefore, simultaneous disruption of multiple targets in multiple pathways may be more effective. In addition, as seen in other solid cancers, HGAs consist of complex tissues with tumor cells and the microenvironment such as endothelial cells, pericytes, bone marrow-derived and immune cells (Fig. 9.3). Thus targeting cellular elements that are pivotal in both tumor cell biology and microenvironment-related tumor growth and angiogenesis may improve treatment efficacy. Two strategies to simultaneously disrupt several protein kinases essential for cancer maintenance are by using multtargeted kinase inhibitors (MTKIs) or combinations of several single-targeted kinase inhibitors. MTKIs, also termed “dirty,” “promiscuous,” or “multiselective” inhibitors, may achieve a higher therapeutic index than single-targeted kinase inhibitors or traditional cytotoxics. While MTKIs may be more resilient to drug resistance, the crossreactivity of MTKIs also poses a safety concern. Several MTKIs have undergone or are undergoing preclinical and clinical evaluation in HGA [161]. Most MTKIs target both tumor and associated endothelial cells (with activity against VEGFRs). MTKIs are generally safe and well tolerated. Common adverse events of most MTKIs include skin reaction, gastrointestinal toxicity, and hypertension (linked to VEGFR inhibition) that are usually manageable. Combination of single-targeted inhibitors is another strategy to simultaneously disrupt several targets. It may allow the exact titration of each agent to achieve optimal inhibition of its respective target. However, concomitant administration of two agents may result in drug–drug interaction and additive toxicities. For example, gefitinib or erlotinib plus rapamycin or its analogues are associated with higher toxicities than either agent alone [162]. Recent parallel Phase I/II studies failed to demonstrate efficacy of erlotinib plus sorafenib, erlotinib plus temsirolimus, or sorafenib plus temsirolimus in recurrent GBM [163–165]. Novel clinical trial designs such as factorial or adaptive randomization may be able to evaluate combination of targeted agents more efficiently and cost-effectively [166].

Molecularly targeted agents can be combined with radiation therapy or traditional cytotoxic chemotherapies. Carefully designing clinical trials of such multimodality treatments is important. The sequencing and timing of drug administration in relation to radiation treatment is crucial since there is differential efficacy in an animal study [167].
Identification of biomarkers of response or resistance is one of the priorities in neuro-oncology research. Selection of patients who are likely to respond to certain molecular-targeted agents may be more rational and cost-effective. Retrospective studies of archival tumor samples from GBM patients treated with EGFR inhibitors, erlotinib, or gefitinib, demonstrated expression of EGFR-vIII and wild-type PTEN in one study and high expression of activated AKT in another study as molecular determinants of response [168, 169]. However, more recent studies have failed to confirm the predictive value of these biomarkers [139, 140, 143]. Ideally, patients should be treated with a given drug when its target is present in the tumor. Pharmacodynamic studies of tumors in treated patients should be performed to validate target modulation, determine optimal biological dose, and reveal the mechanisms of drug resistance. A recent Phase I study exploited a neoadjuvant trial design by administering rapamycin, an mTOR inhibitor, in patients with PTEN-deficient GBM followed by surgical resection/biopsy [170]. This surgically incorporated trial was able to confirm and monitor target inhibition and also demonstrate AKT activation (due to loss of negative feedback in the PI3K pathway) as a mechanism of resistance to rapamycin in these patients [170]. As repeated tumor biopsies may not be feasible in brain tumor patients, identification of biomarkers using alternative approaches such as imaging or circulating cells/proteins should be vigorously explored.

**Anti-angiogenic Therapy**

Among molecular-targeted therapies, anti-angiogenic drugs represent one of the most promising therapeutic agents for HGA. Angiogenesis, the formation of neovascularity from preexisting blood vessels, is a key pathologic characteristic for GBM. Therefore, targeting angiogenesis may represent a promising therapeutic strategy for HGA. Angiogenesis is tightly regulated by a balance of proangiogenic and anti-angiogenic factors. Among proangiogenic factors, vascular endothelial growth factor (VEGF) is the most studied and prominent target for cancer therapeutic development. The VEGF family consists of five members including VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placenta growth factor (PlGF). Three receptors associated with tyrosine kinase activity include VEGFR-1 (Flt-1), VEGFR-2 (KDR/Flk-1), and VEGFR-3. VEGFR-2 is the major mediator of VEGF-A, also known as vascular permeability factor (VPF), for regulating endothelial cell behaviors (proliferation, survival, and migration/invasion) and vascular permeability.

Bevacizumab (Avastin™; Genentech-Roche, South San Francisco, CA, USA), a monoclonal antibody that neutralizes VEGF, has been approved for use in conjunction with chemotherapies for metastatic colorectal cancer, advanced/metastatic non-small cell lung cancer, metastatic breast cancer, and renal cell carcinoma. Bevacizumab demonstrated antiglioma activity with temozolomide in an orthotopic model of human GBM xenografts [171]. The initial reluctance to evaluate bevacizumab in GBM was due to the apprehension of inducing intracerebral hemorrhage.
In 2005, Stark-Vance reported the encouraging efficacy of bevacizumab in combination with a topoisomerase-I inhibitor, irinotecan (Camptosar; CPT-11, Pfizer, NY, USA) in a series of patients with recurrent GBM [172], which was confirmed in a Phase II trial at Duke University (Table 9.2) [173]. This combination demonstrated a remarkable radiographic response with promising survival benefit. The 2-year overall survival rate was 15% for GBM patients [174]. Severe adverse events were infrequent with two CNS hemorrhages (occurred in the ninth and the tenth cycle of therapy), eight venous thromboemboli, one episode of thrombotic thrombocytopenic purpura, and one ischemic stroke. Another Phase II study conducted at the National Cancer Institute evaluated the efficacy of bevacizumab monotherapy (10 mg/kg every 2 weeks) in 48 patients with recurrent GBM [175]. Upon progression, 19 patients were treated with bevacizumab plus irinotecan. The PFS-6 was 29% with median overall survival of 31 weeks. Radiographic response (Fig. 9.5) rates were 35% by Macdonald criteria and 71% by modified Levin criteria [175]. Of 19 patients treated with bevacizumab plus irinotecan at progression, there were no objective radiographic responses, and most patients experienced progression by 8 weeks with a median PFS of 30 days. Other independent clinical studies have confirmed the promising efficacy of bevacizumab-based therapies in recurrent GBM patients [176–181]. Subsequently, a multicentered, randomized, Phase II study of bevacizumab versus bevacizumab plus irinotecan was evaluated in patients with recurrent GBM [182]. In this non-comparative study, 167 GBM patients at first or second relapse were randomized to receive either 10 mg/kg of bevacizumab (n = 85 patients; arm A) or bevacizumab plus irinotecan (n = 82; arm B). Irinotecan was administered at 125 mg/m^2 for patients not on CYP3A4 enzyme-inducing antiepileptic drugs (EIAEDs) or 340 mg/m^2 for patients on EIAEDs every 2 weeks. Patients in arm A were allowed to receive bevacizumab plus irinotecan as a salvage regimen if they experienced progression. The radiographic response rates were 28% in arm A and 38% in arm B and the PFS-6 rates were 43% in arm A and 50% in arm B. Most patients reduced corticosteroid use by 50% or more. Despite the remarkable response rates, PFS-6 and symptomatic benefits, the overall survival rates were less impressive with 9.2 months for bevacizumab monotherapy and 8.7 months for bevacizumab plus irinotecan. Serious adverse events were found in 26% in arm A and 43% in arm B. Adverse events leading to the discontinuation of bevacizumab were observed in 5% of those treated with bevacizumab and in 18% of those treated with bevacizumab and irinotecan. There were two CNS hemorrhages (grade 3 in one patient). Other grade 3 or higher adverse events included gastrointestinal perforation (n = 1), arterial thromboses (n = 3), venous thromboembolism (n = 10), posterior reversible encephalopathy syndrome (n = 1), proteinuria (n = 1), wound healing complications (n = 3), and infection (n = 19). Based on results from these studies, the US FDA granted accelerated approval for bevacizumab in progressive GBM in 2009. However, bevacizumab was not approved by the EMEA for the similar indication. Several questions regarding bevacizumab in GBM remain including optimal dose and timing, assessment of radiographic response, actual survival benefit, and optimal partners for combinatorial use [183, 184]. Phase III trials of bevacizumab for both recurrent and newly diagnosed GBM are in progress. Also,
Table 9.2  Selected Phase II trials of anti-angiogenic agents in HGA

<table>
<thead>
<tr>
<th>Targets</th>
<th>Agents</th>
<th>Phase</th>
<th>N</th>
<th>Results</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF</td>
<td>Bevacizumab</td>
<td>2</td>
<td>48</td>
<td>Recurrent GBM: PFS-6: 29%, RR: 35%, OS 31 weeks</td>
<td>[175]</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab plus irinotecan</td>
<td>2</td>
<td>35</td>
<td>Recurrent GBM: PFS-6: 46%, RR: 57%, OS 42 weeks</td>
<td>[173]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>33</td>
<td>Recurrent AG: PFS-6: 55%, RR: 61%, OS 65 weeks</td>
<td>[185]</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>2</td>
<td>85</td>
<td>Recurrent GBM: PFS-6: 43%, RR: 28%, OS 37 weeks</td>
<td>[182]</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab plus irinotecan</td>
<td>82</td>
<td></td>
<td>Recurrent GBM: PFS-6: 50%, RR: 38%, OS 35 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bevacizumab plus etoposide</td>
<td>2</td>
<td>27</td>
<td>Recurrent GBM: PFS-6: 44%, RR: 23%, OS 46 weeks</td>
<td>[186]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>Recurrent AG: PFS-6: 41%, RR: 24%, OS 63 weeks</td>
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<tr>
<td></td>
<td>Bevacizumab plus erlotinib</td>
<td>2</td>
<td>25</td>
<td>Recurrent GBM: PFS-6: 29%, RR: 50%, OS 45 weeks</td>
<td>[187]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>Recurrent AG: PFS-6: 44%, RR: 31%, OS 71 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bevacizumab and stereotactic</td>
<td>2</td>
<td>20</td>
<td>Recurrent GBM: PFS-6: 65%, RR: 50%, OS 12.5 months</td>
<td>[107]</td>
</tr>
<tr>
<td></td>
<td>radiotherapy</td>
<td></td>
<td></td>
<td>Recurrent GBM: PFS-6: 30%</td>
<td></td>
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<tr>
<td></td>
<td>Aflibercept</td>
<td>2</td>
<td>48</td>
<td>Recurrent GBM: PFS-6: 30%</td>
<td>[188]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrent AG: PFS-6: 50%</td>
<td></td>
</tr>
<tr>
<td>VEGFR</td>
<td>Cediranib</td>
<td>2</td>
<td>31</td>
<td>Recurrent GBM: 56% PR, PFS-6: 26%</td>
<td>[189]</td>
</tr>
<tr>
<td></td>
<td>Pazopanib</td>
<td>2</td>
<td>35</td>
<td>Recurrent GBM: 6% PR, PFS-6: 3%</td>
<td>[190]</td>
</tr>
<tr>
<td></td>
<td>XL-184 (VEGFR, MET, RET)</td>
<td>2</td>
<td>31</td>
<td>Recurrent GBM: 17% PR, PFS-6: 21%</td>
<td>[191]</td>
</tr>
<tr>
<td>Multiple kinases</td>
<td>Sunitinib (VEGFR, PDGFR, c-Kit,</td>
<td>2</td>
<td>21</td>
<td>Recurrent GBM: median TTP 1.6 and OS 3.8 months</td>
<td>[192]</td>
</tr>
<tr>
<td>including</td>
<td>FLT-3)</td>
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</table>

**Abbreviations:** AG, anaplastic gliomas; FLT-3, FMS-like tyrosine kinase-3; GBM, glioblastoma multiforme; OS, overall survival; PDGFR, platelet-derived growth factor receptor (PDGFR); PFS-6, progression-free survival at 6 months; RR, radiographic response; TTP, time-to-progression; VEGF, vascular endothelial growth factor.
Fig. 9.5 Radiographic response to bevacizumab in GBM. Pretreatment MRI demonstrates (a) right frontal T1-enhancing lesion associated with (c) hyperintense FLAIR abnormality. After 6 months of bevacizumab treatment (10 mg/kg every 2 weeks), MRI reveals significant decrease in contrast enhancement (b). Post-bevacizumab FLAIR sequences (d) demonstrate typical bilateral radiation-induced leukoencephalopathy changes in addition to marked improvement in tumor-associated edema.

several Phase I/II clinical trials of bevacizumab in combination with other treatment modalities such as chemotherapy, radiotherapy or other targeted agents in both recurrent and newly diagnosed GBM are ongoing. Bevacizumab has also been evaluated as either monotherapy or in combination with chemotherapies in recurrent AG. In these studies, radiographic response rates were 24–64% and PFS-6 rates were 41–60% [185–187, 193].

Another agent that blocks VEGF by disrupting ligand–receptor binding is a potent soluble decoy receptor of VEGF, aflibercept (VEGF-trap; Sanofi-Aventis and Regeneron, Tarrytown, NY, USA). In a Phase II study of 48 patients with recurrent malignant glioma (GBM, \(n = 32\); AG, \(n = 16\)), aflibercept treatment was associated with radiographic response rates (including stable disease) of 30% for GBM and 50% for AGs [188]. The main grade 3 adverse events included fatigue, hypertension, hand–foot syndrome, lymphopenia, thrombosis, and proteinuria. One CNS ischemia and one grade 4 systemic hemorrhage were reported.
Cediranib (Recentin™, AZD2171; AstraZeneca, Wilmington, DE, USA) is an orally available pan-VEGFR inhibitor with additional activity against PDGFR and c-Kit [189]. A Phase II study of cediranib has demonstrated anti-angiogenic efficacy in 31 patients with recurrent GBM [189]. Common adverse events include hypertension, diarrhea, and fatigue. The radiographic response rate was 56%, while the PFS-6 rate was 26%. All patients could reduce or discontinue corticosteroids during the study. Prolongation of survival associated with cediranib may result from decrease of brain edema despite persistent tumor growth as demonstrated in a mouse model of orthotopic GBM treated with this agent [194]. Based on promising activity of cediranib, an international, multicentered, randomized Phase III trial of cediranib versus an alkylating agent lomustine versus cediranib plus lomustine in 300 patients with recurrent GBM was recently completed and results are expected to be reported soon. Another pan-VEGFR inhibitor pazopanib (Votrient™, GW786034; GlaxoSmithKline, NC, USA) demonstrated 6% radiographic response rate with PFS-6 of only 3% [190]. There are other MTKIs with activity against VEGFR undergoing preclinical and clinical evaluation (Table 9.2). Among these agents, XL-184 (BMS-907351; inhibitor to MET, RET, and VEGFR-2) is planned for Phase III evaluation in recurrent GBM after promising efficacy has been observed in a Phase II study [191].

Despite an initial response to anti-angiogenic agents, most HGA patients eventually develop disease progression. Unfortunately, patients who progressed on bevacizumab rarely responded to bevacizumab plus other chemotherapies. The median progression-free survival after adding a second chemotherapy with bevacizumab was only 5–6 weeks [195]. Similarly, salvage bevacizumab in patients who failed VEGFR inhibitors (cediranib, sorafenib, pazopanib, or sunitinib) was associated with median time-to-progression of 8 weeks and PFS-6 of 11% [196].

Predictive biomarkers, which include circulating cells and proteins [189], advanced neuro-imaging [197], and tumor angiogenic/genomic profiling [198, 199], may identify a subset of patients who will likely respond to certain anti-angiogenic drugs, while several mechanisms of failure including evasive and intrinsic resistances have been elucidated [200]. Two recent preclinical studies demonstrated that potent anti-angiogenic agents may increase tumor invasion and metastasis [201, 202]. This phenomenon of increased infiltrative growth appears to occur in many GBM patients who develop non-enhancing disease progression with bevacizumab therapy [176]. Therefore, strategies to combine agents targeting invasion with anti-angiogenic therapy may improve disease control and survival for malignant glioma patients.

**Other Molecular Targets**

Integrins are cell adhesion molecules important in tumor cell migration and angiogenesis [203]. Cilengitide (EMD121974; EMD Serono Pharmaceuticals, Rockland, MD, USA), an intravenous inhibitor of $\alpha_\text{v}\beta_3$ and $\alpha_\text{v}\beta_5$ integrins, demonstrated preclinical efficacy as monotherapy or in combination with radiation against malignant glioma [204]. Cilengitide monotherapy was well tolerated in recurrent GBM.
patients with PFS-6 rate of 15% in a Phase II study [156]. Single-arm Phase II studies in newly diagnosed GBM patients have also shown encouraging activity [205, 206]. A randomized Phase III (CENTRIC) study of cilengitide plus RT–TMZ/TMZ versus standard RT–TMZ/TMZ in newly diagnosed GBM with methylated MGMT promoter is in progress.

Autocrine glutamate activation can promote glioma proliferation and migration [207]. Talampanel is an oral glutamate-blocking agent targeting the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. In 72 newly diagnosed GBM patients, the addition of talampanel to standard RT–TMZ resulted in a median OS of 20.3 months and a 2-year survival rate of 41.7% [208]. However, talampanel failed to demonstrate efficacy in recurrent HGA with the PFS-6 rates of 4.6 and 0% for GBM and AG, respectively [209].

Histone deacetylase (HDAC) inhibitors can induce cell cycle arrest and apoptosis in cancer cells [210]. A Phase II study of vorinostat in recurrent GBM demonstrated safety and tolerability but modest antiglioma activity. Pharmacodynamic studies validated target inhibition by vorinostat with increased acetylation of histones in post-vorinostat tumor samples compared to pretreatment [157].

The ubiquitin–proteasome system represents a final common path of multiple signaling pathways, which are important in regulating cell proliferation and apoptosis [211]. Disruption of the temporal degradation of these regulatory molecules by proteasome inhibitors can induce cell growth arrest and apoptosis in preclinical glioma models [212]. Phase I/II studies of bortezomib in newly diagnosed and recurrent GBM are ongoing [213].

Targeting cancer stem cells (CSCs) may represent a novel therapeutic approach as these cell subpopulations are critical in therapeutic resistance to chemotherapy and radiation. Potential stem cell targets, including NOTCH, STAT3, CHK-1/2, HIFs, and BMPs, were reviewed in an earlier chapter [26]. Ideal CSC therapeutic targets should be uniquely presented on cancer but not normal neural stem cells, as these two stem cell populations may share some common regulatory molecules and stem cell-mediated pathways. Clinical trials of CSC-specific inhibitors in HGA seem warranted, but a careful trial design with appropriate endpoints and pharmacodynamic studies is required.

Other New Treatment Approaches

During the past decades, several cutting-edge treatment approaches for HGA have been developed. These experimental therapies, which include gene/virus therapy [214], cell-based and stem cell therapy [215], immunotherapy [216, 217], alternating electric fields (TTFIELDS; NovoCure, Israel) [218] have demonstrated promise in preclinical and early clinical studies. For example, preclinical studies have demonstrated efficacy of EGFR-vIII peptide vaccine in syngeneic murine models [217]. A multi-institutional Phase II trial of CDX-110 (EGFR-VIII-KLH; Pfizer and Celldex Therapeutics) in combination with RT–TMZ in newly diagnosed GBM patients with EGFR-vIII mutation is ongoing.
Conclusions

Treatment of HGA has remained one of the most challenging fields in clinical oncology. Standard-of-care treatments include resection, radiation therapy, and adjuvant chemotherapy. TMZ has become a standard treatment for newly diagnosed GBM by extending overall survival and offering a durable response in selected patients with a 5-year survival rate of 10%. Several strategies have been evaluated to improve the efficacy of temozolomide, as we understand more about mechanisms of response and resistance. Tumor $\text{MGMT}$ methylation status represents a potential correlative biomarker for temozolomide response. However, the neuro-oncology community eagerly awaits a prospective validation of MGMT status as a TMZ-response predictor in the RTOG-0525 trial. The fundamental challenges of limited therapeutic delivery and molecular/genetic heterogeneity of tumors need to be overcome in order to improve patient outcome. Locoregional therapeutics, molecularly targeted agents, and immunotherapy represent new promising approaches for HGA treatment. Most targeted agents of growth and survival pathways, when administered as monotherapies, have failed to achieve a survival benefit in unselected glioma patient populations. Targeting multiple signaling pathways by multitargeted kinase inhibitors or combinations of single-targeted kinase inhibitors may increase treatment efficacy. Several other strategies have been developed to improve effectiveness of targeted therapeutics, which may include genomic or network analyses to identify new targets and promising combinations, more predictive preclinical models for drug testing, improved therapeutic delivery systems, pharmacokinetic, and pharmacodynamic or biomarker studies and novel clinical trial designs and endpoints. Identification of correlative biomarkers will eventually lead to rational “individualized” targeted therapy based on molecular or genetic signatures of tumors from each patient [219]. Identification of CSCs and their therapeutic implications in GBM has generated a paradigm shift in neuro-oncology research. As the molecular and genetic abnormalities of CSCs are rigorously investigated, therapies against CSC-specific targets will be simultaneously developed.

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Chapter 10
Anaplastic Oligodendrogliomas and Mixed Gliomas

Jacoline E.C. Bromberg and Martin J. van den Bent

Keywords Anaplastic oligodendroglioma · Anaplastic oligoastrocytoma · 1p/19q co-deletion · IDH1 · Temozolomide · PCV

Introduction

Until some 15 years ago, the diagnosis of an anaplastic oligodendroglioma (AOD) or anaplastic oligoastrocytoma (AOA) was merely a pathological entity. The only clinically relevant meaning of this histological diagnosis was the observation that in general the prognosis of OD was better than that of astrocytic tumors of similar grade. This changed with the recognition of the marked sensitivity of these tumors to procarbazine, lomustine, and vincristine (PCV) chemotherapy [1, 2]. A major step forward was the identification of the combined loss of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q) as the typical genetic lesions of OD, followed by the recognition that in particular these 1p/19q co-deleted tumors have an excellent response to chemotherapy [3–5]. It is now clear that AOD and AOA with this combined loss of 1p/19q do not only have a better response to chemotherapy, but they also have a more indolent clinical behavior and a longer lasting response to radiotherapy (RT). These observations have led to the current tendency to consider AOD and AOA with 1p/19q loss as a separate biological entity, at least within clinical trials [5, 6].

The histological criteria for distinguishing ODs from astrocytomas are subjective, prone to interobserver variability. The recognition in the 1990s of the sensitivity to chemotherapy of AOD and AOA resulted in a widening of the histological criteria for OD, with emphasis on other histological features, such as microgemistocytes, gliofibrillary oligodendrocytes, and protoplasmic astrocytes [7]. The presence of these features was also considered to suggest the tumor to be of oligodendrogial...
origin. These changes in criteria for OD lead to an increase of oligodendroglial tumors from about 5% of all glial tumors to about 20% [7]. With the recognition that combined 1p/19q loss correlates with a favorable clinical outcome, and the finding that oligodendrogliomas with 1p/19q co-deletion usually have classical oligodendroglial morphology, the pendulum is swinging back again and pathologists are today less inclined to make the diagnosis of OD in the absence of typical OD features. However, it would be erroneous to consider only those ODs with 1p/19q loss as true ODs. Despite ongoing attempts to classify oligodendroglial tumors and grade III glial tumors according to their genetics, the new WHO classification continues to classify these tumors according to their histological appearance.

**Incidence, Clinical Presentation, Localization**

Oligodendroglioma and mixed oligoastrocytoma constitute 5–20% of all glial tumors. The anaplastic tumors are predominantly tumors of adulthood, with a peak incidence between the fourth and sixth decades of life. Most ODs arise in the white matter of cerebral hemispheres, predominantly in the frontal lobes. They can, however, arise throughout the CNS, including infratentorial sites and the spinal cord. Similar to other gliomas, AOD and AOA tend to remain localized to the CNS. Extra-CNS metastases (especially bone metastases) have been described but this is very rare and typically occurs in the occasional patient at later stages of the disease. Leptomeningeal spread is not rare, but this does usually not develop until the time of recurrence.

The presenting signs and symptoms of all gliomas are non-specific and depend on the localization and progression of the tumor. Patients may present with seizures, cognitive deficits, or focal deficits; patients with anaplastic oligodendroglial tumor (AOT) often develop focal deficits, increased intracranial pressure, or cognitive deficits early in the course of their disease.

**Pathology and Genetics**

The finding that the majority of oligodendrogliomas are characterized by combined loss of 1p/19q and that this deletion defines a specific subgroup of OD has significantly altered the approach toward these tumors. Anaplastic oligoastrocytoma (AOA) is often lumped together with AOD, and in this chapter these two entities combined will be referred to as AOT. Table 10.1 summarizes the differences between tumors with and without combined 1p1/19q loss.

**Histology**

Like all diffuse gliomas, AOT diffusely infiltrates brain tissue but, in contrast to astrocytoma, areas of remarkable sharp borders with surrounding brain tissue
Anaplastic Oligodendrogliomas and Mixed Gliomas

Table 10.1 Clinical, radiological, and genetic features of anaplastic oligodendroglial tumors with and without 1p/19q co-deletion

<table>
<thead>
<tr>
<th></th>
<th>1p/19q loss</th>
<th>No 1p/19q loss</th>
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<tbody>
<tr>
<td>Histological features</td>
<td>Classical oligodendrogial morphology</td>
<td>Presence of astrocytic elements</td>
</tr>
<tr>
<td>Localization</td>
<td>Frontal, parietal, occipital</td>
<td>Temporal, deep basal ganglia, diencephalon</td>
</tr>
<tr>
<td>MRI features</td>
<td>More indistinct borders and mixed signal intensity on T1-weighted and T2-weighted images</td>
<td>Homogeneous T1-signal and T2-signal intensities, distinct borders</td>
</tr>
<tr>
<td>Behavior</td>
<td>Often present with indolent tumors and seizures only</td>
<td>More rapid clinical progression</td>
</tr>
<tr>
<td>Enhancement on MRI imaging</td>
<td>Diffuse, patchy</td>
<td>Ring enhancement, necrosis</td>
</tr>
<tr>
<td>Genetic alterations</td>
<td>p16 deletions (in anaplastic tumors), frequent IDH1 mutations</td>
<td>p53 mutations, EGFR amplification, 10 and 10q loss, rarely IDH1 mutations</td>
</tr>
<tr>
<td>Responsiveness to chemotherapy</td>
<td>From 80 to 100% of tumors respond, with relatively long duration of response</td>
<td>Less frequent objective response rate and of shorter duration</td>
</tr>
<tr>
<td>Median survival</td>
<td>More than 6–7 years</td>
<td>Median 2–3 years</td>
</tr>
</tbody>
</table>

can often be found. The 2007 WHO definition of oligodendroglioma is “a well-differentiated, diffusely infiltrating tumor of adults, typically located in the cerebral hemispheres and composed predominantly of cells morphologically resembling oligodendroglia” [8]. The WHO definition for AOD is, “An oligodendroglioma with focal or diffuse histological features of malignancy and a less favorable prognosis.” Histologically, low-grade ODs are characterized by uniformly round to oval cells with round nuclei and bland chromatin. The cell density is usually low to moderate. The morphology of these cells is often referred to as having a “fried egg appearance” because of a perinuclear halo. A delicate network of branching blood vessels (chicken wire pattern) is also indicative of low-grade OD. Over time, oligodendrogliomas gradually evolve from low-grade, “well-differentiated” tumors into high-grade gliomas with anaplastic features (high cell density, mitosis, nuclear atypia, microvascular proliferation, and necrosis). Since these morphologic changes which are characteristic of high-grade glioma appear gradually within a glioma, the exact delineation of low-grade and high-grade (or anaplastic) oligodendrogliomas is unclear. AOD may also present as anaplastic tumors, without clinically manifest low-grade precursor lesions. No specific immunohistochemical markers for OD exist. Oligodendrogliomas may exhibit sparse glial fibrillary acidic protein (GFAP) staining which is usually due to the presence of reactive astrocytes. Occasionally, central neurocytomas, ependymoma, and pilocytic astrocytomas may resemble oligodendroglial tumors.
By definition, mixed oligoastrocytoma tumors have morphologic characteristics of both astrocytic tumors and oligodendrogliomas. AOAs typically have areas that are GFAP positive. This staining pattern may not only be due to the astrocytic component of the tumor but may also be due to reactive astrocytes. There are no widely accepted histological criteria that specify how much of an oligodendroglial component needs to be present in a predominantly astrocytic lesion before a tumor may be called oligoastrocytoma. Recent trials used an arbitrary cut-off point the presence of more than 25% oligodendroglial elements, but these scores are also subject to inter-observer variation [9]. Based on clinical trials showing a worse outcome in AOA with necrosis, the 2007 WHO classification no longer considers a tumor to be an AOA if necrosis is present, but endothelial proliferation is still allowed in an AOA [10, 11]. Because of this change, the former “AOA with necrosis” is now considered to be glioblastoma with oligodendroglial morphology (GBM-O).

**Genetics**

The most frequent chromosomal lesions in classical OD are the combined allelic losses of 1p and 19q, occurring in 60–90% of ODs [3, 10, 12, 13]. This combined 1p/19q loss is mediated by an unbalanced translocation of 19p to 1q. Most likely, a centrosomal or pericentrosomal translocation of chromosomes 1 and 19 results in two derivative chromosomes der(1;19)(p10;q10) and der(1;19)(q10;p10), after which the derivative chromosome with the short arm of 1 and the long arm of 19 is lost [14, 15]. A possible explanation for this translocation is the strong homology of the centromeric regions of chromosomes 1 and 19, although that by itself does not explain why combined 1p/19q loss is not observed in more cancers. Typically the loss of 1p/19q is maintained at the time of progression, regardless of morphological changes, emphasizing that 1p/19q loss is an early genetic event [16]. Co-deletion of 1p/19q is much more frequent in oligodendroglial tumors with a classical histological appearance (perinuclear halo, chicken wire vascular pattern) compared to tumors with an atypical oligodendroglial appearance [5]. It occurs in 61–89% of AODs, but in only 14–20% in patients with AOA [10, 17]. In mixed OA with predominant oligodendroglial morphology the percentage of tumors showing 1p/19q loss drops to 39%, emphasizing that even the presence of minor astrocytic elements significantly reduces the chance of finding 1p/19q loss [16]. Still, some atypical ODs have 1p/19q co-deletions and some typical OD tumors do not show 1p/19q loss. Oligodendroglial tumors with 1p/19q co-deletion are more often localized in the frontal, occipital, and parietal lobes, whereas tumors in the insular region, temporal lobes, and diencephalon are less likely to show 1p/19q loss [17–19]. This also adds support to the notion that the 1p/19q co-deleted tumors are derived from different precursor cells.

More recent studies have shown that mutations in the IDH1 gene occur in 60–80% of grade II and grade III oligodendrogliomas, with or without 1p/19q
mutations [20, 21]. Of note, these mutations occur also in grade II and grade III astrocytomas, with or without TP53 mutations, and are likely to represent early events in tumorigenesis affecting a common glial precursor cell population. It is unclear if these mutations represent an inactivating lesion in a tumor suppressor gene or an activating lesion in an oncogene. IDH1 mutations appear to be of independent prognostic significance [22, 23].

Anaplastic ODs usually have additional chromosomal deletions; in particular loss of heterozygosity for 9p and/or deletion of the CDKN2A gene (p16) occurs in 33–50% of AODs, and deletions on chromosome 10 occur in 19–25% of cases [16, 24]. Polysomies are more frequent in high-grade tumors [16].

MGMT promoter methylation is frequent (up to 80%) in anaplastic oligodendroglioma and strongly correlated to 1p/19q co-deletion (with some studies showing complete concordance between 1p/19q co-deleted tumors and methylation) [25–27]. In grade III gliomas, epigenetic silencing of the MGMT gene was found to be of prognostic significance, even in patients treated with radiotherapy alone [27, 28]. There is yet no clear explanation for this observation.

As a rule, in low-grade and in high-grade ODs with atypical features other chromosomal abnormalities are found, which are typically associated with astrocytoma and which are usually mutually exclusive with 1p/19q co-deletion (e.g., TP53 mutations, EGFR amplification, 10q loss, PTEN mutations) [16, 29–32]. This suggests that these tumors are derived from different precursor cells. It is now often assumed that mixed tumors represent either oligodendrogial tumors with 1p/19q loss, or tumors with genetic changes consistent with an astrocytic lineage [30]. This hypothesis is supported by the marked difference in outcome, with an improved survival in the presence of 1p/19q loss and with poor survival in AOD with the loss of 10q and/or the amplification of EGFR [31, 33]. Many of these tumors have a mixed histology and show necrosis. With the recent change in WHO criteria for gliomas these tumors are considered GBM-O. Indeed, the presence of 10q loss or EGFR amplification in pure AOD is sufficiently rare to suggest an alternate diagnosis (e.g., small cell glioblastoma) [16].

**Diagnosis**

On computed tomography (CT), ODs appear as low-density masses which may exhibit calcifications (Fig. 10.1a). The presence of calcification is suggestive of OD (and may be more frequent in 1p/19q loss tumors) but certainly not specific [34]. On magnetic resonance imaging (MRI) most anaplastic ODs are characterized by increased signal intensity on T2-weighted images [35]. Enhancement, which is presumed to be the macroscopic equivalent of microvascular proliferation, occurs in a majority. However, the absence of enhancement does not rule out the possibility of an anaplastic tumor, and vice versa, as some faint contrast enhancement may be present in low-grade ODs [34, 36, 37].
Fig. 10.1 CT scan (a) and MRI scan (b–d) of a left frontal anaplastic oligodendroglioma, T1-weighted image before contrast (b), T1-weighted image after intravenous gadolinium administration (c), and T2-weighted image (d). Note the clear calcifications visible on the CT image which are barely seen on the MR images and the somewhat faint but clear contrast enhancement on T1-weighted images after contrast administration without clear areas of necrosis typical of glioblastoma.

In contrast to the rim-enhancing configuration often seen in GBM and AOT without 1p/19q co-deletion, co-deleted AOTs often have a patchy and more homogeneous enhancement pattern (Fig. 10.1b and c). In addition, 1p/19q co-deleted ODs frequently have indistinct borders and a mixed signal intensity on T1-weighted and T2-weighted images (Fig. 10.1d), whereas ODs without 1p/19q loss more often have a distinct border and uniform signal intensity on T1-weighted and T2-weighted images (Table 10.1) [34, 38].

Although the presence of enhancement, MR spectroscopic findings, and perfusion-weighted MRI may aid in prediction of tumor grade, none of these imaging findings are highly specific; therefore, microscopic examination of tumor tissue remains mandatory for definitive diagnosis [37, 39]. However, in view of the significant interobserver variation among pathologists and the possibility of sampling error in biopsied patients, neuro-imaging characteristics should be taken into consideration for the final determination of tumor grade. Even if the histology is suggestive of a low-grade tumor, the presence of significant and nodular enhancement on imaging is suggestive of a high-grade tumor [40].

For all tumors with oligodendroglial morphology the assessment of 1p and 19q losses should be considered. This can be done by a variety of techniques (fluorescence in situ hybridization [FISH], loss of heterozygosity [LOH], and comparative genomic hybridization [CGH]). Care should be taken that the loss of the entire short arm of chromosome 1 is assessed to avoid confusion with the partial 1p deletions that are mainly observed in high-grade astrocytic tumors. These partial losses are not associated with 19q loss and carry a poor prognostic significance [41]. In high-grade oligoastrocytomas or in atypical AOD, assessment of EGFR amplification and loss of chromosome 10 or 10q can be considered, which may identify tumors with poor prognosis and suggest an alternative, non-oligodendrogliol diagnosis [16, 42].

There is no need for routine specific staging procedures (like craniospinal axis imaging or CSF cytology) in newly diagnosed patients. In patients with recurrent disease, the presence of leptomeningeal spread may alter treatment options and this
should therefore be taken into account. In the majority of cases, leptomeningeal spread is readily recognized by the presence of distant tumor nodules along the ventricular surface on MRI. Occasionally, these may not be enhancing, under which circumstances T2-weighted images may be more sensitive for this diagnosis.

**Prognosis**

**Histology**

Pure oligodendroglial tumors have a better prognosis than astrocytic tumors of the same grade; the prognosis of mixed oligoastrocytoma is intermediate between these histologies [10]. Most likely, this is due to underlying genetic lesions (in particular the absence or presence of 1p/19q co-deletion; see below). Despite the relatively favorable clinical prognosis of OD, the outcome is ultimately fatal for virtually all patients.

**Genotype**

Both the presence or absence of the 1p/19q co-deletion and the \textit{IDH1} mutations are independent prognostic factors for survival in oligodendroglial tumors [13, 27, 43, 44]. In AOT without 1p/19q loss the median overall survival is 2–3 years, whereas it is more than 6–7 years in tumors with combined 1p and 19q loss. 1p/19q co-deleted tumors are more likely to respond to chemotherapy and have a longer progression-free survival after radiotherapy or chemotherapy [44–46].

**Clinical Characteristics**

The most important clinical prognostic factors include the age of the patient and the performance status, with elderly patients and patients in poor condition (functional deficits) doing less well.

**Treatment**

Until recently most randomized phase III trials on glial tumors included both astrocytic and oligodendroglial tumors, the exception being the American and European randomized studies on (neo)adjuvant PCV chemotherapy in anaplastic oligodendrogial tumors [43, 44]. The German NOA4 study included all grade III tumors and showed no difference in outcome among patients with AOD as compared to AOA, although both groups of patients fared better than patients with AA [28]. Currently ongoing studies on grade III tumors are distinguishing between
patients with and without 1p/19q loss, but it will take many years before results are available. All data on radiotherapy in anaplastic oligodendroglial tumors are derived from retrospective surveys, with their inherent pitfalls. A large number of prospective but uncontrolled single-arm studies on chemotherapy in recurrent oligodendroglial tumors are available, mostly on PCV and temozolomide chemotherapy.

**Surgery**

Surgery serves three goals: verification of the nature of the lesion, relief of signs and symptoms in patients suffering from a lesion with mass effect, and improvement of the prognosis. The relevance of the first two are generally acknowledged, but so far no trial has definitively confirmed that extensive surgery improves survival. All available data on extent of resection in oligodendroglial tumors come from retrospective studies or from post hoc analyses. A limitation of these uncontrolled studies is that superficial and small tumors are more likely to undergo extensive resection. In contrast, deep-seated lesions, large tumors, or tumors with in growth in midline structures, which may have a worse prognosis regardless of the extent of resection, will never undergo near-complete resections \[47\]. Both prospective randomized studies on PCV chemotherapy in anaplastic oligodendroglial tumors, however, observed an association between extent of resection and survival \[43, 44\]. In view of these and similar studies, it is considered that standard treatment is to resect the tumor as extensively as safely possible.

**Radiotherapy**

No prospective randomized trials on the role of RT specifically in AOT are available. Randomized trials in high-grade gliomas have demonstrated that adjuvant RT provides significant yet modest improvements in survival \[48\]. In AOD/AOA, 60–65 Gy in 30–35 fractions should be given. AOTs with 1p/19q loss have a superior outcome after RT, compared to those without 1p/19q loss \[43, 44\].

**Chemotherapy**

The responsiveness of AOD to chemotherapy was established in trials on recurrent tumors. The initial studies investigated the PCV regimen, with more recent studies focusing on temozolomide. No clear explanation is yet available for the favorable response of AOT as compared to astrocytic tumors. The nuclear enzyme alkyltransferase, which mediates at least a part of the cellular resistance to alkylating and methylating agents, is less expressed in AOD and perhaps even more so in 1p/19q
co-deleted tumors [49]. MGMT promoter methylation was observed in up to 80–90% of 1p/19q co-deleted tumors [25–27, 50]. MGMT promoter gene methylation occurs in only 30–45% of GBM; most likely this event alone does neither account for the entire difference in sensitivity to chemotherapy between astrocytic tumors and ODs, nor the increased sensitivity in 1p/19q co-deleted tumors.

Chemotherapy at Recurrence

The PCV Schedule

Cairncross and Macdonald were the first to demonstrate the sensitivity of AOD to chemotherapy. They observed very favorable responses in recurrent AOD treated with PCV. Approximately two-thirds of patients with recurrent AOD after prior radiotherapy have either a complete response (CR) or partial response (PR) to PCV chemotherapy. The time to progression in these patients is in general 12–18 months, but occasionally much longer than 24 months [1, 2, 51]. Because of the cumulative hematological toxicity and gastrointestinal side effects associated with PCV chemotherapy most patients do not tolerate the six cycles which are usually intended. The intensified PCV-I regimen appears to be of similar activity but was found to be considerably more toxic (especially hematological and general side effects, including malaise and weight loss) [2, 52]. In the absence of better results, this regimen cannot be recommended. A study on PCV chemotherapy followed by an autologous bone marrow transplantation after a myeloablative procedure with melphalan in previously irradiated patients proved too toxic, without clearly producing superior results [53]. Several studies suggested that AOA may be less responsive, which is most likely related to the lower frequency of combined 1p/19q loss in AOA.

Temozolomide

The reported response rate of recurrent OD to first-line temozolomide after failure of radiotherapy varied between 46 and 55%, with 12 months progression-free survival between 40 and 50% and median progression-free survival of 10–12 months [26, 54]. Objective responses are more frequent and of longer duration in patients with combined 1p/19q loss, with 60–82% of tumors responding [55]. These response rates seem modest compared to historical PCV trials, in which virtually all patients with 1p/19q loss responded [4, 5].

Which Regimen Is Preferable?

No formal comparison between PCV and temozolomide in recurrent oligodendroglioma is available. A major advantage of TMZ is the good tolerability, with in general modest myelosuppression and usually easily controlled nausea/vomiting as its major side effects. In this respect, TMZ compares favorably to the PCV regimen, and TMZ constitutes a clear alternative for the PCV regimen. The better tolerability
and the ease of administration of temozolomide as compared to PCV have made temozolomide the drug of first choice.

Second-Line Treatment with PCV or Temozolomide

Most trials on recurrent ODs after prior chemotherapy with PCV (either given adjuvant or at first recurrence) observed objective response rates to temozolomide (PR and CR) of approximately 25%, with 30–50% and 10–30% of patients free from progression at 6 and 12 months, respectively [54, 56–58]. A fourth trial predominantly selected patients who had responded favorably to PCV (response rate to first-line PCV: 83%) [59]. In this study the objective response rate to TMZ was 44%, with 50 and 25% of patients free from progression at 6 and 12 months. Objective responses to second-line PCV after failure to temozolomide were observed in only 17%, nevertheless 50% of patients were free from progression at 6 months (and 21% at 12 months) [60]. Occasionally, patients who do not respond to one regimen are responsive to the other. However, the relatively poor response rates even in 1p/19q loss ODs to second-line chemotherapy (and regardless of the sequence chosen, temozolomide first or PCV first) show that for further improvement of outcome other therapies need to be developed.

Bevacizumab

Bevacizumab, the humanized monoclonal antibody against circulating VEGF, was studied retrospectively in two series of patients with progressive AOT after treatment with radiotherapy and at least one line of chemotherapy. In one of these studies bevacizumab was combined with irinotecan [61, 62]. In the bevacizumab monotherapy study only patients with loss of 1p/19q were included whereas in the combination therapy study 75% of patients had no 1p/19q co-deletion. Response rates were similar (68–72%) but 6-month progression-free survival was higher in the bevacizumab monotherapy study (68 and 42%, respectively), which could simply be due to the difference in genetic background. As in patients with glioblastoma, decrease in enhancing tumor occurred quickly in responding patients, sometimes accompanied by clinical improvement and reduction in corticosteroid dose. However, in some patients clinical deterioration occurred in the presence of the development of a progressive non-enhancing, high signal, gliomatosis-like lesion on T2/FLAIR images despite an ongoing response of the enhancing lesion.

Other Agents

Only a few other agents (in particular paclitaxel, irinotecan, carboplatin, etoposide, cisplatin, and imatinib) have been systematically investigated as second-line or third-line chemotherapy agents in patients with AOT [61, 63–65]. In general, the response rates are low (in the 10–15% range) with one-third of patients free from progression at 6 months and virtually all patients progressing at 12 months. A drawback of some of these agents (e.g., paclitaxel, irinotecan) is their metabolism
through the cytochrome P450 3A4 pathway (CYP3A4). Because many glioma patients take enzyme-inducing anti-epileptic drugs, exposure to these agents may be reduced. This phenomenon may be responsible in part for the limited activity observed in the abovementioned trials. Despite the upregulation of platelet-derived growth factor (PDGF) signaling pathways in most ODs, the PDGF receptor tyrosine kinase inhibitor imatinib did not show any activity in recurrent AOT [66].

**Adjuvant Chemotherapy in Newly Diagnosed AOT**

The two prospective randomized controlled trials in anaplastic oligodendrogial tumors have shown that compared to PCV given at the time of recurrence, (neo)adjuvant PCV chemotherapy does not increase overall survival, although it does increase progression free-survival (Table 10.2). The first of these trials, RTOG 9402 randomized patients to either four cycles of upfront intensified PCV chemotherapy followed by radiotherapy to a dosage of 60 Gy or to radiotherapy only [43]. The second trial (EORTC 26951) randomized patients to 60 Gy radiotherapy followed by six cycles adjuvant PCV or to 60 Gy radiotherapy only [44]. Table 10.2 summarizes progression-free survival and overall survival in these studies. In both trials the majority of patients randomized to the RT arm received PCV (or temozolomide) at progression; the effectiveness of this salvage treatment explains the increased progression-free survival in the absence of increased overall survival. Because of this, these trials in fact investigated early (adjuvant) versus delayed (at the time of progression) PCV chemotherapy. Even in the 1p/19q loss subgroup analysis no overall survival benefit of early (i.e., adjuvant or neoadjuvant) PCV could be demonstrated.

The German NOA4 trial has shown in grade III tumors including AOT that OS and PFS are similar in patients managed initially with either RT or chemotherapy. Moreover, a similar outcome was observed in PCV and in temozolomide-treated

<table>
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<th>Chromosomal loss</th>
<th>Overall survival</th>
<th>5 years (%)</th>
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<tr>
<td></td>
<td>Median (months)</td>
<td>RT/PCV</td>
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<tr>
<td>Combined 1p/19q loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>RTOG</td>
<td>NR</td>
<td>NR (5.4, NR)</td>
</tr>
<tr>
<td>No combined 1p/19q loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC</td>
<td>25.2 [18.9, 42.6]</td>
<td>21.4 [17.6, 30.0]</td>
</tr>
<tr>
<td>RTOG</td>
<td>2.7 [2.0, 5.5]</td>
<td>2.8 [1.9, 4.4]</td>
</tr>
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</table>

Table 10.2 Median survival and 5-year overall survival (%) according to “combined 1p/19q loss” status in eortc 26951 and rtog 9402, on (neo)adjuvant pcv chemotherapy in anaplastic oligodendroglial tumors [43, 44]

Between brackets: 95% confidence interval
NR, not reached
patients [28]. The last trial is at odds with earlier trials in high-grade glioma, which showed a superior outcome of RT as compared to chemotherapy [48, 67]. With the current data, however, it appears that it does not matter if grade III glioma patients receive initial treatment with radiotherapy or with chemotherapy.

The findings of the two PCV trials are somewhat contradictory to the observed survival benefit after combined chemo-irradiation with temozolomide in GBM, especially in tumors with a methylated $\text{MGMT}$ gene promoter [68, 69]. The current clinical question is whether combined chemo-irradiation with temozolomide should be used for AOT. A particular concern for AOTs with 1p/19q co-deletion, which have a median survival over 6–7 years, is that late neurotoxicity due to combined chemotherapy and radiation may be an issue. This is clearly less of a problem for tumors without 1p/19q loss, but even here the benefit of the combined regimen is unproven. Current studies are investigating the role of combined chemo-irradiation in anaplastic oligodendrogial tumors, with separate trials for tumors with and without combined 1p/19q loss. In view of the outcome of the PCV trials, the relevance of any adjuvant chemotherapy given after the end of radiotherapy is at least unclear.

**Upfront Chemotherapy in Newly Diagnosed AOT**

The chemosensitivity of OD has made upfront chemotherapy strategies (with or without subsequent radiotherapy) increasingly popular. In the North American randomized study, progression-free survival for non-1p/19q co-deleted tumors was similar whether patients received radiation therapy with or without neoadjuvant PCV [43]. Most likely, this result is explained by the limited sensitivity of these tumors to PCV chemotherapy.

The German NOA4 study in grade III tumors has shown that there is no survival difference between patients managed initially with RT and with initial chemotherapy. The major rationale for upfront chemotherapy is the wish to defer RT and its associated delayed neurotoxicity [70]. A few medium-sized and uncontrolled studies in oligodendroglioma are available, in particular employing TMZ. One showed in a young, healthy population (median age 42 years of age, 81% of patients with Karnofsky performance status of at least 90%) a median progression-free survival of 27 months with a 1 week on/1 week off TMZ regimen [71]. A small trial on upfront temozolomide chemotherapy also showed a very short time to progression (8 months) in patients without 1p loss, in contrast to all seven patients with 1p loss who were still free from progression at 24 months [72]. In a phase II trial in 69 patients with newly diagnosed anaplastic or aggressive oligodendroglioma, the intensive PCV regimen was followed by high-dose thiotepa with autologous stem cell rescue, without radiotherapy. The median progression-free survival in the 39 patients who received the autologous stem cell procedure was 78 months, and median overall survival has not been reached. Eighteen patients (46%) have relapsed [73]. In view of the likely patient selection and the absence of a control arm, final conclusions are difficult to draw. It is clear that many patients with AOT have similar survival without such intensive treatments. The study shows, however, that prolonged progression-free survival without initial radiotherapy is possible.
One should realize that the choice of chemotherapy or radiotherapy may simply come down to exchanging the relatively short-term local side effects or RT for longer-term systemic side effects of (expensive) chemotherapy. Still, the currently available data in AOT support withholding RT in the presence of a favorable response to upfront chemotherapy.

References


Chapter 11
Ependymomas

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Keywords  Ependymoma · Myxopapillary ependymoma · Collaborative Ependymoma Research Network

Introduction

Although classified as glial tumors, ependymomas have distinct molecular and clinical characteristics that warrant separate discussion and consideration. Despite a rapidly increasing body of scientific literature and expanding interest in these tumors, ependymoma remains a rare primary central nervous system neoplasm, particularly in adults. Combining both brain and spinal cord tumors, ependymomas are estimated to constitute 8–10% of pediatric tumors and less than 4% of adult nervous system tumors. Although the origin has not been proven, these tumors are thought to arise from the ependymal cells or progenitors lining the cerebral ventricles, spinal cord central canal, and cortical rests.

The most recent WHO classification has subclassified ependymomas into grades 1, 2, and 3 [1]. Grade 1 tumors include myxopapillary ependymomas and subependymomas. Grade 2 tumors are called ependymoma, whereas the grade 3 tumors are designated anaplastic ependymoma. Typical imaging appearance of intracranial and spinal cord anaplastic ependymomas is shown in Figs. 11.1 and 11.2, respectively. The WHO does provide distinct grading criteria, however, the prognostic relevance of the grade 2 versus grade 3 distinction remains controversial, particularly for pediatric tumors (reviewed in Ref. [2]). Further complicating the prognostic impact of grading are the recent reports that demonstrate great molecular heterogeneity between histologic subtypes as well as significant differences between spinal cord and brain ependymomas, even of the same histologic subtype [3]. Age
Fig. 11.1 Right frontal anaplastic ependymoma in a 56-year-old patient

Fig. 11.2 (a) Anaplastic ependymoma in the conus medullaris in a 63-year-old patient at the time of diagnosis. (b) Tumor re-growth over 3 months after initial surgical resection

appears to also impact the molecular heterogeneity even when comparing pediatric and adult tumors of the same location and histology. However, tumor location has a more profound impact on profile than patient age. Tumor location (supratentorial, infratentorial, or spinal cord) has the most important impact on prognosis, trumping either WHO grade or patient age.

Large series of patients are rarely reported; hence most publications include a disparate group with many ependymoma subtypes, grades, and often patients of all ages. This paucity of large studies in adults has prevented a consensus of treatment for these patients, although the efforts of multicenter pediatric groups do provide some guiding principles for treatment. These limitations and concerns have prompted studies designed to systematically characterize the molecular alterations
in a large series of ependymomas. These will correlate molecular profiles with prognosis and use these comparisons to subcategorize ependymomas to develop new therapies and optimize individual patient treatment.

Pathology and Classification

The WHO classification system grades tumors on a scale from 1 to 4 with increasing degree of malignancy. The classification of ependymoma ranges from grade 1 to grade 3 and includes types designated as grade 1 (myxopapillary or subependymoma), grade 2 (ependymoma with possible designations as cellular, papillary, clear cell, or tanycytic), or grade 3 (designated anaplastic ependymoma) [1]. Grade 1 tumors tend not to infiltrate into surrounding normal brain or spinal cord and are therefore biologically distinct from either grade 2 or grade 3. This makes cure possible with complete surgical excision. Furthermore, malignant transformation into a higher grade tumor is extremely rare. Conversely, grade 2 ependymomas have a lower rate of cure with even extensive resection and do have the potential to undergo malignant transformation to a grade 3 neoplasm. Grade 3 ependymomas are almost never cured with surgical resection as there is infiltration into surrounding normal parenchyma, although this feature is less prominent than malignant astrocytomas. Unlike other glial neoplasms, such as astrocytoma, the prognostic implications of a grade 2 compared with grade 3, particularly in the pediatric population, are not clearly defined [2, 4]. Several studies suggest that the distinction may be predictive of event-free survival but not overall survival [4, 5].

The pathologic diagnosis of ependymoma may be difficult as there are several primary central nervous system tumors that are similar in appearance and imaging studies do not show any truly distinct tumor characteristics. Pathologic “look-alikes” include oligodendroglioma, central neurocytoma, pilocytic astrocytoma, astroblastoma, papillary glioneuronal tumor, and monomorphic angiocentric glioma [2]. Central neuropathologic review has uncovered that in some series, nearly 30% were actually misdiagnosed [6].

Prognostic Factors

Although the prognostic factors for ependymoma may differ between adult and pediatric patients, most reports either focus exclusively or represent an analysis of all age groups. The Surveillance, Epidemiology, and End Results (SEER) database, encompassing all patients with a diagnosis of ependymoma recorded between 1973 and 2005, yielded a total of 2,408 cases [7]. A multivariate analysis showed that higher grade, younger age, male gender, intracranial tumor location, and failure to undergo extensive surgical resection were associated with a worse clinical outcome. However, central pathology review is not mandatory for inclusion in the
SEER registry causing concern that some of the reported cases were not truly ependymoma.

Studies exclusively examining clinical prognostic factors in adults with ependymomas are uncommon. Reni et al. described the outcomes in 70 adult (over age 17 years) patients with intracranial ependymoma and determined that older age and supratentorial location were significant on univariate analysis of survival factors, and only age was significant on multivariate analysis [8]. Guyotat and colleagues examined prognostic factors in 106 adult patients with infratentorial ependymomas and reported that a good preoperative Karnofsky performance score (>80), no extension of the tumor into the lateral recess of the fourth ventricle, and a low histologic grade were associated with a significant improvement in survival [6].

Adult patients with ependymoma treated at MD Anderson were compiled and analyzed for predictors of outcome [9]. A total of 123 patients over 17 years of age, comprising 80 patients with spinal cord tumors and 40 patients with intracranial tumors including 16 with supratentorial tumors and 24 with infratentorial tumors were evaluated. Three patients had both spinal cord and intracranial tumors and 90% were grade 2 tumors at diagnosis using WHO criteria. However, 15 of these patients were found to have a grade 3 ependymoma at the time of tumor recurrence. Multivariate analysis determined that grade 3 classification and intracranial location were significantly associated with both a worsened progression-free and overall survival time. Although not found by either the Reni or Armstrong report, other clinical variables such as extent of tumor resection and use of post-operative adjuvant radiation have also been reported as potential prognostic factors [10–12].

In addition to the clinical prognostic factors reported above, molecular prognostic factors have also been reported for ependymoma. These include worse prognosis with chromosomal gain of 1q [13], amplification, and increased expression of the epidermal growth factor receptor (EGFR) [13] and hTERT overexpression [13, 14].

Although ependymomas are typically much less invasive than other gliomas, studies have found that the extent of tumor invasion, as assessed by evaluation of tumor histologic preparations, combined with expression of selected matrix metalloproteinases (MMPs) correlate with outcome [15]. Tumors demonstrating microinvasion and elevated levels of MMP2 and MMP14 were more likely to recur after resection, suggesting that these laboratory findings may help identify patients most likely to benefit from adjuvant (post-surgical) treatment.

Incidence and Epidemiology

Overall, ependymomas represent 3–6% of all central nervous system (CNS) tumors with a higher incidence in children. In the pediatric age group, ependymomas represent the third most common form of CNS tumor, accounting for 8–10% of all pediatric CNS tumors. Tumor location appears to vary by patient age. Data from the SEER database confirmed that ependymoma is more frequent in men and that pediatric tumors were mostly intracranial, whereas adult tumors were more frequently
in the spinal cord. Further analysis confirms that younger children are more likely to have tumors in the posterior fossa, whereas supratentorial tumors occur more commonly in older children and adults [16].

The incidence and outcomes for patients with ependymoma are monitored by both the SEER database and the Central Brain Tumor Registry of the United States (CBTRUS) [17, 18]. However, both combine all grades of ependymomas together for reporting purposes. CBTRUS reported that between 1998 and 2002, 1,126 ependymomas and anaplastic ependymomas were diagnosed for an adjusted rate per 100,000 person-years of 0.26; slightly higher in males (0.29) than in females (0.22) and in whites (0.27) versus blacks (0.12).

**Molecular Profiles**

Ependymomas have not been as extensively studied as other primary brain tumors such as the malignant gliomas or medulloblastomas [19, 20]. However, published data provide some insights into the pathogenesis of the disease. These findings may help to define the origin of the ependymoma stem cell, generate prognostic markers, and, most importantly, yield therapeutic targets, particularly focused on signal transduction modulators. Several studies suggest that the tumor biology and outcome are more closely related to tumor location (spinal cord vs. intracranial and supratentorial vs. infratentorial for the brain ependymomas) than age or grade.

**Chromosomal Abnormalities**

Intramedullary spinal cord ependymomas have a very high incidence of loss of heterozygosity (LOH) on chromosome arm 22q, often with accompanying NF2 mutations [21, 22]. An 11q LOH is also common and is typically associated with mutations in the MEN1 gene (located at 11q 13). The 11q LOH was mostly found in tumors that do not demonstrate the 22q LOH. In a few cases, the MEN1 gene was intact when the tumor was low grade (WHO grade 2), but the MEN1 mutation was found at tumor recurrence when the tumor had undergone a malignant transformation to grade 3, suggesting that the MEN1 gene mutation is associated with malignant transformation. Less commonly, genomic losses have been reported on 2q, 4q, 5q, 6q, 7q, 15q, 16q, 17p, and 19p [23–25] but chromosome 10q LOH is rare. Comparative genomic hybridization (CGH) studies have determined that a high proportion of ependymomas have chromosome gains including both arms of chromosomes 17, 9q, 12p, 13q, 20q, and 22q, although there is a high degree of variability. Distinct patterns of chromosomal changes, based on tumor location, specifically differentiating spinal, infratentorial, and supratentorial locations, have been reported [24]. Although a wide variety of chromosomal abnormalities have been reported, the relationship of these to tumorigenesis or tumor biology has not been well defined.
Molecular Pathway Abnormalities

Molecular pathway analyses of ependymomas have yielded some potential therapeutic targets. The overexpression of ErbB2 and ErbB4 receptors was found in over 75% of pediatric ependymomas and correlated with tumor proliferative index and prognosis [26] with similar findings in adult supratentorial ependymoma. An increased expression of the integrin αvβ3 was found in a high percentage of intracranial ependymomas, as was expression of annexin A1 and cyclo-oxygenase-2 [27–29]. Additionally, the platelet-derived growth factor (PDGF) pathway that may have a functional role in tumor biology as a single-nucleotide polymorphism in the PDGF receptor α (PDGFRα) gene promoter region in ependymomas has been reported [30].

Gene Array-Based Profiles

Microarray technology has been used to study gene expression in a variety of ependymomas [31–33]. The analysis of 39 newly diagnosed ependymomas by Korshunov and colleagues uncovered molecular profiles that distinguished grade 2 from grade 3 supratentorial ependymomas and spinal from cranial tumors but could not find a similar pattern for infratentorial tumors. Furthermore, typical spinal cord ependymomas could be distinguished from myxopapillary tumors. Comparing gene expression arrays from normal brain and 19 pediatric ependymomas, Suarez-Merino found 112 genes that were abnormally expressed in the tumor samples including genes involved in cell cycle, cell adhesion, and proliferation, notably the oncogene WNT5A and the p53 homologue p63. The NF2-associated gene SCHIP-1 was underexpressed, a potential alternative to NF2 loss as described above. A prognostic marker set comprised of 27 genes that was able to identify patients with survival of greater than 10 years was reported by Lukashova-v. Zangen and colleagues from 47 ependymomas. However, no uniform set of prognostic, “location,” or age-specific genes was identified, likely the consequence of the diversity of the specimens investigated including patient age, tumor location, histology, and tumor grade.

Epigenetic Studies

Some gene inactivation in ependymoma may be explained by epigenetic mechanisms. For example, hypermethylation of the promoter region may help account for the relative infrequency of mutations of established tumor suppressor genes [3]. Gene promoter region methylation of several known tumor suppressor and related genes has been examined in ependymomas [34–36]. A high percentage of ependymomas demonstrates methylation of the tumor suppressor gene RASSF1A [34, 35]. However, the MGMT gene was rarely methylated in ependymomas, a possible
Ependymomas are neoplasms that arise from the ependymal lining of the cerebral ventricles, spinal canal, and fourth ventricle. They are classified into ependymomas and subependymomas based on their histological features. Ependymomas are typically low-grade tumors, and they present with symptoms related to increased intracranial pressure or structural distortion of the brain or spinal cord. The treatment of ependymomas is usually surgical resection, with radiation therapy and chemotherapy used for more aggressive cases.

Ependymomas respond modestly to alkylating agent chemotherapy, and the role of molecular markers in predicting treatment response is under investigation. Apoptosis-associated TRAIL pathway genes have been reported to be hypermethylated, and the putative tumor suppressor gene HIC-1 has also been found to be hypermethylated in intracranial, but not spinal cord, ependymomas, suggesting differences in tumor pathogenesis.

Ependymoma Stem Cells

Radial glia have been proposed as the stem cells for ependymomas. Ependymoma stem cells derived from cranial and spinal cord tumors recapitulate the molecular profiles of the location-specific radial glial cells found during development. Therefore, given this probable association of radial glial cells with ependymoma formation, studies in the radial glial cells may provide insights into the pathogenesis of ependymomas and potential therapeutic targets. Studies have already demonstrated that radial glial cells emulate ependymoma activity if either there is loss of the adherence gene αE-Catenin or dysregulation of the Notch cell signal pathway.

Implications for Prognosis and Treatment

Several potential therapeutic targets have emerged from laboratory investigations, including ErbB2 (HER2) and in some cases, ErbB1 (EGFR). Targeting the PDGFR pathway may be an effective treatment as a polymorphism of the PDGFRα gene promoter has been found that causes dysregulation of this pathway. Similarly, a high percentage of ependymomas overexpress the αβ3 integrin, making this an attractive approach with the new specific agents that target this integrin. Overexpression of MGMT is common in ependymomas, a possible explanation for the overall poor response of ependymoma to alkylating agent chemotherapy. Strategies to modulate MGMT activity may therefore have benefit in ependymomas.

Treatment

Intracranial Tumors

Surgical resection remains the most important therapeutic intervention. Surgery with tumor resection establishes the diagnosis, in some cases re-establishes normal cerebrospinal fluid flow and reverses hydrocephalus. Extensive tumor resection may directly impact survival as most series report that extensive resection is associated with improvement in both progression-free and overall survival. Using MRI for verification, complete resection can be achieved in 50–75% of
patients. Re-operation is recommended if the initial procedure was incomplete and a complete resection is possible [11, 44, 48]. However, some tumors are not amenable to complete resection, as tumor location or adherence to vascular structures, cranial nerves, or the ventricular surface may make resection inadvisable. Use of a short course of chemotherapy to reduce tumor volume to make complete resection more feasible has been proposed, although this approach has not been carefully studied.

Although reports vary considerably, dissemination of ependymoma in cerebrospinal fluid or into other central nervous system areas has been estimated to occur in approximately 15% of patients, but is more common in patients with posterior fossa tumors and in anaplastic ependymoma. Therefore, staging of the central nervous system is highly recommended before initiating treatment [49]. Analysis of cerebrospinal fluid may be misleading soon after tumor resection, therefore waiting a minimum of 2 weeks after surgery is advisable. The frequency of surveillance of the spine for evidence of dissemination in patients with ependymoma remains uncertain; however, although the incidence is relatively low, early diagnosis may impact treatment options and avoid irreversible neurologic injury.

There is consensus that radiation treatment is indicated for patients with anaplastic (grade 3) ependymoma, however, a clear dose–response relationship has not been established [50, 51]. In the absence of dissemination, regional radiation with total doses up to 60 Gy is of equal benefit with less toxicity compared with craniospinal radiation [52, 53].

Radiation treatment for grade 2 ependymoma is more controversial [8, 44]. Radiation treatment for post-operative residual disease has been shown to be beneficial with better local control if the radiation dose exceeds 50 Gy [44, 54–56]. Although less well established, patients with posterior fossa ependymomas, even following complete resection, may benefit from adjuvant radiation therapy. However, some authors advocate that if the surgical resection is complete, then radiation can be deferred but with the plan for careful monitoring. Therefore in the absence of randomized studies, for completely resected grade 2 ependymoma, either early provision of radiation or careful observation are acceptable options.

The role of chemotherapy has been less well established for treating adults with ependymoma. Most series reporting chemotherapy results are retrospective collections, often a compilation of a divergent series of patients or treatment regimens used [57, 58]. Some series suggest that the response rate with platinum-based regimens is higher than those without a platinum agent, with cisplatin chosen over carboplatin, based on results from pediatric studies [59]. There are anecdotal reports using a variety of chemotherapy regimens including irinotecan, ifosfamide, idarubicin, and tamoxifen in combination with isotretinoin [49, 60].

Despite widespread use for other gliomas, temozolomide has only been tested in small series of patients. Aside from a single report of a prolonged response, there have been conflicting reports regarding the level of activity of temozolomide when administered using conventional dosing schedules [61–63]. The report by Chamberlain showed minimal activity, whereas the ongoing study at the University of Torino is showing promising early results. However, alternative “dose-dense” temozolomide schedules may demonstrate better efficacy as a high percentage of
Ependymomas express high levels of MGMT, an enzyme that confers resistance to alkylating agents such as temozolomide [42]. These alternative schedules have been shown to deplete MGMT in peripheral blood mono nuclear cells [64] and may have similar effect in tumor cells.

Signal transduction pathways have not been extensively investigated as potential therapeutic targets in ependymoma although a recent paper in the pediatric oncology literature advocates that developing individualized treatment regimens based on tumor-specific molecular profiles represents the best chance for progress [65]. Bevacizumab use for ependymoma was reported in a retrospective series of patients with objective responses noted in six of eight patients [66]. Some of these responses were not durable and the median progression-free survival was only 6.4 months. The Collaborative Ependymoma Research Network (CERN) is currently accruing to a clinical trial that combines a dose-dense schedule of temozolomide with lapatinib, a dual inhibitor of both EGFR and HER-2 (ErbB2), both potential targets based on laboratory studies.

**Spinal Cord Ependymomas**

Spinal cord ependymomas predominantly occur in adults and fall into one of two distinct histologic subtypes. Myxopapillary ependymomas are classified as WHO grade 1 and usually arise in the cauda equina with occasional extension into the conus medullaris. Although uncommon, myxopapillary ependymoma can disseminate via the cerebrospinal fluid throughout the neuraxis. The second type of spinal cord ependymoma is the classic ependymoma, similar in histologic findings to the intracranial ependymoma. These tumors are typically classified as grade 2 by WHO criteria, although a small subset are anaplastic. They occur most commonly in cervical spinal cord and less frequently in the thoracic region.

Although spinal cord ependymomas are thought to have a relatively low risk of dissemination, recent studies suggest that dissemination is a potential life-limiting outcome if myxopapillary ependymomas are removed piecemeal, as the opening of the tumor capsule allows for tumor cell spillage into the surrounding cerebrospinal fluid [67, 68]. For both myxopapillary ependymoma and classic ependymoma, intracranial spread is rare.

As with intracranial ependymoma, extent of surgical resection remains one of the key determinants of prognosis for spinal cord tumors. An en block resection of an intrinsic spinal cord ependymoma, either myxopapillary or classic, may result in cure [68]. Conversely, as described above, compromise of the tumor capsule may lead to tumor dissemination for myxopapillary tumors. Incomplete resection of classic spinal ependymomas results in a high recurrence rate and often requires additional treatment. Most investigators support the use of post-operative local radiation treatment for incompletely resected tumors and for the rare anaplastic ependymomas [69–72]. Some studies suggest that total radiation doses over 50 Gy may be superior to lower doses when given to the region of the tumor [73], but this does
increase the risk of radiation-induced myelopathy. However, a total dose of 55 Gy has a less than 2% risk of significant spinal cord injury [74]. More extensive radiation treatment, such as complete spine or craniospinal radiation, is reserved for patients with evidence of dissemination.

Management of patients with recurrent disease may include re-resection often followed by re-irradiation with either conventional external beam treatment or use of a more focused radiation technique such as fractionated stereotactic radiotherapy [75, 76]. This approach may provide good local control although the risk of treatment-induced myelopathy increases with the repeat treatment.

Chemotherapy does not have a proven role in the treatment of patients with spinal cord ependymoma. A variety of agents have been tried including chronic oral etoposide, with only modest success [77]. A minor response was reported using imatinib in a patient with a spinal ependymoma that had high PDGFR expression [78].

**Future Directions**

Despite increasing interest and collaborative efforts, challenges remain in the management of patients with ependymoma. Large-scale clinical trials are difficult because of accrual issues. This is further complicated by the increasing evidence of disease heterogeneity despite similar histologic appearance. Collaborative endeavors will therefore be required to make significant advances, combining a strong clinical research effort with tumor-based correlative studies. These studies will identify clinical and molecular profiles that will hopefully select the optimal treatment regimens for ependymoma subtypes. This should warrant great interest, attention, and support, as success with ependymomas would provide compelling evidence that this integrated approach is a useful paradigm. The Collaborative Ependymoma Research Network (CERN – [www.cern-foundation.org](http://www.cern-foundation.org)) has been established to follow this research plan with ongoing clinical trials and concordant tumor molecular investigations.

**Conclusions**

Adult patients with ependymomas remain uncommon in most practices. Treatment approaches and regimens have frequently been adopted from experience from pediatric ependymoma studies, allowing certain principles of therapy to be established for both populations. These include the benefit of maximum surgical resection and in the case of spinal cord myxopapillary ependymoma, removal of tumor without breaching the tumor capsule may prevent dissemination. Additionally, postoperative “adjuvant” radiation in cases of low-grade tumor with residual disease and in patients with the higher grade, anaplastic ependymoma is commonly recommended. Treatment of recurrent disease is less well defined, although re-irradiation is commonly used for pediatric patients and is feasible in many adults. The role of
chemotherapy is evolving and the optimal choice of chemotherapy is uncertain at present, but ongoing clinical trials with correlative molecular studies will hopefully help individualize treatments in the future.

References


Introduction

Brainstem glioma (BSG) refers to a heterogeneous population of tumors that arise in the pons, midbrain, cervicomedullary junction, or tectal plate (Table 12.1). These are often classified as diffuse or focal neoplasms. Diffuse BSGs are characterized by their infiltrative growth pattern, resistance to radiation and chemotherapy, and poor prognosis. Focal BSGs are characterized by their localized growth pattern, indolent behavior, response to radiation therapy, and favorable prognosis [1].

Epidemiology

The exact prevalence of BSG in adults is unknown but is estimated at 0.5–2% of all gliomas [2]. This is far less frequent than in children where 10–20% of all brain tumors occur in the brainstem [2, 3]. The mean age at diagnosis in the adult population is 20–40 years and in the pediatric population is 7–9 years, with an equal sex distribution [1, 4, 5]. Most tumors are sporadic, but some may be familial. There is an increased incidence of BSG in patients with neurofibromatosis type I, although tumors in these patients have a more benign course [6, 7].
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**BSG** = brain stem glioma, **PA** = pilocytic astrocytoma, **PXA** = pleomorphic xanthoastrocytoma, **CN** = cranial nerve, **MRI** = magnetic resonance imaging, **CT** = computed tomography, **EGFR** = endothelial growth factor receptor, **MGMT** = O6-methylguanine-DNA methyltransferase, **BRAF** = V-raf murine sarcoma viral oncogene homolog B1
Clinical Presentation/Diagnosis

The major difference in clinical presentation between adults and children is the longer duration of symptoms and signs in adults [8, 9]. An array of symptoms and signs are observed in patients presenting with BSG, depending on the specific structures involved. Patients with diffuse-infiltrating tumors often present with subacute-to-acute onset of symptoms. Common symptoms include ipsilateral V and VI cranial nerve palsies, ataxia, and contralateral weakness. Occasionally, hydrocephalus may be the presenting problem. Hemorrhage may be present at the time of diagnosis or present later as a manifestation of tumor necrosis after treatment.

In contrast to diffuse-infiltrating tumors, focal brainstem tumors have a more insidious onset. Dorsal exophytic tumors often present with headache, vomiting, and ataxia. These symptoms result from hydrocephalus caused by tumor obstruction of cerebrospinal fluid (CSF) flow through the fourth ventricle. Cervicomedullary tumors present with vomiting, dysphagia, dysphonia, ataxia, and altered respiratory patterns. Intrinsic tectal tumors present with symptoms of hydrocephalus due to obstruction of the cerebral aqueduct.

Magnetic resonance imaging (MRI) has revolutionized the diagnosis and treatment of BSG. Diffuse-infiltrating tumors are characterized by hypointense signal on T1-weighted sequences and hyperintense signal on T2-weighted images (Fig. 12.1). These tumors have indistinct margins and usually expand the brainstem. Contrast enhancement is often absent or minimal, except in high-grade tumors where ring enhancement is frequently observed [10]. Encasement of the basilar artery is common. Since leptomeningeal spread may occur in up to one-third of patients, spine MRI should be considered in patients with appropriate symptoms or signs [11].

Fig. 12.1 MRI scan from a 20-year-old woman who presented with headaches, dysarthria, and unsteady gait. The T1 post-gadolinium sequence (left) shows diffuse pontine enlargement with foci of hypointensity and no abnormal enhancement. The fluid-attenuated axial inversion recovery (FLAIR) sequence (right) shows marked hyperintensity with encasement of the basilar artery (arrow). These findings are typical for diffuse pontine glioma.
Focal BSGs are more discrete and occupy less than half of the axial diameter of the brainstem. They typically have sharp borders and enhance intensely with contrast. Despite the general imaging principles discussed for diffuse and focal tumors, interpatient variability makes definitive diagnosis challenging in some cases [1]. Intrinsic tectal gliomas do not often enhance. They can cause hydrocephalus from obstruction of the cerebral aqueduct.

Radiographic changes following treatment may be difficult to distinguish from recurrent disease. Cystic and necrotic changes within 3–4 months of radiation often represent treatment effects [3]. As in supratentorial glioma, imaging modalities such as positron emission tomography (PET), MR spectroscopy, and diffusion and perfusion-weighted MRI are being investigated in BSG to help differentiate between treatment effect and recurrent disease [12, 13]. Using noncontrast computed tomography (CT) or gradient echo MRI is useful in tracking intratumoral hemorrhage that may occur as the result of treatment or spontaneously. Diffusion tensor imaging has been used to quantify white matter tract changes [14, 15].

In some cases, imaging findings may be atypical. The differential diagnosis for brainstem lesions that do not have typical imaging characteristics for tumor includes demyelinating disease and inflammatory, vascular, or infectious etiologies. A longer duration of symptoms or episodic character of symptoms may suggest these alternative diagnoses. Stereotactic biopsy can be useful in these atypical cases. Diagnostic accuracy of a stereotactic biopsy has been reported to range between 87 and 100% [16–19]. With modern neurosurgical techniques, the risk of biopsy is estimated to be between 1 and 5.6% [20].

Pathology/Classification

Diffuse-infiltrating BSG is the most common type of BSG in adults, and low-grade variants represent the majority of cases [10, 21]. High-grade diffuse BSG occurs in approximately one-third of cases and is seen more commonly in the elderly [10]. Tumors that cause symmetric expansion of the brainstem are usually diffuse fibrillary astrocytomas; most of these are found in the pons where they may engulf the basilar artery [1]. In adults, 56% of BSGs develop in the pons, 30% in the medulla, and 12% in the midbrain [22, 23]. Diffuse tumors rarely spread to distant sites. Rather, they tend to follow white matter tracts into the cerebellum and thalamus.

Focal tumors with exophytic growth patterns are often lower grade [24]. These tumors tend to be pilocytic astrocytomas (WHO grade I), grade II astrocytomas, or ependymomas. They may be found anywhere in the brainstem, but more commonly in the midbrain and medulla. They can arise out of the floor of the fourth ventricle and grow into the ventricle rather than invading the parenchyma. They may obstruct CSF flow. They are rarely found in the pons [1].

Microscopically, BSG has a similar appearance to astrocytic tumors in other locations. Rare brainstem tumors include oligodendroglioma, ganglioglioma, ependymoblastoma, hemangioma, mixed glioma, and primitive neuroectodermal tumors [1, 25].
**Prognostic Factors**

In general, BSG is less aggressive in adults than in children. In particular, the adult form of diffuse BSG has a much better prognosis than in children. Factors associated with longer survival include low-grade histology, long symptom duration, and absence of contrast enhancement [9, 10]. In a cohort of 101 adult patients with mixed histologies, the 5-year survival was 58% and 10-year survival was 41% [26]. This is one of the largest series of adult BSG patients reported in the literature. Another study reported on 48 adult patients. Based on MRI imaging, 50% of the patients had diffusely infiltrating tumors, 31% had focal, enhancing tumors, 8% had isolated tectal tumors, and 11% had tumors with other imaging patterns. This study reported a median survival time of 5.4 years, which is in agreement with previous reports [10].

Focal tumors have a much better prognosis than diffuse tumors. Because of the paucity of cases, there is no survival data in the adult population. In the pediatric population, the estimated 5-year survival is greater than 50% [27].

**Treatment**

Definitive treatment of BSG is dictated by whether the tumor is diffuse or focal. There is no role for surgery in diffuse tumors unless a biopsy is necessary to confirm the diagnosis. A meaningful resection is rarely possible and may carry a high risk of morbidity, as the tumor is interwoven within the white matter tracts of the brainstem.

**Diffuse Tumors**

Standard treatment for diffuse tumors is external beam, involving field radiation therapy to the tumor mass with a 1- to 2-cm margin at a dose of 54–60 Gy in divided fractions over 6 weeks. Radiation improves progression-free survival (PFS) but may not prolong overall survival (OS) [3, 28, 29]. Importantly, radiation may provide transient improvement in neurologic function and decrease the need for steroids. Several studies have compared hyperfractionation to conventional radiation schedules and found them to be equivalent with respect to OS [29–31]. Similarly, hypofractionation appears to be equivalent to conventional fractionation [29–31]. A recent Dutch pilot study evaluated 9 pediatric patients with an aggressive hypofractionation schedule of 39 Gy over 13 treatments and found PFS and OS to be similar to outcomes seen with conventional radiotherapy and without major toxicity [32]. The advantage of hypofractionation is that it may allow patients to realize treatment benefits more rapidly while shortening the total treatment time. Stereotactic radiosurgery has not been shown to improve outcomes in diffuse tumors [33].

Radiation to the brainstem in any form poses significant risks of toxicity as a result of necrosis and inflammatory changes. The posterior fossa is a more confined space that does not accommodate these changes as well as the supratentorial space.
Patients often require high doses of steroids for prolonged time periods to compensate for the toxicity of radiation. Radiation alone has minimal efficacy with the expense of significant side effects. As a result, various chemotherapeutic approaches have been investigated.

Most studies of chemotherapy for diffuse BSG have been conducted in the pediatric population. Several studies in the pediatric population have evaluated chemotherapy prior to radiation and have not shown any clear benefit. However, these studies have been confounded due to the fact that many patients did not receive the full course of radiotherapy or chemotherapy due to early progression [34]. In one series of 19 pediatric patients, carboplatin was given prior to radiotherapy. Two patients had a minor response and six patients had stable disease. The overall median survival in this study was 11 months [35]. Other series have reported outcomes with various combinations of cisplatin, etoposide, vincristine, and cyclophosphamide prior to hyperfractionated radiation. There was no difference in response rate or OS compared to historical controls in these studies [36, 37].

Concurrent chemotherapy and radiation therapy for pediatric BSG has been investigated in several studies. One study reported a median OS of 12 months in 34 patients treated with carboplatin and hyperfractionated radiation [38]. Likewise, a median OS of 8.3 months was reported in 32 patients treated with topotecan and conventional radiotherapy [39] and 9 months in 30 patients treated with vincristine and etoposide concurrent with radiotherapy [40]. Other studies have shown similar outcomes [41, 42].

The combination of radiation and temozolomide has shown a survival benefit in adults with supratentorial high-grade gliomas [43]. Temozolomide has also been evaluated in pediatric patients with BSG. One study investigated 33 patients treated with adjuvant temozolomide (200 mg/m^2) after being treated with irinotecan prior to conventional radiotherapy. The median OS in this study was 12 months [44]. A more recent study of 12 pediatric patients treated with temozolomide (75 mg/m^2) concurrent with radiotherapy followed by adjuvant monthly cycles of temozolomide (200 mg/m^2) for 5 days and cis-retinoic acid (100 mg/m^2) for 21 days demonstrated a median OS of 13.5 months [45]. In contrast, a recent study of 20 pediatric patients treated with temozolomide (75 mg/m^2) concurrent with radiotherapy followed by adjuvant monthly cycles of temozolomide (200 mg/m^2) over 5 days demonstrated a median OS of only 9 months [46]. Likewise, a study of 18 adult patients with BSG treated with a similar regimen of chemoradiation and adjuvant chemotherapy with temozolomide revealed a median OS of 59 months which is comparable to radiation alone in the adult population [21]. These small series of patients provide conflicting results, but suggest that prospective studies on larger series of patients should be conducted to more definitively assess the efficacy of temozolomide in diffuse BSG.

Thus far, adjuvant chemotherapy after radiation has not improved PFS or OS in diffuse BSG. A study of 76 patients randomized after radiation to carmustine, vincristine, and prednisone or no chemotherapy showed no prolongation of survival in the chemotherapy arm [47]. Another study looked at the combination of busulfan and thiotepa following radiotherapy in 35 patients with progressive diffuse
pontine glioma. The median OS was 10 months [48]. More recently, trofosfamide and etoposide were used in combination in 20 patients yielding a median OS of 8 months [49].

Several studies have investigated marrow ablative chemotherapy with autologous stem cell rescue in pediatric BSG. Various combinations of busulfan, thiotepa, etoposide, carboplatin, BCNU, and cyclophosphamide have been used without demonstrating any survival advantage over radiotherapy [50–54].

Overall, the results of salvage chemotherapy after radiotherapy have been disappointing. Newer, targeted therapies that have undergone trials in adult high-grade supratentorial glioma have not been studied extensively in BSG. Part of the problem is that BSG has not undergone extensive molecular characterization since tumor tissue is rarely resected, and biopsy tissue is often inadequate for molecular studies. A recent case report described an adult patient with progressive BSG who demonstrated a durable clinical and radiographic response after treatment with combined bevacizumab and irinotecan [55]. Agents targeting other growth factors and their receptors such as epidermal growth factor and platelet-derived growth factor have not been evaluated in progressive BSG.

In summary, various schedules and combinations of chemotherapy given before radiation, concurrent with radiation, or following radiation have not clearly benefitted adult patients with diffuse BSG. Therefore, the standard treatment for diffuse BSG remains conventional radiotherapy to a dose of 54–59.4 Gy[56].

**Focal Tumors**

Unlike in diffuse BSG, surgery has an important role in focal BSGs, especially for tumors with an exophytic component. Because of obstructive hydrocephalus, shunting is often required. Small focal tumors without contrast enhancement can sometimes be observed after shunting, as these features predict a benign clinical course [57, 58].

In most cases, patients with dorsal exophytic tumors benefit from surgery. Only when vital brainstem structures are involved by tumor is surgery not advisable. Patients may not require adjuvant therapy after surgery, even in the setting of subtotal resection [59]. Prolonged survival after surgery was demonstrated by a small series of 16 pediatric patients who underwent subtotal resection for dorsal exophytic tumors. Twelve of 16 patients underwent surgery and remained free from recurrence during long-term follow-up. Of the remaining four, two of the patients were still alive after re-resection for recurrent tumor and two patients were still alive after radiotherapy for recurrent tumor [60]. Another small study of 12 pediatric patients who underwent surgery for dorsal exophytic BSG demonstrated a 2-year OS and PFS of 100% and 67%, respectively [61]. In patients with dorsal exophytic tumors, radiation therapy is generally reserved for recurrent disease.

Other focal tumors such as cervicomedullary, midbrain, and tectal tumors may also benefit from surgery, but the value of surgery as compared to radiation
therapy is uncertain. Several authors have reported promising results of modern microsurgical techniques for resection of these tumors [23, 62–64]. These studies are difficult to interpret due to small sample sizes, heterogeneous pathology, and varied tumor locations [65]. Radiation therapy is often provided to residual disease after surgery, but there is no convincing evidence that post-surgical radiation is superior to delayed radiation at the time of progression [59, 61]. Radiation can be administered as conventional involved field radiotherapy or stereotactic radiosurgery (SRS). Some small case series describe patients who responded to conventional radiation therapy post-operatively [60, 66]. Similarly, some retrospective studies have demonstrated good outcomes with SRS [33, 65, 67]. Similar to upfront treatment, there is no data to support re-resection over radiation therapy for recurrent disease [59]. Patients with high-grade tumors and recurrent tumors should be considered for radiation therapy [3]. The role of chemotherapy in focal BSG is undefined.

Tumors in the midbrain tectum fall into a special category. These tumors can very frequently be observed after shunting or third ventriculostomy for hydrocephalus. Rarely, these tumors present with hemorrhage requiring surgical intervention [68]. Patients with tectal tumors are often stable for several years and may never require definitive therapy [69].

**Pilocytic Astrocytoma**

**Introduction**

Pilocytic astrocytoma (PA) is a well-circumscribed, benign tumor found primarily in the posterior fossa of children and young adults. In adults, PA is more often supratentorial and has a predilection for the temporal lobes (Table 12.1). It is important to distinguish PA from low-grade diffuse astrocytoma, as PA has a much more favorable prognosis. Because of its rarity, few case series of PA in adults have been published.

**Epidemiology**

The exact incidence and prevalence of PA in adults are unknown. Several retrospective studies have demonstrated that PA accounts for 1–6% of all brain tumors [2, 22]. PA is the most common glioma in the pediatric population, representing 20% of all intracranial tumors [2, 3, 70]. Only 20–25% of all PAs occur in patients over the age of 18 years [71].

**Clinical Presentation/Diagnosis**

Presenting symptoms vary depending on the location of the tumor. The most common locations for PA in adults are the temporal lobe, optic pathways, and the
region of the third ventricle. Less commonly, adult tumors are located in the cerebellum, in contrast to the predilection for the cerebellum in the pediatric population. Common signs and symptoms include headache, seizure, gait abnormalities, homonymous hemianopia, papilledema, abnormal reflexes, and incoordination [72, 73]. Headaches and seizures are the most frequent presenting symptoms reported in several series [72–74].

Pilocytic astrocytoma appears as a discrete, well-circumscribed mass on CT and MRI. The mass is isodense or hypodense on CT. On T1-weighted MRI, the mass appears hypointense or hyperintense to brain and hyperintense to brain on T2-weighted imaging (Fig. 12.2). Calcification can be seen in up to 40% of tumors on CT, but is poorly visualized on MRI [75]. Cysts of various sizes are often present, appearing hypointense on T1-weighted images and hyperintense on T2-weighted images. Most tumors demonstrate very little peritumoral edema. PA often show homogeneous contrast enhancement on both CT and MRI. The contrast enhancement often involves the cyst wall and in many cases, a mural nodule.

![Fig. 12.2](image-url) MRI scan from a 41-year-old woman who had a subtotal resection of a left temporal pilocytic astrocytoma 16 years prior to presenting with headache, right-hand paresthesias, and a right visual field deficit. The T1 post-gadolinium axial sequence (left) shows a cystic lesion in the left temporal lobe with a large enhancing mural nodule. There is significant mass effect with left to right shift. The fluid-attenuated axial inversion recovery (FLAIR) sequence (right) shows that the contents of the cyst are isointense, unlike cerebrospinal fluid, which appears markedly hypointense on FLAIR imaging. Histopathology confirmed the diagnosis of recurrent pilocytic astrocytoma (WHO grade I)

**Pathology/Classification**

PA is classified as a grade I astrocytoma by the WHO. These tumors are most often cystic with a single, large mural nodule. Small hemorrhages and calcifications can be seen within solid portions of the tumor. Often the margins of the tumor are distinct or encapsulated. However, diffuse or infiltrative features are seen in up to 50–60% of cases [76].
There are two recognized histologic variants of PA, the juvenile and adult variants. The juvenile variant exhibits a biphasic pattern with mild-to-moderately cellular areas of elongated fusiform unipolar and bipolar cells interspersed with hypocellular, microcystic areas. Adult variants do not demonstrate a biphasic pattern, but rather display densely packed bundles of broad bipolar fibrillated cells. The tumor cells have no predilection for microcystic degeneration. Rosenthal fibers are abundant. Anaplastic degeneration is more commonly seen in the adult variant [77].

PA may have features of anaplasia including mitoses, pleomorphism, and necrosis. Anaplastic transformation of PA has been reported in patients who have been treated with radiation therapy, but no causal relationship has been demonstrated [78, 79]. Reports vary on the rate of malignant transformation in adults. In one series, PFS was 94%, and there were no cases of malignant transformation [72]. In another series, there was a 30% recurrence rate with 50% (four of eight) of patients demonstrating malignant transformation on tissue analysis [80]. Similarly, a recent study found a 30% incidence of tumor recurrence and findings consistent with malignant transformation in three out of four tumors requiring repeat resection [81].

In the past, the molecular patterns underlying the behavior of PA had been elusive. The genetic loci characteristically involved in higher grade gliomas do not play a role in the biologic behavior of PA [82]. However, a recently observed rearrangement of the \(BRAF\) gene has been shown to be a common event in PA [83–86]. \(BRAF\) is a member of the Raf family and acts as a downstream target of Ras in the mitogen-associated protein kinase (MAPK) pathway, promoting tumor cell proliferation [87]. A recent study confirmed the high rate of \(BRAF\) mutations in PA but demonstrated that the presence of \(BRAF\) rearrangement did not predict tumor behavior [82]. Another study showed that the presence of \(BRAF\) mutations is highly specific for PA when compared to grade II astrocytoma [88]. These findings are important because they suggest a potential therapeutic target for tumors that are unresectable or recur following standard therapy.

PA rarely presents with hemorrhage. In a series of 138 patients, 11 (8%) presented with hemorrhage prior to surgery [89]. Proposed mechanisms for hemorrhage include endothelial proliferation, rupture of encased aneurysms, and dysplastic capillary beds [90, 91].

**Prognostic Factors**

Extent of resection is the only factor that has been traditionally associated with prolonged survival in patients with PA. In one study, 10-year OS was 100% in the patients with gross total resection as compared to 74% in the patients with subtotal resection [73]. Patients who undergo biopsy alone have a much shorter OS, on the order of 44% [73]. Neither histologic features nor administration of radiation therapy clearly influence OS [73]. Based on the location, optic pathway gliomas usually cannot be fully resected and as a result have been associated with a worse prognosis than PA in other locations [92–94]. In contrast to previous studies, a recent study reported several histologic features associated with worse prognosis in 107 patients with PA. These histologic features include necrosis, oligodendrogial-like features, hyalinization, and calcification [94].
**Treatment**

Since gross total resection (GTR) increases cure rates, patients with imaging features suggestive of PA should undergo GTR whenever possible [73]. PA lends itself well to GTR, as the tumor is well circumscribed and often does not infiltrate surrounding tissue. For cystic tumors, the most important goal is complete resection of the mural nodule [95]. Although no randomized trials have been conducted, most authors agree that adjuvant radiation is unnecessary following GTR [73].

Some tumors may not be amenable to GTR because of location in eloquent brain. For patients who undergo subtotal resection, observation is reasonable with additional surgery at the time of recurrence. It is difficult to assess the benefit of adjuvant radiation and chemotherapy in PA, as most studies have analyzed PA patients together with patients with diffuse astrocytoma. Several small studies have reported favorable outcomes for patients receiving radiation after subtotal resection, biopsy, or at the time of recurrence [96–98].

Chemotherapy has been used to treat PA located in eloquent brain as well as recurrent disease. The majority of studies have been completed in the pediatric population. Carboplatin has often been used alone or in combination with vincristine. One study of carboplatin monotherapy in 81 pediatric patients with progressive glioma, 38 of which were PA, showed a 3-year OS and PFS of 84 and 64%, respectively [99]. Another study reported a 3-year OS of 97% and PFS of 68% in 78 pediatric patients with low-grade glioma, 17 of which were PA, treated with carboplatin and vincristine [100]. Because of its critical role in high-grade glioma, temozolomide has been evaluated in the low-grade glioma population. In a series of eight recurrent PA patients who completed 1 year of temozolomide, two had complete responses, three had partial responses, and three had minor responses [101]. In another series of 12 patients with recurrent PA, 10 (83%) had stable disease with follow-up ranging from 9 to 62 months [102]. Bevacizumab and irinotecan may also be active in recurrent PA. In a low-grade glioma series that included two patients with PA, one achieved partial response and the other minor response [103].

**Pleomorphic Xanthoastrocytoma**

**Introduction**

Pleomorphic xanthoastrocytoma (PXA) is a relatively new clinicopathologic entity that was originally described in 1979 [104]. PXA is classified as a WHO grade II astrocytoma (Table 12.1). PXA is most often found along the superficial cortex and leptomeninges of the temporal lobe. PXA generally has a favorable prognosis, although anaplastic forms may be resistant to treatment.

**Epidemiology**

PXA is an extremely rare tumor, and exact figures of incidence and prevalence are not known. One report estimated that PXA accounts for less than 1% of all astrocytic
tumors [105]. PXA is typically a tumor of children and young adults with a median age at diagnosis of 14, with the majority of tumors diagnosed between ages 7 and 25 [106]. However, PXA has been reported in patients as young as 2 and as old as 82 years [106]. There is an equal sex distribution.

**Clinical Manifestations/Diagnosis**

PXA typically involves the cerebral hemispheres and is most commonly found in the temporal lobe followed by the parietal lobe, occipital lobe, and frontal lobe [105, 106]. Rarely, PXA has been reported in extracortical locations including the cerebellum, thalamus, retina, and spinal cord [107–111]. Four cases of PXA with widespread dissemination at the time of diagnosis have been reported in the literature [112–115]. Seizures and headaches are typical presenting symptoms, but seizures are often the only symptom and are frequently difficult to control [116, 117]. The median duration of seizures prior to diagnosis is 3 years [105]. Symptoms may be insidious in onset, evolving over months to years. However, these tumors can present subacutely due to mass effect or increased intracranial pressure.

The radiographic appearance of PXA is variable and may be difficult to distinguish from other lesions (Fig. 12.3). The most typical appearance on CT or MRI is of a partially calcified, cystic or solid lesion in the superficial temporal cortex abutting the leptomeninges. On CT, PXA can appear hypodense or hyperdense with contrast enhancement. On MRI, PXA is of variable signal intensity on T1, hyperintense on T2, and has a variable degree of contrast enhancement. Leptomeningeal enhancement is rare. The absence of enhancement or minimal enhancement of the cyst wall often differentiates PXA radiographically from pilocytic astrocytoma. PET imaging reveals low metabolic activity [118]. The radiographic differential

**Fig. 12.3** MRI scan from a 38-year-old man with a long-standing seizure disorder, who presented with headaches. The T1 post-gadolinium sequence showed a large mass with rim-enhancing cystic and solid components. Histopathology confirmed the diagnosis of pleomorphic xanthoastrocytoma. The imaging findings shown here are relatively nonspecific; this lesion was presumed to represent glioblastoma prior to resection.
diagnosis includes meningioma, dysembryonic neuroectodermal tumor (DNET), ganglioglioma, and PA.

**Pathology/Classification**

PXA is a distinct entity from other types of astrocytomas. PXA usually involves the superficial cortex with extension into perivascular spaces and often involves the leptomeninges. The tumor has the gross appearance of a firm nodule, often with a cystic component. Microscopically, the tumor has moderate cellularity consisting of astrocytes with pleomorphic nuclei, nuclear atypia, spindle cells, and bizarre, multinucleated giant cells. PXA has a dense reticulin network. Cells often stain strongly positive for GFAP which led to PXA being classified as astrocytoma [104]. Lipid droplets are present in many cells (xanthic). Extracellular granular bodies are nearly always present [105]. Cells may stain positive for S-100.

Neuronal markers in PXA such as synaptophysin, class III beta-tubulin, NF proteins, and MAP2 have been described [118–120]. This supports the theory that PXA is a neuroglial tumor derived from a primitive neuroectodermal precursor [118]. This is further supported by the finding of composite tumors such as composite PXA and ganglioglioma [121]. PXA often adheres to the leptomeninges but rarely infiltrates beyond the meninges [107].

The high cellularity, atypical nuclei, and giant cells may result in PXA being misdiagnosed as giant cell glioblastoma. However, despite this undifferentiated histologic appearance, typical PXA lacks anaplastic features such as necrosis, endothelial proliferation, hypercellularity, and mitotic figures. Additionally, PXA is well circumscribed, unlike its high-grade glioma counterpart. However, anaplastic features such as necrosis, endothelial proliferation, hypercellularity, and mitotic figures are sometimes observed in PXA. Such tumors behave more aggressively and may require more aggressive treatment. An elevated mitotic index correlates with decreased PFS and OS. The term “PXA with anaplastic features” is used to distinguish this subtype from anaplastic astrocytoma. In one series, anaplastic transformation was reported in 15–20% of cases [105]. Anaplastic PXA can evolve into anaplastic astrocytoma or glioblastoma. This tendency to transform distinguishes PXA from other circumscribed neuroectodermal tumors such as PA and ganglioglioma.

Molecular alterations in PXA are poorly understood. One study found a paucity of genetic aberrations commonly seen in other infiltrating astrocytomas such as loss of \( CDN2KA, CDK4, MDM2, \) or \( EGFR \) [122]. Another study demonstrated that \( TP53 \) mutation is an uncommon finding in PXA [123]. These findings suggest that the molecular pathogenesis of PXA is likely distinct from diffuse astrocytoma.

**Prognostic Factors**

The 5-year PFS and OS for PXA has been reported in several series as 50% and 70–80%, respectively [105, 106, 116, 124]. Patients with PXA tend to have a
worse prognosis than patients with other circumscribed low-grade gliomas such as pilocytic astrocytoma and subependymal giant cell astrocytoma. Anaplastic PXA appears to have an even worse prognosis, but the published literature about these tumors is very limited. In tumors with histological evidence of necrosis at diagnosis or recurrence, outcomes are particularly poor with a median post-operative survival of 1 year [106]. Extent of resection is an important prognostic factor [105, 125]. In one series, 15-year PFS was 50% for patients who underwent STR, as compared to 80% for patients who underwent GTR [105]. GTR has also been shown to prolong OS [106].

Treatment

The mainstay of treatment for PXA is complete surgical excision. The overall 5-year and 10-year survival for patients with complete surgical excision is 85 and 70%, respectively [105]. A significant improvement in seizure control is usually achieved after maximal surgical resection [116, 126]. The approximate recurrence rate after surgical excision is 15–20% [114]. Tumor is most likely to recur at the site of initial resection. Leptomeningeal involvement at the time of recurrence is common [116]. Despite the low-grade histology, it is important to follow PXA patients, as anaplastic transformation at the time of recurrence has been reported in more than one series [116, 127]. Surgical resection is often appropriate at the time of recurrence. The role of radiation and chemotherapy has not been established in PXA. However, these modalities may be appropriate for anaplastic PXA or transformed PXA. In a recent series of 17 patients with anaplastic PXA, there was no therapeutic benefit demonstrated with conventional fractionated radiotherapy [128]. Likewise, no benefit was demonstrated for radiotherapy in patients with PXA with necrosis [106]. In one case of anaplastic PXA with dissemination to the spine, repeated stereotactic radiosurgery achieved effective disease control [129].

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Part III
Other Tumor Types
Chapter 13
Pediatric Tumors

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Epidemiology

Tumors of the central nervous system (CNS) are the leading cause of cancer-related mortality in children. Brain tumors account for approximately 25% of pediatric cancers. They rank second behind leukemia as the most common pediatric cancer diagnosed in the United States each year, and they are the most common form of solid tumor in children. Improvement in outcome for pediatric brain tumors has lagged far behind that of many other cancers, especially childhood leukemia. The complexity of curing pediatric brain tumors is related to the large number of different histologies within the CNS and the need to modify therapies to spare neurocognitive function in young patients. These complexities are in addition to the difficulties of treating brain tumors generally, including decreased drug delivery due to the blood–brain barrier and limited surgical options in critical areas of brain function. This chapter will discuss the different types of brain tumors in children based on the modified World Health Organization (WHO) classification of central nervous system tumors [1].

According to the most recent National Cancer Institute Surveillance Epidemiology, and End Results (SEER) Cancer Statistics Report (CSR) published in 2007, the annual age-adjusted incidence rate of pediatric malignant brain and other nervous system tumors is 2.8 cases per 100,000 children [2]. The 2007–2008

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Central Brain Tumor Registry of the United States (CBTRUS) Statistical Report includes primary non-malignant as well as malignant pediatric CNS tumors and reports the annual CNS tumor incidence as 4.5 cases per 100,000 children. The rate is higher in males (4.7 per 100,000) compared to females (4.3 per 100,000) and in Whites (4.7 per 100,000) compared to Blacks (3 per 100,000). The prevalence rate for all malignant and benign pediatric CNS tumors (ages 0–19) is estimated at 9.5 per 100,000, with more than 26,000 children estimated to be living with this diagnosis in the United States in 2000 [3].

Approximately 3,750 new cases of childhood primary CNS tumors will be diagnosed in the United States each year. Of these, an estimated 2,820 will be in children less than 15 years of age. The most common histologies in the younger age group (0–14 years) include pilocytic astrocytoma and embryonal tumors (predominantly medulloblastoma), which account for 30% and 16%, respectively. The most common histologies in the adolescent age group (15–19 years) include pilocytic astrocytoma and pituitary tumors, which account for 15% and 14%, respectively. The broad category glioma accounts for 56% of tumors in children less than 15 years of age and 45% of tumors in adolescents aged 15–19 years [3].

Primary CNS tumors develop from an accumulation of genetic changes. These changes can result from inherited mutations or they can be acquired from exposure to chemical, physical, or biologic agents that damage DNA. Different from adults where exposures accumulate over a lifetime, most pediatric tumors are thought to be the result of random genetic mutations that occur during neural development. Ionizing radiation (including that from therapeutic radiation to the CNS or potentially from computed tomography scans), immunosuppression, and certain hereditary genetic disorders are the only factors associated with risk for childhood CNS malignancy. The vast majority of patients have no easily identifiable risk factors to explain the cause of their tumors. For a small percentage, inherited genetic mutations will be the cause.

Pediatric Brain Tumors and Genetic Syndromes

Known hereditary cancer predisposition syndromes account for only a small minority of pediatric malignancies, although the true incidence of underlying genetic diseases may be higher than is clinically recognized [4]. All of the syndromes described below, and indeed most cancer predisposition syndromes, demonstrate autosomal dominant inheritance and may be caused with varying frequency by de novo germline mutations [5]. Manifestation of characteristic features is quite variable; diagnosis requires a careful history and examination and a high degree of suspicion. Accurate diagnosis may have implications both for screening and for therapy: the long-term sequelae of irradiation, for instance, are markedly increased in many or most of these syndromes.

Neurofibromatosis 1 (NF1), the most common genetic syndrome in North America, is an autosomal dominant neuroectodermal disorder attributable to a
mutation in the neurofibromin gene, \textit{NF1}. The syndrome is characterized by cafe-au-lait spots and fibromatous tumors of the skin. Other common features include hamartomas of the iris (Lisch nodules), scoliosis, cognitive problems, and epilepsy [6–8]. Focal T2 changes in the brain and cerebellum without mass effect, the so-called Unidentified Bright Objects or UBOs, are a characteristic imaging finding; these are not clinically significant and should not be biopsied [9]. Optic glioma is the most common tumor in \textit{NF1}, occurring in 5–15\% of patients. These tumors in this setting tend to follow an indolent course, and a majority may never require treatment. Brainstem, cerebral hemispheric, and basal ganglia gliomas are also seen at significantly increased frequency, as well as pheochromocytomas, ependymomas, and meningiomas. Radiation should be avoided where feasible in \textit{NF1} patients, who are at increased risk of sequelae including moyamoya syndrome [10, 11] and second malignancies.

\textit{Neurofibromatosis 2 (NF2)} is characterized by bilateral vestibular schwannomas, as well as peripheral schwannomas and neurofibromas. Affected individuals also have a higher incidence of intracranial meningiomas and, to a lesser extent, gliomas and spinal tumors [12]. The syndrome is due to mutations in the gene at 22q12.2 that encodes merlin (also known as schwannomin) [13, 14]. The onset of symptomatic tumor growth is uncommon in childhood and most patients are diagnosed in adulthood.

\textit{Tuberous sclerosis (TS)} is characterized by hamartomas of multiple organs, as well as epilepsy, cognitive and behavioral problems, and characteristic skin lesions (“ash leaf” spots and adenomata sebaceum). Between 5 and 14\% of affected individuals develop brain tumors. The subependymal giant cell astrocytoma (SEGA) is the pathognomonic lesion. SEGAs usually originate in the ependymal walls of the lateral ventricles and are associated almost exclusively with TS [15]. Gliomas and ependymomas are also seen at increased frequency. Other characteristic non-cancerous intracranial lesions include cortical tubers (hamartomas), subcortical glioneuronal hamartomas, and subependymal glial nodules. The syndrome is due to mutations in either \textit{Tsc1} (hamartin) [16] or \textit{Tsc2} (tuberin).

\textit{Li–Fraumeni syndrome}, one of the more potentially devastating familial cancer predisposition syndromes, is due in most cases to mutations in the \textit{TP53} tumor suppressor gene [17–19]. The classic Li–Fraumeni syndrome is defined as: (1) a proband diagnosed with sarcoma at age less than 45 years, with (2) a first-degree relative diagnosed with any cancer also at age less than 45 years, and (3) another first-degree or second-degree relative diagnosed with either any cancer at age less than 45 years or a sarcoma at any age [20]. The Li–Fraumeni-like syndrome encompasses the larger group of patients, some with a germline \textit{TP53} mutation, who do not meet the classic criteria [19]. Patients are at markedly increased risk for multiple malignancies, both CNS (including gliomas, primitive neuroectodermal tumors [PNET], medulloblastoma, and choroid plexus carcinoma) and systemic (sarcomas, adrenocortical carcinoma, acute leukemia, and premenopausal breast cancer, among others) [18, 20]. Manifestation of this syndrome is variable; the index of suspicion should be high in evaluating any childhood malignancy, especially in the setting of a positive family history [5].
Von Hippel–Lindau syndrome (VHL), also known as retinocerebellar hemangioblastosis, is attributable in almost all cases to mutations in the VHL gene on 3p25–26 [5, 21]. Central nervous system hemangioblastomas in children occur almost exclusively in the setting of VHL. The syndrome manifests primarily as WHO Grade I hemangioblastomas of the retina, cerebellum, and spine, as well as a number of both benign and malignant systemic abnormalities, including pancreatic cysts, renal angiomas, renal cell carcinomas, and pheochromocytomas [5, 22]. Hemangioblastomas present a therapeutic challenge: surgical resection is the most effective treatment [23–26], but tumor location and multifocality may render complete resection infeasible. Embolization [27] and radiosurgery [28, 29] may be useful adjuvant modalities. Vascular endothelial growth factor (VEGF) inhibition may also prove an effective strategy [30]. Multifocality and recurrence of hemangioblastomas are common and likely represent new spontaneous tumors, rather than metastatic disease. Non-CNS neoplasms, including renal angiomas, renal cell carcinomas, and pheochromocytomas, are frequently seen in adulthood [5]. Life-long screening is required [23]. Recommendations for management and screening are published and updated by the VHL family alliance at http://www.vhl.org/.

Gorlin's syndrome, also known as nevus basal cell carcinoma syndrome, is attributable to deregulated Sonic hedgehog pathway activation caused by mutations in Ptc (9q22.3), which encodes the receptor for the Sonic hedgehog ligand [31–36]. The defining feature is multiple basal cell nevi or carcinomas that usually develop around puberty. Other features include odontogenic keratocysts or polyostotic bone cysts and palmar and plantar pits; rib or vertebral anomalies; large head circumference with frontal bossing; cardiac or ovarian fibromas; and lymphomesenteric cysts [37]. Between 3 and 10% of affected individuals develop medulloblastomas in early childhood, primarily the desmoplastic subtype [38]. Incidence of other tumors, including rhabdomyosarcoma, is also increased [39, 40].

Turcot's syndrome is defined by the occurrence of malignant brain tumor in a patient with hereditary colon cancer. There are two subtypes, corresponding to the two main hereditary colon cancer syndromes: familial adenomatous polyposis coli (FAP) and hereditary non-polyposis colon cancer (HNPCC) [41, 42]. Patients with FAP, due to mutations in APC (5q21), are at increased risk for medulloblastoma [42]. Affected individuals may show other abnormalities, including retinal lesions, osteomas, and desmoid tumors of the skin [43]. HNPCC, also known as Lynch syndrome, is usually attributable to mutations in mismatch repair genes MLH1, MSH2, or PMS2 [44] and is associated with an increased risk of malignant glioma in childhood and adolescence [42].

Cowden syndrome, also known as multiple hamartoma syndrome, is attributable to mutations of the gene encoding the phospholipid phosphatase PTEN, with resultant deregulation of Akt signaling [45–47]. The syndrome is characterized by hamartomas of the skin, bone, eyes, and gastrointestinal or genitourinary mucosa, as well as of the CNS, with a predisposition for breast, endometrial, and thyroid malignancies [46, 48]. A characteristic feature is the development in young adulthood of hamartomatous cerebellar gangliocytoma (Lhermitte–Duclos disease) [45, 49]. Of note, childhood Lhermitte–Duclos disease is usually sporadic and not associated with germline PTEN mutation [50].
**Hereditary retinoblastoma** is characterized by markedly increased risk for unilateral or bilateral retinoblastoma \[51\]. It is attributable to mutations in the retinoblastoma gene, \textit{RB1}, which was the first tumor suppressor gene identified and the foundation for Knudson’s “two-hit” hypothesis \[51, 52\]. Affected individuals are at increased risk for other CNS malignancies, particularly pineoblastoma, termed “trilateral retinoblastoma” \[53\], as well as osteosarcoma, rhabdomyosarcoma, and meningioma \[54\]. For patients who receive radiotherapy, risk of second malignancy (typically, osteosarcoma within the irradiated field) is particularly high \[55\]. Genetic evaluation is indicated for the family of any child diagnosed with retinoblastoma, and regular ophthalmologic screening should be performed for any identified siblings or progeny.

**Rubinstein–Taybi syndrome**, also known as broad thumb–hallux syndrome, is a syndrome of congenital anomalies attributable to mutations in either the gene encoding CREB-binding protein (CBP) \[56, 57\] or less commonly EP300 \[58\], both histone acetyltransferases. The syndrome is characterized by moderate-to-severe mental disability, microcephaly, small stature, broad thumb and great toe, cryptorchidism, and distinct facies (highly arched eyebrows, down-slanting palpebral fissures, broad nasal bridge, beaked nose, and a characteristic grimace) \[56, 59\]. Patients are at increased risk for several tumors, including medulloblastoma, meningioma \[60\], and leukemia \[61\].

**Presentation of Pediatric Central Nervous System Tumors**

The presenting symptoms for patients with brain tumors can usually be categorized into one of two patterns: direct compression of brain tissue and obstructive hydrocephalus. The location of the tumor, histologic subtype, rate of tumor growth, and age of the patient are major determinants in the length of time between clinical symptoms and diagnosis \[62\]. Multiple visits to primary care providers before a diagnosis of brain tumor is made \[63\] are especially likely for young children who cannot verbalize their symptoms.

**Direct Compression of Brain Tissue**

A mass within the brain takes up space, resulting in the displacement of normal structures within the fixed structure of the cranium. As a tumor compresses adjacent normal structures, it causes a constellation of symptoms that can be referred back to a specific region within the CNS. Based on detailed functional and anatomical understanding, a few common patterns of symptoms account for a significant percentage of patient complaints at presentation with a brain tumor. Supratentorial lesions in gray matter of the frontal, parietal, temporal, and occipital lobes can result in seizures, while those in white matter tend to result in focal neurologic deficits. Frontal lesions may result in changes in mood and behavior. Parietal lobe
lesions cause focal sensory deficits, while thalamic lesions can result in significant hemiparesis. Hypothalamic and suprasellar lesions can result in endocrine dysfunction. Pineal lesions cause Parinaud’s syndrome (paresis of upward gaze, enlarged pupils that are poorly reactive to light, and limited convergence). Posterior fossa lesions, which include the brainstem, 12 cranial nerves, descending and ascending fibers that connect the upper and lower central nervous system, and cerebellum, may result in cranial nerve dysfunction, lower motor neuron deficits, or ataxia/dysmetria. Recognizing these patterns of brain tumor localization can facilitate evaluation and also anticipation and management of brain tumor-related issues.

**Obstructive Hydrocephalus Causing Increased Intracranial Pressure**

The brain and spine float within the cranium and spinal canal, supported by cerebrospinal fluid (CSF) that is largely localized to the subarachnoid space. CSF is initially made by the choroid plexus within the lateral ventricles (and to a lesser degree in the third and fourth ventricles) and is eventually resorbed by the arachnoid villi. Obstruction by tumor anywhere above the exit from the ventricles to the subarachnoid space (posterior fossa or above) will therefore result in obstructive hydrocephalus. The speed of the accumulation of fluid determines in part the rapidity and severity of symptoms. In children, as in adults, three common symptoms of obstructive hydrocephalus include headaches that are often severe, vomiting especially in the morning, and visual changes (blurred vision due to swelling of the optic discs or impaired upgaze). The final common symptom of obstructive hydrocephalus is due to pressure on the motor tracts in the brainstem and on the cerebellum causing difficulties with balance and gait. In infants, the symptoms of obstructive hydrocephalus differ. The presence of open sutures in the skull permits the head to expand, thereby relieving the buildup of pressure and thus the associated symptoms. As the head size expands, infants may begin to show some signs of delay in achieving developmental milestones. Routine monitoring of head circumference can identify infants with obstructive hydrocephalus early, whether the cause is due to tumor or some other condition.

**Gliomas**

Gliarial tumors include a wide range of neoplasms that differ in terms of location, grade, imaging characteristics, histology, degree of invasiveness and metastasis, and prognosis. These tumors include astrocytic and oligodendroglial lineages, which are discussed together. The related ependymal tumors are discussed separately. Astrocytomas can be classified as low grade or high grade. Low-grade gliomas may consist of relatively pure tumors, like pilocytic astrocytomas, or mixed populations
of both glial and neuronal lineages, like ganglioglioma. Pediatric gliomas can also be classified with respect to location. Both variables will be used to describe gliomas here.

**Glioma Location Often Predicts Presentation**

**Supratentorial and Cerebellar Astrocytomas**

Supratentorial tumors often present with progressive focal neurologic deficits in children and large head size in infants. Cerebellar tumors usually present with symptoms of increased intracranial pressure such as headache, nausea, and vomiting due to obstruction of the fourth ventricle causing increased intracranial pressure.

**Optic Pathway/Hypothalamic Gliomas**

Optic pathway gliomas can involve the optic nerves, chiasm, optic tract, and optic radiations and may also infiltrate the adjacent hypothalamus/diencephalon and temporal lobes. These tumors represent at least 4–6% of all primary pediatric brain tumors [64], and they are evenly distributed between boys and girls. Most optic pathway gliomas are pilocytic astrocytomas (WHO Grade I) [65]. Optic pathway gliomas are strongly associated with *NF1*, although sporadic lesions are not uncommon. Optic pathway gliomas often present with the classic triad of visual loss, proptosis, and optic nerve atrophy [66]. Chiasmatic involvement may lead to unilateral or bilateral visual loss, a bitemporal field defect, and obstructive hydrocephalus due to obstruction of CSF flow in the third ventricle. Hypothalamic extension may result in endocrine abnormalities. Invasion into the brain parenchyma may result in visual field abnormalities and hemiparesis. Diencephalic gliomas typically occur in young infants [67]. They are more frequently associated with pilomyxoid astrocytomas (WHO Grade II), and a high incidence of dissemination throughout the neural axis can also occur [68]. These patients may present with diencephalic syndrome characterized by the three Es (emaciation, emesis, and euphoria) with normal linear growth [69, 70]. They are at high risk for surgery-induced hypothalamic damage resulting in obesity.

**Thalamic Gliomas**

Thalamic tumors account for less than 5% of intracranial tumors. In children, approximately 60% are low-grade astrocytomas while the remaining 40% are high-grade lesions [71, 72]. Thalamic tumors occur at a slightly older age than many other low-grade gliomas of childhood. They can be described as unilateral or bilateral, with a worse prognosis attributed to the latter. The most common presenting symptoms include increased intracranial pressure, tremors, motor deficits, seizures, and mood changes [73].
Midbrain and Brainstem Astrocytomas

Diffuse intrinsic pontine gliomas make up the majority of brainstem gliomas. They are characterized by rapid onset of neurologic symptoms (usually cranial nerve dysfunction, long-tract signs, and cerebellar dysfunction) usually of less than 6 months in duration and characteristic neuroimaging. Even with intensive therapy, most patients succumb to the disease within 2 years from diagnosis. Still, approximately 20% of brainstem tumors are low-grade astrocytomas involving the tectum, midbrain, or medulla or the junctions between them. In spite of the eloquent function of these areas, most of these patients have a very indolent course with subtle neurologic findings including cranial nerve dysfunction with head tilt or lower motor neuron weakness with subtle hemiparesis. Most parents have difficulty defining the start of the symptoms and refer to the child as having always been clumsy or weak.

Tectal gliomas in particular are typically hamartomas or low-grade astrocytomas. Most patients with tectal gliomas present with symptoms of obstructive hydrocephalus due to expansion of these lesions to the periaqueductal space. Biopsy or resection of tectal gliomas is usually not required, as diagnosis is based on MRI appearance of the lesion. Rather, most patients require immediate CSF diversion through a third ventriculostomy [74, 75]. Therefore, tectal gliomas appear to represent a unique variant of glioma, based on their positive long-term outcome with relief of hydrocephalus as the sole therapeutic intervention. The overall survival for patients with this tumor approaches 100% [76], and thus avoidance of unnecessary surgical or radiation-related long-term morbidity is critical.

Glioma Grade Often Predicts Prognosis and Treatment

Low-Grade Astrocytomas

Low-grade astrocytomas encompass both WHO Grade I and II glial tumors. Grade I tumors are the most common low-grade gliomas found in children, representing 30% of all childhood brain tumors. Most WHO Grade I tumors in children are the well-circumscribed pilocytic astrocytomas (PAs) [1]. Other WHO Grade I gliomas include gangliogliomas, dysembryoplastic neuroepithelial tumors, and desmoplastic infantile gangliogliomas. WHO Grade II gliomas include pilomyxoid astrocytomas, fibrillary astrocytomas, pleomorphic xanthoastrocytomas, and oligodendrogliomas. Each of these is discussed individually below. The overall survival of children and adolescents with low-grade astrocytomas at 10 years is 70–80% [77–79].

Pilocytic astrocytomas typically appear in the first two decades of life and have no clear gender predominance. They are usually slow-growing, although they can present with acute deterioration due to obstructive hydrocephalus. Low-grade astrocytomas in children behave differently than low-grade astrocytomas in adults with a varied course that ranges from persistent recurrence or dissemination to spontaneous regression without therapy [80, 81]. Management of pilocytic and low-grade gliomas is discussed below.
Gangliogliomas are WHO Grade I glial–neuronal tumors. They represent 4–8% of primary brain tumors in children, with a mean age of presentation under 10 years [82]. Gangliogliomas can be identified throughout the CNS [83, 84] and are typically slow-growing. Seizures are the first manifestation in half of all cases of ganglioglioma, and many patients have a prolonged history of seizures for more than 2 years [82]. Complex partial seizures are common since gangliogliomas are frequently located in the parietal and temporal lobes [82], particularly the temporo-mesial region [85]. Patients who undergo complete resection are often cured. Even patients who have undergone subtotal resection may remain progression free. Therefore, treatment should be reserved for those lesions that show clear evidence of progressive disease [86].

Dysembryoplastic neuroepithelial tumors (DNET) are a recently described WHO Grade I tumor [1] with an average age of onset of 9 years. They may comprise as many as 1% of all brain tumors in patients younger than 20 years of age [87]. Two-thirds of DNETs are located in the temporal lobe, and DNETs are found in 5–15% of temporal lobe resections for intractable epilepsy. Patients typically present with a long history of complex partial seizures, possibly due to localization of these tumors in superficial cortical locations. These tumors are thought to be developmental in nature and are considered to have limited proliferative potential. Their stable behavior over time results in an excellent prognosis after either gross total or partial resection [88]. Gross total resection also typically alleviates seizures. Adjuvant chemotherapy or radiation therapy is not recommended. In spite of this, recurrences of DNET can occur [89] and, rarely, malignant transformation following radiation and chemotherapy has been reported [90].

Desmoplastic infantile gangliogliomas (DIGs) are WHO Grade I supratentorial tumors involving the leptomeningial surface that are identified predominantly in children under the age of 2 [91]. Although precise estimates of their incidence is lacking, they make up less than 1% of pediatric brain tumors. These lesions are often very large, in part due to the presence of cysts, and they frequently involve the dura. Young patients present with increasing head circumference, bulging fontanelle, and lethargy, while older patients present with focal motor deficits. Complete resection is associated with long-term survival [92], but chemotherapy may be used in symptomatic or progressive cases where surgical resection is not feasible [93, 94].

Pilomyxoid astrocytomas are a newly defined group of WHO Grade II pediatric tumors in the 2007 WHO classification [1, 95] that were previously grouped together with pilocytic astrocytomas [96, 97]. Their variable histologic appearance compared to pilocytic astrocytomas [98], magnetic resonance spectroscopy signal changes [99], and higher incidence of progression and dissemination support their distinction from pilocytic astrocytomas [96]. They are found most commonly in the midline of the brain and spine [100] and may be solid or cystic. Many patients with pilomyxoid astrocytomas are infants and have diencephalic syndrome with dissemination, so complete surgical resection is not possible. Thus, most patients will require treatment with chemotherapy. The prognosis of pilomyxoid astrocytoma is difficult to assess with certainty as confounding issues of unresectable deep lesions, patients of young age, and the presence of metastatic disease likely impact
the overall poor prognosis of patients with these rare tumors. At recurrence, tumors can appear as classic pilocytic astrocytomas, suggesting a development relationship between the two tumors [101].

Fibrillary astrocytomas, WHO Grade II, are low-grade astrocytomas that are distinct from pilocytic astrocytomas. Precise determination of the incidence of fibrillary astrocytomas is difficult since many tumors, especially those in deep structures of the midbrain or brainstem, cannot be fully resected to provide sufficient material for accurate pathologic classification. The peak age at diagnosis is 6–10 years, and no gender predilection exists. Unlike adult fibrillary astrocytomas, in which degeneration to malignant gliomas is common, pediatric fibrillary astrocytomas remain low grade even after multiple recurrences [71, 102]. Patients with fibrillary astrocytomas have a poorer outcome than patients with WHO Grade I astrocytomas [103]. Since pilocytic astrocytomas are focal and easier to resect than fibrillary astrocytomas, prognosis may be related to the ease of resection rather than to biologic differences between these histologic variants.

Pleomorphic xanthoastrocytomas (PXAs) are uncommon WHO Grade II or III cortical tumors that mainly occur in children and adolescents and account for less than 1% of brain tumors.

The median age at the time of diagnosis is 14 years. PXAs are typically large and superficially located, especially in the temporal lobes. Seizures are the most common initial feature. PXAs typically demonstrate intratumoral cysts and calcification, and tumors usually extend to the meninges. Gross total resection is usually curative [104].

Oligodendrogliomas are uncommon lesions in children, representing less than 1% of all pediatric brain tumors [105, 106]. The mean age at diagnosis is approximately 10–13 years old with a male predominance [107, 108]. Oligodendrogliomas are diffusely infiltrating WHO Grade II or III tumors that tend to occur in the white matter of the cerebral hemispheres. Patients frequently present with seizures or with headache, visual field defects, paresis, and cranial nerve palsies [107]. Higher grade tumors may present with evidence of increased intracranial pressure due to more rapid growth [109]. In pediatric patients, the extent of resection is a sensitive predictor of outcome [110]. The loss of chromosome 1p and/or 19q in adult oligodendrogliomas that correlates strongly with chemotherapy responsiveness and outcome [111] is not recapitulated in pediatric oligodendrogliomas, where the incidence of 1p and/or 19q deletions is much lower [112, 113]. Since fewer pediatric low-grade oligodendroglial tumors progress to high-grade tumors, patients with subtotally resected tumors may still have a good outcome. Management follows that for low-grade gliomas generally and is discussed below.

**High-Grade Astrocytomas**

High-grade astrocytomas (HGAs) are much less common in children than in adults. While over 30% of all pediatric brain tumors are low-grade gliomas, supratentorial high-grade astrocytomas represent only 6–12% of all primary pediatric brain tumors. High-grade gliomas are either anaplastic astrocytoma (WHO Grade III) or
glioblastoma (WHO Grade IV). The clinical prodrome is usually short and rapidly evolving with signs and symptoms of elevated intracranial pressure and/or focal neurologic deficits. Dissemination of malignant glioma into the CSF is less common than for medulloblastoma and other brain tumors but is being recognized more frequently [114]. Most of these patients eventually succumb to their disease, even with maximal resection, radiation therapy, and adjuvant chemotherapy. The study of adult glioblastoma may be less informative regarding the molecular pathways involved in pediatric glioblastoma than previously thought [115, 116].

Congenital glioblastoma is observed at birth or within the first 3 months of life and appears genetically distinct from its childhood and adult counterparts. Infants with malignant glioma have a significant long-term survival rate (estimated around 25%) after surgery and chemotherapy, even without radiation therapy, emphasizing the unique characteristics of these tumors in infants [117–123].

Gliomatosis cerebri is more common in adults but can be identified in children [124]. These lesions are often WHO Grade III astrocytomas that diffusely infiltrate the brain and frequently cross the corpus callosum. The overall prognosis is very poor due to their diffuse nature and unresectability. The mainstay of therapy is radiation to the involved region. In pediatric patients, this can be difficult and requires near whole brain therapy. Younger age, lower grade histology, and chemoresponsiveness were associated with slightly longer survival times [125].

Diffuse brainstem gliomas represent 10% of pediatric brain tumors. The median age at diagnosis is 7–9 years of age, but these tumors may occur throughout childhood [126]. Diffuse intrinsic pontine gliomas are a unique subset of brainstem tumors with a dismal prognosis [127, 128]. Patients often present with a several months’ history of symptoms and may have multiple cranial neuropathies, long-tract signs, and cerebellar signs. Hydrocephalus is observed in less than 10% of patients. Patients with diffuse pontine gliomas are often not biopsied in order to try and minimize the damage to the brainstem. The diagnosis of diffuse pontine gliomas has typically been based on the classical MRI appearance of a diffusely expanded pons with encasement of the basilar artery [129]. These tumors can be either low grade or high grade [130]. Over the last 30 years, little progress has been made in the treatment of these lesions [131]. Radiation therapy has improved the median overall survival from weeks to months and can allow for relief of neurological symptoms and reduction of steroid use. Patients with diffuse intrinsic pontine gliomas typically demonstrate rapid progression and death, with less than 10% of patients alive by 2 years [132].

**Imaging**

The typical MRI appearance of a WHO Grade I pilocytic astrocytoma is an intensely homogeneous, well-circumscribed, enhancing lesion with minimal surrounding edema. Lesions may have both nodular and cystic components (see Figs. 13.1a, b). They are typically bright on both T1-weighted and T2-weighted sequences. Tumoral
cysts are more prevalent in the cerebellum than in the cerebrum and often possess a contrast-enhancing mural nodule. Optic pathway gliomas usually show a solid, cystic, or mixed tumor with strong gadolinium enhancement. Other WHO Grade I astrocytomas usually appear hypointense on T1-weighted sequences and hyperintense on T2-weighted images but do have some distinguishing characteristics. Gangliogliomas show gadolinium enhancement that varies from absent to significant and can be nodular, solid, or circumferential [133]. Dysembryoplastic neuroepithelial tumors show minimal if any gadolinium enhancement. Desmoplastic infantile gangliogliomas are isointense on T1-weighted sequences and show variable intensity on T2-weighted sequences; they usually enhance with contrast administration.

There is considerable overlap and variability in the imaging characteristics of WHO Grade I versus WHO Grade II astrocytomas, so accurate diagnosis cannot be based on MRI characteristics alone. Pilomyxoid astrocytomas appear similar to pilocytic astrocytomas with well-circumscribed margins and little peritumoral edema [134]. They are usually bright on T1-weighted, T2-weighted, and FLAIR (fluid-attenuated axial inversion recovery) sequences [135] with contrast enhancement that is often heterogeneous [136, 137]. By comparison to pilocytic astrocytomas, fibrillary astrocytomas are usually hypointense on T1-weighted sequences and hyperintense on T2-weighted sequences, and they are less enhancing after contrast administration with the exception of dorsally exophytic brainstem tumors. Pilocytic xanthoastrocytomas usually are enhancing on MRI. Oligodendrogliomas show gadolinium contrast enhancement more commonly in tumors that grow as solid masses and less commonly in purely infiltrative tumors.

Typical high-grade astrocytomas have an MRI appearance of either a heterogeneously enhancing or diffuse non-enhancing tumor with significant edema on the T1-weighted image, compressing or displacing adjacent ventricular structures and occasionally causing hydrocephalus. The T2-weighted signal is often more diffuse,
consistent with both infiltrative tumor and edema. Magnetic resonance spectroscopy demonstrates a markedly elevated choline to N-acetylaspartate (NAA) ratio. \(^{99m}\)Tc-MIBI single-photon emission computed tomography (SPECT) imaging can also detect malignant gliomas [138]. Lesions tend to be fluorodeoxyglucose (FDG) avid on positron emission tomography (PET). Areas of hemorrhage within pediatric GBMs at diagnosis are not uncommon [139]. Similarly, the majority of diffuse brainstem tumors appear to be hypointense on T1-weighted MRI and hyperintense on T2-weighted imaging (Fig. 13.2). Prominent edema is common. The ventral pons may appear swollen and infiltrated. Contrast enhancement can be variable, from homogeneous rim enhancement to patchy enhancement to complete absence of enhancement. PET imaging in this area tends to be negative even in the presence of a high-grade lesion.

**Histology**

Histological examination of pilocytic astrocytoma reveals a biphasic pattern with a compact component containing bipolar cells with Rosenthal fibers and a loose cellular component containing microcysts and eosinophilic granular bodies. Rosenthal fibers and eosinophilic granular bodies are pathologic hallmarks of pilocytic astrocytomas, although they can be observed in other diseases of the CNS. Rosenthal fibers are brightly eosinophilic, hyaline masses composed of \(\alpha\)B-crystalline and are best seen on tumor smear preparations. Eosinophilic granular bodies that are globular aggregates within astrocytic processes are also best visualized with smear preparations. Pilocytic astrocytomas stain intensely with the glial fibrillary acid protein (GFAP) immunoreagent. Invasion of the overlying meninges and adjacent brain
parenchyma is commonly observed. Mitoses are rare and the MIB-1-labeling index is usually less than 4% [140].

Other WHO Grade I astrocytomas have distinct appearances on pathology. Gangliogliomas demonstrate synaptophysin and NeuN-positive ganglion cells as well as GFAP-positive astrocytes [94]. Dysmorphic neoepithelial tumors show a “specific glioneuronal element” manifested by GFAP-negative “oligodendroglia-like” cells and neurons in a mucinous eosinophilic background that give the appearance of “floating neurons” [141]. Desmoplastic infantile gangliogiomas demonstrate a desmoplastic stromal background with neoplastic neurons and astrocytes. They may have areas with elevated MIB-1, although this does not represent transformation to a more malignant phenotype.

WHO Grade II tumors also differ in their histologic appearances. Fibrillary astrocytomas have greater cellularity and infiltrating boundaries than pilocytic astrocytomas [1]. In contrast to Grade III or Grade IV astrocytomas, however, fibrillary astrocytomas must lack features of malignancy. Pilocytic astrocytomas lack many features of pilocytic astrocytomas including Rosenthal fibers and biphasic pattern. Rather, there is a monophasic pattern and myxoid background with strong GFAP and synaptophysin staining [142]. Pleomorphic xanthoastrocytomas have pleomorphic appearance of the astrocytic component with significant cellular atypia and bizarre multinucleated giant cells with intracellular lipid accumulation. Oligodendrogliomas show a monotonous pattern of cells with round nuclei and clear perinuclear halos (“fried egg” appearance), an artifact of formalin fixation that is not seen in frozen sections or tumor smears.

High-grade gliomas demonstrate malignant features on pathological examination including atypia, nuclear pleomorphism, mitoses, necrosis, endothelial proliferation, and a high MIB-1-labeling index. Most pediatric malignant gliomas are nestin positive on immunohistochemistry [143]. The distinction between WHO Grade III and WHO Grade IV astrocytoma is significant, as the subtypes differ with regard to duration of symptoms and prognosis.

**Treatment**

Surgery is the mainstay of therapy for pilocytic and other low-grade astrocytomas [144]. Many pilocytic astrocytomas can be completely surgically resected, depending on location, and 10-year progression-free survival following gross total resection alone approaches 90% [145–147]. Gross total resection is often curative, even though residual microscopic disease is often left behind. Radiation and chemotherapy are typically not required as part of up front therapy after a complete resection [77]. Even in patients with incompletely resected lesions, treatment is not always required and, depending on the patient and clinical scenario, observation can be considered unless tumor or symptom progression is documented [148]. Some exceptions to the general approach to treating pilocytic and low-grade astrocytomas for different tumor histologies are discussed above.
Adjuvant treatment may be required for symptomatic, progressive, or unresectable pilocytic or low-grade astrocytomas [149]. Various chemotherapy regimens such as carboplatin and vincristine, or thioguanine, procarbazine, lomustine (CCNU), and vincristine (TPCV) have produced consistent, durable responses [150–152]. With the multiagent combinations above, stabilization of tumors occurs in almost 50% of patients, while radiographic response is observed in an additional 40%. Median time to progression of 3–4 years is achieved, although up to 70% of patients will eventually demonstrate tumor growth. The ability to retreat these patients with multiple regimens has allowed most patients to avoid radiation therapy, especially early in life when the long-term morbidity of this modality is greatest. While the time to progression may appear short and the overall progression rate appears high, these chemotherapy regimens are well tolerated and have few long-term complications.

Adjuvant treatment with radiation therapy demonstrates not only a significantly improved response rate (95%) and duration of disease control (>10 years) for patients with low-grade astrocytomas, but it also entails significant long-term cognitive, vascular, and hormonal morbidity, and second tumors are occasionally observed. Since the majority of children with low-grade gliomas will be long-term survivors, this is exactly the population in which avoidance of late effects is critical. Ultimately, the quality of survival depends on multiple factors including the tumor location, the extent to which the tumor can be resected, the timing of any radiotherapy, and the side effects of surgery, chemotherapy, and radiotherapy [153].

Optic pathway gliomas present unique management challenges shaped by the clinical course, the age of onset, severity of symptoms, the size and extent of tumor, and the presence or absence of NF1. Preservation of vision for patients with optic pathway gliomas is of paramount concern, so treatment is frequently started promptly in younger patients, patients with progressive symptoms, and those with more extensive CNS involvement. The initial treatment of choice is chemotherapy, which may cause stabilization or regression [154] of the tumor and which is not associated with the neurocognitive decline observed with radiation therapy [155]. The growth rate of these tumors often slows in older children and young adults, so that by the time these patients reach adulthood, the tumors have become quiescent and do not require further therapy.

The presence of NF1 does alter surveillance, diagnosis, and treatment options for patients with optic pathway gliomas. Many patients with NF1 will have longstanding, subtle ophthalmologic abnormalities for which regular visual evaluation is required. Regular surveillance MRI scans are not indicated as many asymptomatic and clinically irrelevant tumors will be diagnosed and create treatment dilemmas [156]. Optic pathway gliomas in NF1 patients do not require surgical confirmation unless atypical features are present [157]. Treatment modifications should be made for patients with optic pathway gliomas and NF1 whenever possible. TPCV should not be used in children with NF1 due to increased risk of secondary tumors associated with alkylator-based treatment. Radiation therapy is contraindicated in children with NF1 due to increased risk of radiation-induced secondary malignancies [158] and high risk for development of moyamoya syndrome [10]. Children with NF1
and optic pathway gliomas have a better progression-free survival than those without $NF1$, and $NF1$ tumors have a more indolent course than sporadic tumors [159], suggesting that they represent different biological entities [160].

Children with high-grade gliomas continue to have a poor prognosis despite the use of multimodal therapy, although prognosis may be better than in adults [119, 161, 162]. Patients with anaplastic astrocytoma have a more favorable prognosis than those with glioblastoma multiforme [163, 164]. Children under the age of 5 also appear to have a better response rate and overall survival than older children [161].

The initial management for children with high-grade glioma following neuroimaging is administration of high-dose corticosteroids to decrease edema and symptoms of hydrocephalus. The goals of neurosurgery include establishing a histological diagnosis and, whenever possible, a radical resection [165]. The degree of surgical resection is positively associated with progression-free survival [166, 167]. A report from the Children’s Cancer Group [167] showed that the 5-year progression-free survival rates for glioblastoma multiforme were 26 ± 9% and 4 ± 3% for children who underwent radical resection versus other types of surgery, respectively. Patients with diffuse thalamic and pontine high-grade tumors have the worst prognosis, in part because these tumors are unresectable [168]. Complete resection is difficult to achieve as a result of the infiltrative properties of high-grade astrocytomas. Internal decompression or debulking makes subsequent radiotherapy more tolerable and probably more effective, given the lower tumor burden. Resection also diminishes the duration of corticosteroid therapy [169]. The role of radiation therapy in the treatment of older children has been clearly established over the past 25 years [170, 171]. Several studies have shown that chemotherapy with radiation may have a clinically significant role in children with high-grade glioma [172, 173]. The overall 5-year survival of children with supratentorial high-grade glioma treated with chemotherapy and radiation is approximately 43%, versus 18% for radiation alone. Pre-irradiation chemotherapy has been studied with the goal of delaying radiation, which is especially important for children < 3 years of age.

**Ependymoma**

Ependymomas are glial tumors that arise from ependymal cells that line the ventricles within the CNS and that play an essential role in the transport of CSF. Ependymal tumors represent approximately 10% of all childhood intracranial neoplasms, constituting the third most common pediatric brain tumor, after astrocytomas and medulloblastoma. They are equally distributed between males and females, and the median age at diagnosis is approximately 6 years old. Ependymomas are significantly less common in Blacks than Whites. Ninety percent of pediatric ependymomas are intracranial, with 75% arising from the posterior fossa and located at or near the ependymal surface. The remaining supratentorial
Ependymomas are often located in the brain parenchyma, away from the ependymal surface and are more common in older children and adults. Ependymomas may occasionally spread via CSF, seeding the leptomeninges or ventricles, either at diagnosis or at recurrence [174]. Spinal cord ependymomas represent less than 10% of pediatric intramedullary spinal tumors, most of which are astrocytomas. In contrast, ependymomas represent over 50% of intramedullary spinal tumors in adults [175]. Comparative genomic hybridization has demonstrated significant differences between infant and childhood ependymoma, suggesting that the pathogenesis of this disease differs by age [176]. Individuals with NF2 have an increased susceptibility to intramedullary spinal cord ependymomas [177]. Expression profiling indicates that histologically similar ependymomas from different parts of the CNS are in fact molecularly and clinically distinct disease subgroups [178, 179].

The WHO classification system recognizes three grades: classic ependymoma (WHO Grade II) and anaplastic ependymoma (WHO Grade III), as well as subependymoma and myxopapillary ependymoma (WHO Grade I). Subependymomas are benign, slowly growing, and often asymptomatic intraventricular neoplasms that are usually found incidentally in the middle-aged and elderly or at autopsy. Myxopapillary ependymomas are slow-growing tumors of the conus medullaris, cauda equina, and filum terminale that manifest primarily in young adults. Presenting symptoms of ependymomas depend on location. The presenting symptoms of infratentorial ependymomas result from the obstructive hydrocephalus that results when tumor fills the fourth ventricle causing headache, irritability, ataxia, nausea, and vomiting. Lethargy, irritability, and increased head circumference can occur in infants [180]. Supratentorial ependymomas present with focal neurologic deficits and seizures. Spinal ependymomas are typically located in the cervical region and present with pain or motor deficits that are localized to the level of the spinal cord lesion, radicular dysesthesias, and, as a late manifestation, progressive spastic quadriplegia. Thoracic ependymomas are associated with scoliosis.

A typical MRI appearance of an infratentorial ependymoma is that of a homogeneously enhancing, well-circumscribed solid mass extending out of the foramina of Luschka and Magendie with obstructive hydrocephalus. Hemorrhage and calcifications can be observed and are more common in supratentorial lesions.

The characteristic microscopic features of a classic ependymoma are dense cellularity intermixed with perivascular pseudorosettes consisting of tumor cells surrounding a neoplastic blood vessel. True ependymal rosettes representing abortive canals are relatively uncommon [181]. Histologically, the anaplastic variants are recognized by the presence of mitoses, necrosis, and vascular proliferation. They tend to be more cellular than Grade II ependymomas but usually remain well demarcated. In cases where the diagnosis of ependymoma is indeterminate, electron microscopic analysis of cilia structure and junctional complexes, which are found in most ependymomas, can be used to confirm or exclude the diagnosis.

The first line of treatment is surgery with the goal of gross total resection. All posterior fossa tumors, independent of grade and degree of resection, should receive
additional treatment. Complete resection with clear margins of a WHO Grade II supratentorial ependymoma may allow adjuvant therapy to be deferred in some patients. Tumors with an infiltrative boundary or those with anaplastic histology require adjuvant therapy.

The current consensus strategy for ependymoma in the United States recommends deferral of adjuvant therapy in supratentorial ependymoma, involved field radiotherapy alone for radically resected posterior fossa ependymoma and use of multiagent chemotherapy for subtotally resected ependymoma followed by second look surgery and involved field radiotherapy [182–184]. Several studies suggest that radiotherapy prolongs progression-free survival after subtotal resection of an ependymoma [185]. Deferral of radiation therapy after initial complete resection can result in reduced likelihood of cure, even when complete resection is achieved a second time [186]. The majority of patients with completely resected ependymoma followed by focal radiation therapy will be long-term survivors. Consideration of advanced radiation planning is critical to minimize long-term neurocognitive morbidity in this population [187]. Proton radiation therapy appears to have equal efficacy when compared to photon therapy and can reduce the potential long-term toxicity by decreasing the volume of normal brain tissue that is targeted [188].

Until recently, there was no clear role for chemotherapy in the management of ependymomas outside of clinical trials [189]. Several small series in newly diagnosed and recurrent disease have shown objective responses to the following drugs: carboplatin, cisplatin, ifosfamide, and etoposide [190]. Chemotherapy is more often used for infants and younger children with incompletely resected or disseminated disease [191–193]. Encouraging results were obtained from the most recent cooperative group clinical trials involving pre-irradiation chemotherapy, which showed a 40% complete response rate in patients who received pre-irradiation chemotherapy because of residual post-operative tumor [194]. Chemotherapy should therefore be used to achieve a complete response or improve the chances of a complete surgical resection at second look surgery. It is not highly effective as sole treatment for this disease, and recurrences occur relatively rapidly in a significant percentage of patients if radiotherapy is not administered early.

The most important prognostic factors for both intracranial and spinal cord ependymomas are age at diagnosis, tumor grade [195], extent of surgical resection, and delivery of radiation therapy to doses of at least 5,400 cGy [196–199]. Of these, the single most important factor in the determination of prognosis appears to be whether or not a complete resection can be accomplished [200]. Children less than 3 years of age, those with WHO Grade III disease, or those with less than a gross total resection have less favorable survival outcomes [201]. The 5-year progression-free and overall survival for patients with subtotal versus total resections of posterior fossa ependymomas are 25% and 66%, respectively. The prognosis of patients with disseminated disease is worse [197, 202]. Patients with elevated MIB1 greater than 5% incompletely resected or greater than 15% incompletely resected ependymomas had a worse prognosis in one study [203]. Patients whose tumors harbor a deletion of 6q15.3 appear to have improved outcomes [204].

Recurrences of intracranial ependymoma can occur throughout the first decade after
initial therapy, although most do so within the first few years [205]. Surveillance scanning is important as it allows smaller asymptomatic tumors to be identified that may be more amenable to re-resection. Most recurrences are within the original radiation field [206]. At the time of recurrence, no standard salvage regimen has been proven effective. Re-operation to achieve a complete resection has been curative in some patients, is typically the first modality considered [207], and can be combined with re-irradiation [208]. Patients with metastatic disease or infiltration into the brainstem or other critical structures have a very poor salvage rate, presumably based on the lack of effective therapies for recurrent disease and the inoperable nature of the lesions.

Myxopapillary ependymomas of the conus medullaris, cauda equina, and filum terminale are distinct entities discussed separately here. They may present with low back pain, radicular pain, saddle anesthesia, and sphincter dysfunction [209]. Spinal myxopapillary ependymomas with a complete surgical resection have an excellent prognosis and do not usually require adjuvant therapy [210]. Recurrence of myxopapillary ependymoma can occur after complete resection and can be associated with dissemination. Pediatric myxopapillary ependymoma may have a higher propensity to spread compared to adult tumors [211]. When these tumors disseminate, they usually do so within the spine [212], although cranial metastases have been reported and thus craniospinal imaging at diagnosis or recurrence should be undertaken [211]. For this reason, frequent surveillance scanning of myxopapillary ependymoma patients is recommended in order to identify recurrent disease early, since many of these patients can be salvaged with radiation therapy.

Embryonal Tumors

Embryonal tumors of the central nervous system comprise the majority of malignant brain tumors in children. Subtypes include medulloblastoma, pineoblastoma, supratentorial primitive neuroectodermal tumor (PNET), and, rarely, brainstem or spinal PNET. Atypical teratoid rhabdoid tumor (ATRT) is a rare embryonal tumor that carries a poor prognosis; it most commonly arises from the cerebellum, and is defined by the loss of INI-1 expression, by which it may be distinguished from medulloblastoma and supratentorial PNET.

Medulloblastoma

Medulloblastoma, formerly known as posterior fossa or cerebellar PNET, is the most common pediatric embryonal brain tumor. First described in 1925 by Bailey and Cushing [213], who hypothesized that these tumors originated from multipotent “medulloblasts,” medulloblastomas are now believed to most commonly arise from multipotent neural progenitor cells in the ventricular zone of the developing cerebellum [214].
Histologically, medulloblastomas, like other embryonal tumors, are characterized by densely packed “small round blue cells” with minimal cytoplasm and commonly demonstrate Homer–Wright and Flexner–Wintersteiner rosettes. Like all embryonal tumors, they are WHO Grade IV and have a propensity to metastasize along CSF pathways.

The most recent WHO classification schema describes five main medulloblastoma subtypes:

1. Classic medulloblastoma is the most common subtype. It is characterized by uniform sheets of densely packed small, round blue cells with small round hyperchromatic nuclei and scant cytoplasm. Most contain GFAP-positive cells, suggesting a component of astrocytic differentiation [1].

2. Nodular/desmoplastic medulloblastoma is characterized by reticulin-free nodules, containing cells with neuronal differentiation, surrounded by reticulin-positive strands of proliferating cells [1, 215]. This subtype is rarer, comprising about 5% of medulloblastomas overall, but over 50% of medulloblastoma in infants [216]. It appears to be associated with better outcome.

3. Anaplastic medulloblastoma is defined by prominent nuclei with a high degree of pleomorphism, high mitotic index, increased cytoplasm, and a higher rate of necrosis. Anaplastic tumors are associated with a higher rate of metastasis at presentation and a poor prognosis.

4. Large cell medulloblastoma is a rare subtype characterized by large nuclei, with abundant mitoses and apoptotic bodies. There is significant overlap between the large cell and anaplastic subtypes. In common usage they are usually grouped together as “anaplastic/large cell medulloblastoma.”

5. Medulloblastoma with extensive nodularity, previously called cerebellar neuroblastoma, is similar to the nodular/desmoplastic subtype but is characterized by larger reticulin-free nodules. It is identified almost exclusively in infants.

Several additional medulloblastoma variants are described, including medulloblastoma with myogenic differentiation (medullomyoblastoma) and medulloblastoma with melanotic differentiation. Myogenic or melanotic differentiation can occur in any of the main subtypes.

Medulloblastoma is primarily a disease of young and early school-aged children. Mean age at diagnosis is 4 years old. There is a significant male predominance. In the United States, it is slightly more common among Whites than Blacks. Incidence may be slowly rising. Environmental factors have been suggested (e.g., by the observation that medulloblastoma is more common among children born in autumn [217]) but none have been definitively identified. A number of genetic syndromes are associated with increased risk of medulloblastoma: Gorlin, Turcot’s, Li–Fraumeni [1, 218, 219]. These represent only a small minority; most cases of medulloblastoma appear to be sporadic.

Clinically, the presenting symptoms of children with medulloblastoma are most often attributable to obstruction of CSF flow, with resulting hydrocephalus and increased intracranial pressure. Headache, nausea and vomiting, irritability,
lethargy, and truncal ataxia are common. As with most pediatric brain tumors, the symptoms may be non-specific, leading often to a delay in diagnosis. Although leptomeningeal dissemination is not uncommon, metastatic disease is usually asymptomatic. Rarely, patients with large spinal metastases may present with symptomatic cord compression. Interestingly, disease stage at diagnosis is usually inversely related to prior symptom duration [220, 221].

CT scan is usually the first imaging modality evaluated in a patient presenting with symptoms of a posterior fossa tumor. Typical findings include enlargement of the third and lateral ventricles, with effacement of the fourth ventricle by a radiodense mass arising from the cerebellum. MR findings are suggestive of increased cellularity; the mass is isointense to gray matter on T1, hyperintense on T2, though less so than other common brain tumors and heterogeneously enhances after contrast injection (see Figs. 13.3a, b). The primary mass in medulloblastoma most often arises from the midline (cerebellar vermis), but a lateral primary (cerebellar hemisphere) can also be seen and may suggest desmoplastic histology. Supratentorial and complete spine imaging with contrast is essential to evaluate for leptomeningeal spread of disease. Where feasible, spine MRI should be performed pre-operatively, as post-operative changes may obscure metastatic tumor.

Fig. 13.3  (a) Medulloblastoma. This T1-weighted MRI image shows a midline posterior fossa tumor characteristic of medulloblastoma. (b) Medulloblastoma. This T1-weighted MRI image from the same patient shows increased ventricle size and evidence of transependymal flow concerning for obstructive hydrocephalus with increased intracranial pressure

Risk stratification in medulloblastoma incorporates disease stage (modified Chang criteria), presence of residual disease, age at diagnosis, and histology. The modified Chang criteria incorporate CSF cytology, brain, and spine MRI (see Table 13.1 [222]). Systemic metastasis is rare; if present, it is most often to the bone or bone marrow. Presence of metastatic disease (positive CSF cytology or metastatic tumor on MRI), > 1.5 cm² residual primary tumor post-operatively, or anaplastic histology, are all independently considered “high risk” features, denoting poorer outcome and the need for more intensive therapy. Patients less than 3 years old at diagnosis are also considered high risk. Craniospinal irradiation is usually avoided
Table 13.1  Modified Chang classification for medulloblastoma

<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>M0</td>
<td>No evidence of gross subarachnoid or hematogenous metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Microscopic tumor cells formed in cerebrospinal fluid</td>
</tr>
<tr>
<td>M2</td>
<td>Gross nodular seeding demonstrated in cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles</td>
</tr>
<tr>
<td>M3</td>
<td>Gross nodular seeding in spinal subarachnoid space</td>
</tr>
<tr>
<td>M4</td>
<td>Metastasis outside the cerebrospinal axis</td>
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Adapted from Harisiadis and Chang [222]

in this age group because of its devastating neurocognitive sequelae in younger children but at the cost of a lower overall survival rate. Desmoplastic histology, on the other hand, is a favorable prognostic indicator, but has not yet been used in treatment stratification. Many molecular indicators have emerged that have prognostic significance: isochromosome 17q (poor), TrkC, or nuclear β-catenin (good). It has been suggested that molecular features will eventually supplant histology, but they have yet to be incorporated into prospective clinical trials or therapeutic decision-making schema. There are currently no biologic or targeted agents that have been proven effective or approved for use in the treatment of medulloblastoma. Pathways of interest include SHH, WNT, and NOTCH, among others.

Treatment of medulloblastoma is multimodal and includes surgery, adjuvant chemotherapy, and craniospinal irradiation for all but the youngest patients, in whom radiation is usually avoided. Complete resection, when feasible, is highly desired. Surgical approach is via resection of the cerebellar vermis in most cases. Posterior fossa syndrome, or cerebellar mutism, is the most common significant operative complication, occurring in approximately 10–20% of cases. It is characterized by mutism, flat affect or emotional lability, decreased mobility ataxia, and decreased oral intake. Symptoms may last from days to months, and recovery is sometimes incomplete [223]. The cause of this syndrome remains unclear.

Historically, patients were treated post-operatively with 3,600 cGy craniospinal irradiation, with boost to the posterior fossa to 5,400 cGy. This radiation dose is associated with significant morbidity; severity of long-term neurocognitive impairment is inversely correlated with age. This remains the radiation dose used most often for higher risk children in the United States. For patients without high-risk features, lower radiation doses have been used. Currently accepted standard therapy for average-risk patients includes 2,400 cGy craniospinal radiation, with boost to the posterior fossa, and even lower doses are under investigation. New modalities, including intensity-modulated radiation therapy (IMRT) and proton beam, reduce but by no means eliminate some of the long-term toxicities of irradiation.

Adjuvant chemotherapy is used for almost medulloblastoma patients. A number of strategies are used. A common approach is to give several (six to nine) cycles of combination chemotherapy as maintenance therapy following the completion of radiation. Typical agents include cisplatin, one or more alkylating agents (procarbazine, CCNU, and/or cyclophosphamide) and vincristine. Additional chemotherapy may also be given concurrently with radiation.
The treatment of medulloblastoma in younger patients, in whom the neurocognitive effects of craniospinal radiation would be devastating, poses a special problem. Various chemotherapy-only approaches have been used both in North America and in Europe. In general, these have employed a dose-intensive induction, followed by a myeloablative consolidation therapy with hematopoietic stem cell rescue. These approaches have been successful in providing cure for a significant number of patients, although the overall survival is poorer than in older irradiated patients with otherwise similar risk features.

**Supratentorial PNET**

PNETs are tumors of neuroepithelial origin. The WHO 2007 classification schema recognizes a number of PNET subtypes: classic PNET, PNET with neuronal differentiation (cerebral neuroblastoma), and cerebral ganglieneuroblastoma. Although histologically similar to their infratentorial counterpart, medulloblastoma, molecular analysis shows CNS PNETs to be a biologically distinct group of tumors. They also are to be distinguished from the similarly named but biologically unrelated systemic PNET [224]. Spinal or brainstem PNETs, on the other hand, seem to be biologically equivalent to their supratentorial counterpart and are treated similarly. The term “CNS PNET” includes PNETs in all three locations.

Supratentorial PNETs are much rarer than medulloblastoma. Precise incidence is difficult to define due in part to inconsistency in classification. Most are diagnosed in childhood (<10 years of age), but supratentorial PNET can be seen across all age groups. Clinically, manner of presentation depends largely on location. If CSF pathways are disrupted, patients will present with symptoms of hydrocephalus. On the other hand, in contrast to medulloblastoma, patients may also present with more focal cortical symptoms, including seizures or paresis.

Histologically, most appear as undifferentiated tumors, although evidence of glial, neuronal, or ependymal or oligodendroglial differentiation can be seen. On MR imaging, tumors present as T1 isointense or hypointense, reflecting increased cellular density. Tumor edema manifests as increased signal intensity on T2 or FLAIR. These tumors usually show heterogeneous enhancement after gadolinium administration.

Supratentorial PNET is typically treated with multimodality therapy, using regimens similar or identical to those used for high-risk medulloblastoma. While long-term progression-free survival is possible for some patients with this approach, overall prognosis remains poorer than for patients with medulloblastoma.

**Pineoblastoma**

Pineoblastoma is a highly malignant neuroepithelial tumor of the pineal gland. Pineoblastomas are rare, accounting for <5% of all pediatric CNS tumors. Little
is known about their biology. While most cases are sporadic, incidence of pineoblastoma is increased in patients with hereditary retinoblastoma (“trilateral retinoblastoma”).

Histologic and imaging characteristics are similar to other CNS embryonal tumors. They typically show immunohistochemical positivity for synaptophysin and neuron-specific enolase (NSE), as well as markers for photoreceptor pathways \[225, 226\]. Evaluation must include MRI of the brain and spine, as well as analysis of CSF cytology. Systemic metastasis is rare, but can occur.

As with other embryonal tumors, treatment is multimodal. After complete resection followed by higher-dose craniospinal irradiation with chemotherapy, 5-year event-free survival for non-metastatic disease is about 50% \[227, 228\]. Outcome is much poorer for patients with residual or metastatic tumor. Meanwhile, radiation-sparing approaches for infants with PNET have yielded 5-year EFS of 20% or less.

**Choroid Plexus Tumors**

Choroid plexus tumors usually arise from the epithelium of the choroid plexus in the lateral or fourth ventricle where the choroid plexus is found. Although choroid plexus lesions represent only 3% of pediatric brain tumors, they comprise 10–20% of tumors that develop in the first year of life and account for a considerable percentage of in utero diagnoses \[229\]. The median age at diagnosis for lateral ventricle tumors is less than 2 years \[230\]. Three histologic choroid plexus variants have been described: papillomas, atypical papillomas, and carcinomas \[231\]. Choroid plexus papillomas outnumber choroid plexus carcinoma by a ratio of at least 5:1. Metastatic disease can occur in choroid plexus papilloma, although these patients still have a good prognosis and many of these tumors will not progress. Leptomeningeal dissemination is common with choroid plexus carcinoma and is a poor prognostic marker due to the limited use of craniospinal radiation therapy in this very young population. Due to the strong association of Li–Fraumeni syndrome and p53 mutations with choroid plexus carcinoma, patients need a comprehensive family history to ascertain the incidence of associated cancers to assist in screening of family members. The presence of p53 germline mutation may mitigate the choice of radiation therapy and would indicate the need for genetic counseling in other family members \[232\].

Choroid plexus papillomas (CPP, WHO Grade I) have the lowest proliferative rate and are composed of fibrovascular fronds covered by a single layer of epithelial cells. They closely resemble normal choroid plexus. Cytokeratin, S-100 protein, and vimentin are typically expressed. GFAP, which is typically not seen in normal choroid plexus, is found in approximately 25–50% of choroid plexus papillomas. In rare circumstances, choroid plexus papillomas can transform into choroid plexus carcinomas \[233\]. In contrast, choroid plexus carcinomas (CPC, WHO Grade III) manifest higher cell density, nuclear pleomorphism, frequent mitoses, high
nuclear:cytoplasmic ratios, and invasive behavior. These tumors also express cytokeratin, while S-100 expression is less frequent. Atypical choroid plexus papillomas (WHO Grade II) refer to instances where the distinction between choroid plexus papilloma and carcinoma is not clear (e.g., only one or two histologic features of malignancy). Clear diagnostic criteria for these atypical tumors have not been established, however, it appears that the presence of mitotic activity ($\geq 2$ mitoses per 10 high-powered fields) is the sole atypical histologic feature independently associated with recurrence [234]. Atypical choroid plexus papillomas account for approximately 15% of all choroid plexus papillomas in one large series [234].

Initial symptoms are usually secondary to elevated intracranial pressure and hydrocephalus and include headaches, nausea and vomiting, and papilledema. Other possible manifestations include lethargy, seizures, and failure to thrive. Because these tumors tend to arise in infants who retain open sutures, the presentation may be relatively delayed and the tumors may reach exceptional size. Infants typically demonstrate irritability, lethargy, vomiting, a tense fontanel, and macrocephaly with splayed sutures.

On MRI, multilobular, calcified, well-delineated, contrast-enhancing intraventricular masses are characteristic of choroid plexus tumors. T1 MRI signals are usually isodense, while T2 is usually bright [235] (see Figs. 13.4a, b). Choroid plexus carcinomas often have more heterogeneous enhancement and edema signal on FLAIR than is routinely seen in choroid plexus papillomas [236]. Unique characteristics of MR spectroscopy can differentiate CPP from CPC on imaging [237].

**Fig. 13.4**  (a) Choroid plexus papilloma. On T1-weighted axial images, this cystic intraventricular ventricular tumor is demonstrated. (b) Choroid plexus papilloma. On T1-weighted coronal images, the position of this tumor within the ventricles is confirmed

Choroid plexus papillomas appear as slightly atypical normal choroid plexus tissue and are highly cytokeratin, vimentin, and podoplanin positive on immunohistochemistry. Atypical choroid plexus papillomas are similar to choroid plexus papillomas but with an increased mitotic index of $\geq 2$ mitoses per 10 high-powered fields. These tumors can possess greater pleomorphism, increased cellularity and
areas of necrosis, but these elements are not required for the diagnosis. Choroid plexus carcinomas are highly malignant tumors possessing four of the five following characteristics: (i) increased mitoses (>5 per 10 high-powered fields); (ii) increased cell density; (iii) nuclear pleomorphism; (iv) blurring of the papillary structure; and (v) necrosis [1, 238]. Choroid plexus carcinomas are positive for cytokeratins but less positive for S-100 than choroid plexus papillomas. Up to 20% of CPCs can be positive for GFAP [234]. The presence of normal INI-1 staining in these tumors can be used to exclude ATRT, which shares many histologic features [239].

Following diagnostic neuroimaging studies, patients are often placed on high-dose corticosteroids when elevated intracranial pressure is suspected. Because the extent of surgical resection is the single most important factor that determines the prognosis for choroid plexus tumors, the goal of the neurosurgeon is to perform a gross total resection [240]. This may require more than one surgical procedure but appears to improve outcome [241]. One obstacle to the surgical removal of choroid plexus tumors is the rich vascular network that is often located within the tumor. The achievement of a gross total resection in cases of choroid plexus papilloma and atypical papilloma is often curative, and as such adjuvant therapy may be deferred following a normal re-staging evaluation.

Since the majority of children diagnosed with choroid plexus carcinoma are under the age of 3, chemotherapy is the treatment of choice in those for whom a complete resection cannot be achieved [230, 242]. A variety of multiagent chemotherapy regimens have been explored and preliminary evidence suggests that choroid plexus carcinomas are chemosensitive tumors. The role of radiotherapy is controversial and is usually reserved for children older than 3 years who have had a subtotal resection, malignant features within the tumor, or dissemination of the tumor along the neuroaxis.

Gross total resection is often curative for choroid plexus papilloma. Even in patients with a subtotal resection, 50% of residual tumors will not demonstrate progression [243]. The 5-year and 10-year progression-free and overall survival of papillomas and carcinomas are 81% and 77% versus 41% and 35%, respectively [230]. Atypical CPP can recur and thus need careful follow-up. The long-term prognosis for this group of patients remains excellent [234]. Patients with dissemination at diagnosis do less well. Several adjuvant platinum-based chemotherapy regimens have been used with some measure of success [244], but at present there is no standard protocol established for choroid plexus carcinoma.

**Germ Cell Tumors**

Central nervous system germ cell tumors (GCTs) are the most prevalent tumors of the pineal region and represent approximately 3–5% of intracranial childhood malignances in the United States. These tumors are much more common in the Far East, particularly Japan [245]. The reason for this geographic variability is unknown. The majority of germ cell tumors occur in early adolescence, and males
are significantly more affected than females [246]. Germinomas are much more common than non-germinomas [247]. Histologically, these tumors resemble the germ cell tumors that arise in the gonads. Most CNS germ cell tumors arise in the pineal or suprasellar regions and are presumed to result from the abnormal migration of primitive germ cells early in embryogenesis within the gonadal ridge [248, 249]. Occasionally, metachronous lesions at both sites are detected at the time of diagnosis [248]. Germ cell tumors can rarely be identified in other locations including the basal ganglia [250].

Malignant central nervous system GCTs are divided into two clinical groups: pure germinomas (60%) and non-germinomatous germ cell tumors (40%) [251, 252]. Non-germinomatous germ cell tumors (NGGCTs) include yolk sac tumor (endodermal sinus tumor), embryonal carcinoma, choriocarcinoma, immature teratoma, teratoma with malignant transformation, and mixed germ cell tumor.

The clinical presentation of germ cell tumors varies as a result of their location. Patients diagnosed with suprasellar germ cell tumors often have a long prodrome, often several years in duration [253], usually involving endocrine dysfunction, particularly with symptoms of diabetes insipidus [254]. Other endocrine manifestations may occur such as growth impairment, delayed puberty, and hypothyroidism. Visual loss and symptoms of raised intracranial pressure are late manifestations when the tumor has either reached appreciable size or spread in a periventricular distribution.

Tumors arising in the pineal region often produce headache, nausea, and vomiting due to obstructive hydrocephalus. Limitation of vertical gaze, convergence nystagmus, impaired pupillary reflexes, and double vision may occur due to tectal compression (Parinaud’s syndrome). Atypical presentations occur when germ cell tumors arise in unusual locations such as the basal ganglia, when they present with widespread leptomeningeal metastases or when they diffusely infiltrate deep white matter structures.

Germ cell tumors can have a heterogeneous appearance on CT and MRI scan [255]. Most are contrast-enhancing solid lesions with isointense signal on T1 and hyperintensity on T2 [256]. These signal characteristics overlap other common tumors of the pineal region and require biopsy or hormone marker analysis for accurate diagnosis [251, 257].

Non-germinomatous germ cell tumors are unique amongst central nervous system tumors in that they can be diagnosed solely on the basis of expression of tumor markers [258]. β-Human chorionic gonadotropin (β-HCG), a normal product of syncytiotrophoblasts, and/or alpha fetoprotein (AFP), a normal product of yolk sac endoderm, can be detected in both the blood and CSF of patients. Because AFP is normally expressed in newborns, considerable attention must be given to interpretation of these levels in infants [259].

Germinoma is the most common CNS germ cell tumor encountered and is considered the equivalent of the testicular seminoma. Unusually large cells, frequent mitoses, and lymphocytic infiltrates are characteristics. Cells stain brightly for both c-kit and OCT4 [260, 261]. Placental alkaline phosphatase has been less reliable. Pure germinomas can possess syncytiotrophoblastic giant cells resulting in low level expression of β-HCG [262].
Non-germinomatous germ cell tumor is typically used to refer to one of three different malignant germ cell variants as well as teratomatous elements with atypical or malignant degeneration: yolk sac tumor, embryonal carcinoma (endodermal sinus tumor), and choriocarcinoma. Teratoma refers to a group of three lesions that have evidence of differentiation along the three embryonic germ cell layers; ectoderm, endoderm, and mesoderm.

Pre-operative evaluation should include contrast-enhanced MRI of the brain and spine, serum and CSF tumor markers for $\beta$-HCG and AFP, CSF for cytologic assessment, endocrine function evaluation, and visual acuity and field examinations for suprasellar tumors. In the absence of elevated CSF tumor markers, a biopsy should be performed. Aggressive resection leading to morbidity is neither necessary nor advisable in germinoma due to the tumor’s exquisite sensitivity to cytotoxic therapies.

RT alone for pure germinoma has a 5-year overall survival (OS) approaching 90% in clinical series, while RT alone is inadequate for NGGCT with 5-year OS ranging from 30 to 40% [263, 264]. Several new treatment strategies are under exploration with an attempt to reduce some of the late effects of RT in long-term survivors of CNS germinomas [265]. Whole ventricular field radiation therapy is now recommended and is curative treatment for most patients with localized intracranial germinomas. Patients with concurrent pineal and pituitary location represent regional rather than metastatic disease and can also be adequately treated with ventricular radiation therapy [266]. However, the late consequences of RT such as cognitive and endocrine deficiencies and RT-induced secondary tumors [265] have led to the development of regimens using chemotherapy followed by response-based radiotherapy to permit a selective reduction in dose (from 45 to 30 Gy) and/or volume (from whole ventricular to involved field) in patients whose tumors completely disappear after neoadjuvant chemotherapy [267–269].

For NGGCT, more aggressive chemotherapy, radical tumor resection and high-dose/volume radiotherapy is required to provide improved survival [267, 270–273]. Immature teratomas are classified as NGGCTs but can often be treated with a more conservative approach. A complete resection may be sufficient therapy and prognosis is good. Those with incomplete resection likely require adjuvant therapy [274].

One phenomenon called “growing teratoma syndrome” is well recognized and is usually seen in the context of ongoing treatment, but significant progression on MRI scan with concurrent clinical decline, in the setting of normalizing tumor markers [275]. These lesions represent non-malignant progression of the teratomatous component of lesions that, when resected, will relieve the clinical symptoms [275, 276]. Patients with growing teratoma syndrome are not considered to have progressive disease even in spite of the dramatic increase in the size of the lesion on MRI. These patients should continue radiation therapy and chemotherapy.

Germinomas have an excellent prognosis due to their sensitivity to radiation and chemotherapy. For these patients, the major treatment challenge is maximizing the quality of life and limiting long-term sequelae of therapy. Non-germinomas have a less favorable prognosis and thus clinical trials are evaluating conventional multi-
agent chemotherapy, dose-intensive myeloablative chemotherapy, and second-look surgery for poor responders, followed by craniospinal radiotherapy. A rise in CSF β-HCG can be a sensitive indicator of pending relapse that may occur in advance of elevated levels in the serum [277].

**Craniopharyngioma**

Craniopharyngiomas are benign non-glial tumors in children that account for 3–5% of all pediatric brain tumors. They have a peak age range of 6–14 years. They arise from Rathke’s pouch epithelium and are classified as WHO Grade I tumors [1]. Craniopharyngiomas grow slowly, typically in the sella and parasellar region, and they are composed of both solid and cystic components which often extend into the parasellar cisterns and occasionally invade adjacent cortical and vascular structures [278]. Calcification is a common finding of these lesions [279], although not pathognomonic for these tumors. Compression of critical intracranial structures can lead to pituitary, hypothalamic, and optic dysfunction. As a result, these patients often have complicated medical courses and long-term sequelae.

The typical onset of craniopharyngioma is insidious and can extend over several years. Symptoms may include progressive visual loss, delay in sexual maturation, growth failure, weight gain, and diabetes insipidus [280]. More than 70% of children have growth hormone deficiency, obstructive hydrocephalus, short-term memory deficits, and/or psychomotor slowing at time of diagnosis. The presenting feature in young adults also includes signs and symptoms of hypopituitarism such as galactorrhea or amenorrhea in females and impotence in males.

MRI features usually include a multicystic and solid-enhancing suprasellar mass [281]. T1-weighted sequences are usually isointense. A classic neuroimaging distinction of craniopharyngiomas from other suprasellar tumors such as a diencephalic glioma or germ cell tumor is the presence of calcifications on a non-enhanced CT scan. The solid components of craniopharyngiomas usually enhance on CT.

Histologically, craniopharyngiomas are divided into adamantinomatous and papillary subtypes. Adamantinomatous craniopharyngiomas are the more common variant in both adult and children and typically consist of both cystic and solid areas with frequent calcifications. Papillary tumors, seen almost exclusively in adults, are predominantly solid without calcification and are less infiltrative.

Surgical resection remains the standard approach for craniopharyngioma [282, 283]. Since patients may have unappreciated panhypopituitarism, baseline hormonal and electrolyte levels should be sent and the child treated with stress doses of hydrocortisone. Despite the surgical accessibility of many of these tumors, radical resection does not guarantee recurrence-free survival. The 3-year event-free survival following a complete resection is 60% [284]. Aggressive resection can result in more extensive hypothalamic deficiencies and visual complications [282]. Diabetes insipidus and other permanent endocrinopathies are commonly seen post-operatively. Behavioral sequelae of surgery include altered regulation of appetite...
and weight control, impulsivity, sexuality, and memory. Recurrent or progressive craniopharyngioma may be treated with re-operation, radiosurgery or fractionated radiotherapy, or chemotherapy. Responses to chemotherapy have been reported with interferon, vinblastine, cisplatin, and other agents [285–291], although well-designed studies to test different agents in craniopharyngioma are lacking [292]. An alternative treatment strategy for the long-term control of craniopharyngiomas is subtotal resection followed by involved field high-dose radiotherapy [293–295]. A temporizing approach to control the cystic components of the tumor is the intracystic instillation of sclerosing agents such as bleomycin or $^{32}$P [296, 297].

The most important factor correlating with progression-free survival is the extent of resection. Larger tumors and those with cysts are more likely to recur [298]. In a surgical series, recurrence or progression occurred in 30% of cases after total resection and in 57% of cases after subtotal resection. However, the recurrence rate drops to 30% when subtotal resection is followed by radiation therapy. The outcome does not appear to differ between adult and pediatric patients [299]. Unfortunately, most long-term survivors experience significant morbidity related to panhypopituitarism [300], cognitive impairment, and obesity [299, 301, 302]. Growth hormone deficiency requiring exogenous replacement is present in 100% of patients [303]. Control of weight and regulation of sleep are problematic. A number of approaches such as stimulants have been tried with preliminary positive results [304], although clear evidence of efficacy for these interventions is lacking [305–307]. Other psychosocial problems can be significant in this patient population and require a comprehensive team approach [308].

**Late Effects**

Late effects of therapy are a critical concern in pediatric neurooncology. The developing nervous system, especially in infancy and young childhood, is vulnerable to the long-term effects of therapy, and these effects may become apparent and progressive during a child’s lifespan. The curability of pediatric CNS malignancies is steadily increasing and more children will be at risk for suffering the late effects of therapy [309], including secondary malignancies [310]. Neurocognitive assessment has increasingly become an important focus in the outcome measures for children with cancer as there is a greater consideration of the quality of survivorship, not just survival [311–313].

Not all late effects are the result of therapy. Many late effects are the direct result of the tumor. Seizures, for example, can occur either from the tumor, the therapy, or both. Seizures that are relatively well controlled and not a major concern in childhood can become a significant problem with respect to work and driving during adolescence. Another example is that of pituitary function and hormonal control which may be impaired by direct invasion of the gland by tumor.

The late effects of specific treatment modalities are reviewed below according to treatment modality:
Care must be taken to assess the effects that tumor and surgery have on the outcome of patients, even those with lesions that do not need chemotherapy or radiation therapy. For example, significant mood lability, behavior issues, and academic difficulties, specifically processing speed and memory, have been identified in surgery-only survivors of pediatric brain tumors [314]. While many surgical morbidities improve over time, many do persist and can affect the quality of life for survivors [315]. The association of cerebellar mutism syndrome and surgical dissection of midline tumors of the posterior fossa has been well documented. Late-onset behavioral and endocrine alterations following resection of a suprasellar mass may have a serious impact on long-term quality of life.

**Radiation Therapy**

Radiation therapy may produce subacute and late effects on the CNS [316]. The subacute effects include the “radiation somnolence syndrome” (RSS) and Lhermitte’s syndrome. RSS typically follows within 1–2 months of large volume cerebral irradiation. Patients typically become lethargic and anorexic and may develop symptoms that recapitulate those at presentation of the initial tumor. The syndrome spontaneously resolves within 3 months in most cases, but occasionally low-dose corticosteroids are required [317]. Lhermitte’s syndrome usually arises within several months of cervico-thoracic spinal irradiation [318]. This usually resolves spontaneously within months.

Late consequences of radiotherapy include subtle, progressive cognitive deficiencies such as inattention [319], memory impairment, or learning disabilities [320] and are related to the dose and volume delivered [321] and age at which time the treatment is delivered. Leukoencephalopathy has been described in children with acute leukemia who received intrathecal and intravenous methotrexate [322] and whole brain irradiation (Hertzberg et al. 1997). In these cases, neuroimaging shows a diffuse periventricular leukomalacia with patchy necrosis and calcifications. High-dose methotrexate following radiation therapy and the use of cytarabine have also been implicated in the development of leukoencephalopathy. Changes in white matter as a result of radiation therapy can have a dramatic impact on cognitive function later in life, and serial assessment of these changes may be used to guide survivorship issues and intervention [323, 324].

Additional late effects of RT include strokes related to a moyamoya-like syndrome [11, 325, 326]. Secondary malignancies, including high-grade gliomas, atypical meningiomas [327], osteosarcomas [328], thyroid carcinomas [329], and schwannomas have been observed within the treatment field several years after the completion of radiation therapy. The prognosis for these radiation-induced tumors is poor [330] and argues for the judicious use of radiation therapy in pediatric patients, especially those with low-grade tumors for whom long-term survival is expected.
Patients with Turcot’s syndrome, Gorlin’s syndrome, and NF1 are more likely to develop a secondary malignant glioma after radiation therapy as compared to patients without these conditions [331], and thus consideration of RT should also be made cautiously.

Growth retardation in children with brain tumors is usually multifactorial [332]. Radiation involving the pituitary gland may impair the production and release of growth hormone [333]. In addition, spinal irradiation (as part of craniospinal treatment) affects the growth of the vertebral bones and overall bone density, both within the radiation field and also throughout the body [334]. Obesity can be a direct impact of radiation therapy on the hypothalamus [335]. Myelopathy may arise as a late consequence of spinal irradiation. Damage to the ovaries in prepubertal females can result from their proximity to the spinal column. Ovarian function can be protected with laparoscopic oophoropexy prior to radiation therapy [336].

**Chemotherapy**

Secondary malignancies are a rare but potential late effect of certain chemotherapy agents. Alkylating agents, epipodophyllin, and platinum-based drugs are commonly implicated. In children, acute myelogenous leukemia is the most common type of secondary malignancy induced by chemotherapy, most frequently caused by intravenous etoposide. The transient genotoxic damage to chromosomes by chemotherapy may account for this [337]. Peripheral neuropathy is a common late effect of several chemotherapies [338], especially vincristine [338]. Cisplatin and carboplatin mainly affect proprioception and spare pain and temperature sensation. The usual presenting symptoms are painful dysesthesias and tingling sensations in the toes and later in the fingers. Motor fibers are spared. In contrast, vincristine produces a sensorimotor neuropathy. The first symptom is usually tingling in the toes and fingers; loss of ankle jerks is typically the first objective sign. Continued therapy leads to loss or decrease in reflexes and motor weakness involving the dorsi-flexors of the feet. Cerebellar syndromes of acute onset may be seen with high-dose cytarabine and occasionally with 5-fluorouracil. These complications are usually reversible within weeks but severe irreversible damage to Purkinje cells may occur if the drug is given for several months or if the drug is re-introduced [339]. Transverse myelopathy is seen with prolonged treatments with intrathecal methotrexate or cytarabine. Ototoxicity is a commonly observed toxicity with platinum agents, particularly concurrently administered with cerebellar RT [340].

The late effects experienced by brain tumor survivors cross multiple domains: medical (across disciplines such as neurosurgery, neurooncology, neurology, endocrinology, ophthalmology, and genetics), neurocognitive, educational and psychosocial, among others. Many pediatric oncology programs have developed specialized “survivorship clinics” to address the multidisciplinary needs of patients. The ultimate goal for the pediatric neurooncologist is maximizing overall survival, minimizing the long-term consequences of therapy, and supporting the needs of the survivor.
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Primary Central Nervous System Lymphoma

Elizabeth R. Gerstner and Tracy T. Batchelor

Keywords Primary central nervous system lymphoma · Diffuse large B-cell lymphoma · High-dose methotrexate

Primary CNS Lymphoma

Non-Hodgkin lymphoma rarely presents as an extranodal lymphoma that is restricted to the CNS known as primary CNS lymphoma (PCNSL). PCNSL can affect multiple parts of the neuraxis including the eyes, brain, leptomeninges, or spinal cord and accounts for approximately 3% of all the primary CNS tumors diagnosed each year in the United States. Between 1970 and 2000, the incidence of PCNSL increased largely due to the HIV pandemic. However, the incidence has stabilized or decreased over the last decade to about 0.47 cases per 100,000 persons [1, 2]. Congenital or acquired immunodeficiency is the only established risk factor for PCNSL and HIV-infected individuals are at greater risk of developing this tumor. Approximately 2–13% of patients with a previous diagnosis of AIDS develop PCNSL. The rarity of PCNSL makes systematic study of the disease challenging so an effective standard of care has been difficult to establish [3, 4]. Although durable remissions may be achieved for a few years, most patients eventually relapse.

Pathobiology

The majority (90%) of non-HIV-associated PCNSL is diffuse large B-cell (DLBCL) type with the remaining 10% being poorly characterized low-grade lymphomas, Burkitt’s lymphomas, or T-cell lymphomas [5]. Less is known about these rare
variants of PCNSL. The DLBCL form of PCNSL has a predilection for blood vessels, resulting in lymphoid clustering around small cerebral vessels. This angiocentric pattern of tumor growth in the CNS is unique for DLBCL. Occasionally T-cell infiltrates are also present, making it difficult for the neuropathologist to discriminate between PCNSL and a reactive process.

PCNSL likely arises from late germinal center or post-germinal center lymphoid cells and localizes to the CNS because of a poorly understood neurotropism [6]. Due to the lack of adequate tumor specimens, systematic studies of the molecular pathology of PCNSL have rarely been performed. The vast majority of PCNSL patients are diagnosed by stereotactic needle biopsy so that most of the tissue specimen is consumed by the diagnostic evaluation. Despite this limitation, gene expression studies have demonstrated three gene “signatures” associated with PCNSL: germinal center B-cell, activated B-cell, and type 3 large B-cell lymphoma [7]. While these three gene expression patterns parallel systemic DLBCL, there are unique molecular features of PCNSL. For example, extracellular matrix-related genes are upregulated in PCNSL compared to systemic DLBCL [8]. Interaction between tumor cells and extracellular matrix proteins specific to the CNS may offer an explanation for the neurotropism of PCNSL.

Several genes associated with interleukin-4 (IL-4), a B-cell growth factor expressed by both tumor vessels and tumor cells, are highly expressed in PCNSL including X-box-binding protein 1 (XBP-1), a regulator of the unfolded protein response (UPR) signaling pathway. The expression of UPR-related genes is important for cell survival under stressful conditions such as hypoxia so activation of this pathway may promote tumor cell survival in the CNS. STAT6, a mediator of IL-4 signaling, is expressed by tumor cells and tumor endothelia in PCNSL. High expression levels of STAT6 are associated with short survival in PCNSL patients treated with methotrexate [7]. Recently, the first mouse model of PCNSL that recapitulates the infiltrative growth pattern of lymphoma was developed and potentially may be used to test new therapeutic agents [9].

Histologically, HIV-related PCNSL is typically a large cell lymphoma with immunoblastic and more aggressive features [10, 11]. These patients are often severely immunocompromised with CD4 counts < 50 cells/mm³ at the time of diagnosis and have had prior AIDS-defining illnesses. Inadequate immune system suppression of the Epstein–Barr virus (EBV) likely has a role in the pathogenesis of HIV-related PCNSL through transformation of normal B cells into lymphoma cells.

**Clinical Features**

The median age of immunocompetent patients with PCNSL is 60 compared to HIV-related PCNSL where the median age is 31 [12]. The presentation of PCNSL in both immunocompromised and immunocompetent patients is similar with signs of a focal mass lesion in 70% and 61.3%, respectively [12, 13]. In 248 immunocompetent patients, 43% had neuropsychiatric signs, 33% had symptoms of increased intracranial pressure, 14% had seizures, and 4% had ocular symptoms [13]. In a series of
111 HIV-related PCNSL cases, 43.2% had headache, 21.6% had seizures, and 18% had ataxia [12]. Seizures are less common than with other types of brain tumors probably because PCNSL involves predominantly subcortical white matter rather than epileptogenic gray matter. Unlike patients with systemic NHL, PCNSL patients do not present with B symptoms such as fever, weight loss, or night sweats.

**Diagnostic Evaluation**

The International PCNSL Collaborative Group (IPCG) has established guidelines for the diagnostic evaluation and response assessment of a patient with suspected PCNSL (Tables 14.1 and 14.2) [14]. These guidelines establish the extent of disease and confirm that the disease is restricted to the CNS. Physical examination should include palpation of the lymphatic chain as well as testicular examination in males since testicular lymphoma has a predilection to disseminate to the brain parenchyma. Diagnostic studies include a contrast-enhanced cranial MRI (or contrast-enhanced cranial CT if MRI is contraindicated), lumbar puncture if not contraindicated (for cell count, protein, glucose, cytology, IgH gene rearrangement, and flow cytometry studies), ophthalmologic examination including slit-lamp

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Clinical</th>
<th>Laboratory</th>
<th>Imaging</th>
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<tbody>
<tr>
<td>Centralized review of pathology</td>
<td>Complete medical and neurological examination</td>
<td>HIV serology</td>
<td>Contrast-enhanced cranial MRI&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Immunophenotyping</td>
<td>Dilated eye examination including slit-lamp evaluation</td>
<td>Serum LDH level</td>
<td>CT of chest, abdomen, and pelvis</td>
</tr>
<tr>
<td></td>
<td>Record prognostic factors (age, performance status)</td>
<td>CSF cytology, flow cytometry, IgH PCR</td>
<td>Testicular ultrasound in elderly males</td>
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<td></td>
<td>Serial evaluation of cognitive function&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Twenty-four-hour urine collection for creatinine clearance&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Bone marrow biopsy with aspirate</td>
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<sup>a</sup>Mini-mental status examination is used commonly although improved instruments are being developed

<sup>b</sup>For patients who will receive high-dose methotrexate

<sup>c</sup>Contrast-enhanced cranial CT should be obtained in patients who have a contraindication for MRI (example: pacemaker) or who cannot tolerate MRI (example: claustrophobia)

Adapted from Abrey et al. [14]
Table 14.2 International primary CNS lymphoma collaborative group (IPCG) guidelines for response assessment for clinical trials

<table>
<thead>
<tr>
<th>Response</th>
<th>Brain imaging</th>
<th>Corticosteroid dose</th>
<th>Eye exam</th>
<th>CSF cytology</th>
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<tbody>
<tr>
<td>CR</td>
<td>No enhancing disease</td>
<td>None</td>
<td>Normal</td>
<td>Negative</td>
</tr>
<tr>
<td>uCR</td>
<td>No enhancing disease</td>
<td>Any</td>
<td>Normal</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Minimal enhancing disease</td>
<td>Any</td>
<td>Minor RPE abnormality</td>
<td>Negative</td>
</tr>
<tr>
<td>PR</td>
<td>50% decrease in enhancement</td>
<td>N/A</td>
<td>Minor RPE abnormality or normal</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>No enhancing disease</td>
<td>N/A</td>
<td>Decrease in vitreous cells or retinal infiltrate</td>
<td>Persistent or suspicious</td>
</tr>
<tr>
<td>PD</td>
<td>25% increase in enhancement</td>
<td>N/A</td>
<td>Recurrent or new disease</td>
<td>Recurrent or positive</td>
</tr>
<tr>
<td>SD</td>
<td>Any new site of disease</td>
<td>All scenarios not covered by responses above</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR, complete response; uCR, unconfirmed complete response; PR, partial response; PD, progressive disease; RPE, retinal pigment
Adapted from Abrey et al. [6]

evaluation, CT of the chest/abdomen/pelvis, and bone marrow biopsy. Blood tests for HIV, complete blood count, basic metabolic panel, and lactate dehydrogenase (LDH) level are also recommended. Testicular ultrasound should be considered in men. Body FDG-PET scans may play an increasingly important role in evaluating patients with PCNSL for subclinical systemic disease. In a retrospective study of 49 PCNSL patients evaluated with body FDG-PET studies, extraneural hypermetabolic lesions were identified in 15% of subjects [15]. Subsequent tissue biopsy was performed and 11% of the lesions were found to be lymphoma while 4% were other types of cancer.

The search for occult systemic disease has become increasingly important as recent evidence suggests that lymphoma cells may not be restricted to the nervous system in a small population of patients with CNS lymphoma. Identical polymerase chain reaction (PCR) products of clonally rearranged immunoglobulin heavy chain (IgH) genes were identified in the bone marrow aspirates, blood samples, and brain tumor biopsy specimens in 2 of 24 patients with “primary” CNS lymphoma. In one of these patients, follow-up IgH PCR 24 months after diagnosis yielded a persistent monoclonal blood product despite a complete radiographic response in the CNS [16]. Prospective, long-term follow-up studies will be necessary to further elucidate the frequency and importance of subclinical systemic disease in CNS lymphoma.
patients and whether the presence of these monoclonal cell populations increase the risk of relapse.

**Neuroimaging**

Contrast-enhanced cranial MRI is the imaging modality of choice in evaluating a patient with a suspected diagnosis of PCNSL. If MRI is not possible or contraindicated, a contrast-enhanced cranial CT scan is recommended. PCNSL tends to enhance homogeneously on both MRI and CT although in HIV-associated disease, lesions are often ring-enhancing (Figs. 14.1 and 14.2) [10]. Since PCNSL is a densely cellular tumor, there may be restricted diffusion on diffusion-weighted imaging and apparent diffusion coefficient imaging may be useful as a biomarker of response to methotrexate treatment [17].

In immunocompetent PCNSL patients, lesions are solitary in 65% of cases and are located in a cerebral hemisphere (38%), thalamus/basal ganglia (16%), corpus callosum (14%), periventricular region (12%), and cerebellum (9%) [18]. HIV-related PCNSL is solitary in 48.6% of cases, localized to the cerebral cortex in 65%, the periventricular region in 56%, the basal ganglia in 33%, the cerebellum in 7%, and the brain stem in 4% [12]. Isolated spinal cord involvement is rare and observed in <1% of cases so spinal imaging is only necessary if warranted based on clinical suspicion or to screen for leptomeningeal involvement if lumbar puncture cannot be performed.

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**Fig. 14.1** Axial CT images in a patient with PCNSL. The left CT image without contrast shows an infiltrative mass that expands the splenium of the corpus callosum (*asterisk*) and spreads into the right parietal lobe (*single arrow*), which is isodense with respect to gray matter. After administration of contrast (*right*), the masses enhance homogeneously. Mild low attenuation edema surrounds the lesions (*double arrows*). Reprinted with permission from NEJM 2005: 352:184–5
Prognostic Markers

The identification of prognostic markers in PCNSL enables physicians to discuss prognosis with individual patients and may eventually allow the application of risk-adjusted therapeutic strategies. In addition, the knowledge of important prognostic markers is critical for prospective study designs. For PCNSL, several different prognostic scoring systems have been proposed. In a retrospective review of 105 PCNSL patients, the International Extranodal Lymphoma Study Group (IELSG) identified age > 60, Eastern Cooperative Oncology Group (ECOG) performance status > 1, elevated serum LDH level, high CSF protein concentration, and involvement of deep regions of the brain as independent predictors of worse prognosis [19]. In patients with 0–1 factors, the 2-year survival was 80%; in patients with 2–3 factors, the 2-year survival was 48%; and in patients with 4–5 factors, the 2-year survival was 15%. Another group of investigators have proposed a prognostic model that divides PCNSL patients into three groups based on age and performance status: those <50 years old; those >50 years old with a KPS > 70; and those >50 years old with a KPS < 70 [20]. Based on these divisions significant differences in overall and failure-free survival were observed. As these variables are easily obtained, this model may prove useful in future clinical trials for risk stratification.

The search for biomarkers of prognosis for patients with PCNSL is an active area of investigation. BCL-6, a proto-oncogene expressed in 22–100% of patients, has
been associated with improved prognosis [21–23]. Both progression-free survival (20.5 months vs. 10.1 months) [24] and overall survival (101 months vs. 14.7 months) [21, 25] are longer in PCNSL patients with BCL-6 expression. These findings are consistent with the observation that BCL-6 expression is a favorable prognostic marker in patients with systemic NHL [23, 26, 27]. However, translocations of BCL-6 may be associated with a worse prognosis [28]. In addition, expression of FOXP1, a transcription factor, is increased in some patients with PCNSL and may be associated with poor prognosis [29].

**Treatment of Immunocompetent Patients with PCNSL**

Due to the infiltrative nature of the tumor, resection of PCNSL is not a recommended treatment option except in the rare patient experiencing brain herniation due to mass effect. In addition, PCNSL may be multifocal involving the leptomeninges, the eyes, or the deep regions of the brain making complete removal unfeasible. Median survival following surgery alone is only 1–4 months [30]. Consequently, once the diagnosis is achieved after a stereotactic biopsy, further surgery is not necessary and treatment includes corticosteroids, chemotherapy, and radiation.

**Corticosteroids**

Corticosteroids can work rapidly to cause tumor regression in as many as 40% of patients likely through direct lymphocytolysis and reduced tumor-associated edema [31]. However, corticosteroids should be withheld, if possible, prior to a diagnostic biopsy since these drugs may disrupt cellular morphology and lead to diagnostic inaccuracy at the time of microscopic analysis. Despite an initial positive response to corticosteroids, patients quickly relapse and require alternate treatment strategies. Nevertheless, initial radiographic response to corticosteroids in newly diagnosed PCNSL patients is a favorable prognostic marker with survival of 117 months in responders versus 5.5 months in non-responders in one study [32].

**Radiation**

Given the multifocal and infiltrative nature of PCNSL, whole brain radiation therapy (WBRT) was historically the treatment modality of choice. However, WBRT alone is inadequate therapy for PCNSL patients, particularly those with CSF dissemination of their tumor. Initial radiographic response to WBRT is observed in 90% of PCNSL patients but relapse usually occurs within a few months [33]. In patients receiving WBRT alone without chemotherapy, median survival varies from 12 to 18 months and 5-year survival ranges from 18 to 35% [34, 35]. A radiation dose–response relationship exists for PCNSL as dose reduction from 45 to 30 Gy
increased relapse risk in one non-randomized study [36]. Despite initial control of
disease, WBRT produces delayed neurotoxicity, especially in those older than 60.
For this reason, WBRT is often deferred in newly diagnosed PCNSL patients > 60
years of age.

**Combined Modality Therapy**

In an attempt to improve survival over surgery or radiation alone, numerous stud-
ies adding chemotherapy to radiation have been reported in PCNSL. Unfortunately,
there is no compelling evidence for the superiority of any one regimen. Methotrexate
(MTX), a folate antagonist that interferes with DNA synthesis, has become the back-
bone of most regimens despite limited penetration into the CNS because of a high
degree of ionization at physiologic pH. The blood–brain barrier (BBB) is an obsta-
cle for many chemotherapeutic drugs that are hydrophilic or for those with a high
molecular weight. Using microdialysis catheters, Olson et al. measured the pen-
etration of MTX (12 g/m²) into high-grade brain tumor tissue [37]. The ratio of
brain extracellular fluid MTX to plasma MTX was only 0.13. This low penetration
is an important reason why high doses of systemic MTX are necessary to achieve
cytotoxic intratumoral concentrations. Shorter infusion duration also appears to be
important as a 3-h infusion of 100 mg/kg MTX resulted in greater tumor shrinkage
than a 6-h infusion in one small study [38].

Combination regimens including MTX and WBRT are associated with a radio-
graphic response in >50% of patients and a 2-year survival of 43–73% [31].
Omission of MTX is associated with worse survival, reinforcing the importance
of building on a MTX backbone for therapy [39]. The majority of MTX-based reg-
imens are associated with similar survival rates, but the toxicity varies depending
on the regimen. MTX, vincristine, procarbazine (MVP) followed by WBRT and
cytarabine in the post-radiation setting is a commonly used regimen. This regimen
is associated with an overall response rate (ORR) of 91%, a progression-free sur-
vival (PFS) of 24 months, and an overall survival (OS) of 36.9 months [40]. Toxicity
associated with this regimen was notable and included 8 patient deaths and 12 cases
of clinically significant neurotoxicity in the 98 patients studied. A subsequent study
tested rituximab, a humanized monoclonal antibody against the B-cell surface anti-
gen CD20, with MVP followed by lower dose WBRT (23.4 Gy) for patients who
achieved a complete response (CR) to chemotherapy or 45 Gy of WBRT if a CR
was not achieved [41]. The ORR was 93% and 2-year median PFS was 57%. At
a median follow-up of 37 months, none of the patients had experienced treatment-
related neurotoxicity. A randomized phase II study of MTX monotherapy (3.5 g/m²)
versus MTX with cytarabine followed by WBRT in both arms demonstrated that
more patients in the combination arm achieved a radiographic response (CR and PR)
but grade 3/4 hematological toxicity was also higher [42]. Other combined modality
regimens are listed in Table 14.3 [43–45]. While the ORR reported in these studies
is encouraging, the high frequency of treatment-related toxicity and eventual relapse
are of concern.
<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>$N$</th>
<th>IT Chemo</th>
<th>WBRT</th>
<th>CR</th>
<th>PR</th>
<th>OS (months)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrey et al. [90]</td>
<td>52</td>
<td>MTX</td>
<td>45 Gy</td>
<td>87% (45/52)</td>
<td>8% (4/52)</td>
<td>60</td>
<td>NA</td>
</tr>
<tr>
<td>DeAngelis et al. [40]</td>
<td>102</td>
<td>MTX</td>
<td>45 Gy</td>
<td>58% $^c$ (29/50)</td>
<td>36% $^c$ (18/50)</td>
<td>36.9</td>
<td>24</td>
</tr>
<tr>
<td>Poortmans et al. [44]</td>
<td>52</td>
<td>Cytarabine, MTX</td>
<td>30 Gy with 10 Gy boost</td>
<td>69% (36/52)</td>
<td>12% (6/52)</td>
<td>46</td>
<td>NA</td>
</tr>
<tr>
<td>Gavrilovic et al. 2007 [90, 91]$^b$</td>
<td>57</td>
<td>MTX</td>
<td>45 Gy in those $&lt;60$ years old</td>
<td>56% (27/48)</td>
<td>33% (16/48)</td>
<td>51</td>
<td>129</td>
</tr>
<tr>
<td>Shah et al. [41]</td>
<td>30</td>
<td>None</td>
<td>23.4 Gy if CR, 45 Gy if not CR</td>
<td>77% (23/30)</td>
<td>NA</td>
<td>2-Year survival 1.67%$^a$</td>
<td>40$^a$</td>
</tr>
<tr>
<td>Ferreri et al. [42]</td>
<td>MTX (3.5 g/m$^2$) ± cytarabine</td>
<td>None</td>
<td>Added based on response and age</td>
<td>MTX alone 18%</td>
<td>MTX alone 23%</td>
<td>MTX alone 32%</td>
<td>MTX + cyt 46%</td>
</tr>
</tbody>
</table>

$^a$2-Year survival

$^b$MTX alone 32\%
<table>
<thead>
<tr>
<th>Chemotherapy regimen</th>
<th>$N$</th>
<th>IT Chemo</th>
<th>WBRT</th>
<th>CR</th>
<th>PR</th>
<th>OS (months)</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy without RT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pels et al. [53]</td>
<td>65</td>
<td>Prednisolone, MTX, cytarabine</td>
<td>None</td>
<td>61% (37/61)</td>
<td>10% (6/65)</td>
<td>50</td>
<td>21</td>
</tr>
<tr>
<td>Hoang-Xuan et al. [52]</td>
<td>50</td>
<td>Cytarabine, MTX</td>
<td>None</td>
<td>42% (21/50)</td>
<td>6% (3/50)</td>
<td>14.3</td>
<td>10.6</td>
</tr>
<tr>
<td>Gerstner et al. [46, 47]</td>
<td>25</td>
<td>None</td>
<td>None</td>
<td>52% (12/25)</td>
<td>NA</td>
<td>55.4</td>
<td>12.8</td>
</tr>
<tr>
<td>Intraarterial chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McAllister et al. [92]</td>
<td>74</td>
<td>None</td>
<td>None</td>
<td>65% (48/74)</td>
<td>19% (14/74)</td>
<td>40.7</td>
<td>NA</td>
</tr>
<tr>
<td>Chemotherapy regimen</td>
<td>$N$</td>
<td>IT Chemo</td>
<td>WBRT</td>
<td>CR</td>
<td>PR</td>
<td>OS (months)</td>
<td>PFS (months)</td>
</tr>
<tr>
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</tr>
<tr>
<td>Doolittle et al. [54]</td>
<td>53</td>
<td>None</td>
<td>None</td>
<td>75% (40/53)</td>
<td>15% (8/53)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>i.a. MTX (5 g total dose), cyclophosphamide, etoposide after BBBD mannitol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Sonoda et al. [93]</td>
<td>63</td>
<td>None</td>
<td>36–50 Gy</td>
<td>75% (43/57)</td>
<td>25% (14/57)</td>
<td>39</td>
<td>26</td>
</tr>
<tr>
<td>i.a. ACNU</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angelov et al. [55]</td>
<td>149</td>
<td>None</td>
<td>None</td>
<td>57.8%</td>
<td>24.2%</td>
<td>37.2</td>
<td>21.6</td>
</tr>
<tr>
<td>i.a. MTX</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

*a* Estimated.

*b* This study is an update of a previous study

*c* Prior to RT since post-RT results not available

RT, radiation therapy; MTX, methotrexate; i.a., intrarterial; i.v., intravenous; BBBD, blood–brain barrier disruption; ACNU, nimustine; cyt, cytarabine
Chemotherapy Alone

Combined modality protocols including radiation and chemotherapy are often associated with delayed neurotoxicity, particularly in those patients older than 60 years with vascular risk factors. In order to avoid this high frequency of toxicity, other studies have explored the use of chemotherapy alone, reserving WBRT for patients who subsequently relapse.

In a phase II, multicenter study of 25 patients treated with intravenous MTX (8 g/m²) monotherapy, 52% of patients achieved a CR, the median PFS was 12.8 months, the median OS was 55.4 months, and median disease-specific survival had not been reached at 72.3 months [46, 47]. In this study, 5 of the 25 patients treated with MTX alone achieved a CR and have not relapsed after a median follow-up of 6.8 years. Duration of maintenance MTX therapy after a patient achieves a CR remains unclear.

A substantial number of PCNSL patients are elderly with potential significant comorbidities so may not be ideal chemotherapy candidates. However, MTX monotherapy has been shown to be safe and effective in elderly patients [48, 49]. MTX combined with temozolomide may also be beneficial in elderly patients or even temozolomide alone [50, 51].

While MTX monotherapy may be effective for a subset of patients, most patients will require combination chemotherapy to achieve a durable response. There have been a large number of phase II trials involving methotrexate-based, multiagent chemotherapy regimens without WBRT. In patients > 60 years old, a regimen consisting of MTX, CCNU, procarbazine, methylprednisolone, intrathecal (i.t.) MTX, and i.t. cytarabine was associated with a median OS of 14.3 months and a decreased risk of neurotoxicity [52]. Another regimen including MTX, cytarabine, vincristine, ifosfamide, cyclophosphamide, and i.t. MTX/cytarabine/prednisolone was associated with a 71% ORR and a median OS of 50 months. Despite these promising results, however, 6 patients died from treatment-related complications and 12 patients had Ommaya reservoir infections [53]. Therefore, the best combination regimen has yet to be identified.

Blood–brain barrier disruption (BBBD) is a strategy aimed at circumventing the BBB in order to deliver higher concentrations of chemotherapeutics directly to the CNS. Doolittle et al. reported complete radiographic responses in 40 of 53 patients with PCNSL treated with intraarterial (i.a.) MTX (total dose 5 g) and i.v. cyclophosphamide and etoposide following BBBD with i.a. mannitol [54]. Moreover, long-term follow-up of the subjects who achieved CR with this therapy demonstrated maintenance of cognitive function (patients did not receive WBRT). In a pooled analysis of 149 patients treated with i.a. MTX, the CR proportion was 57.8% with median overall survival of 3.1 years [55]. However, BBBD is technically complex and should only be performed in centers with expertise and experience in the technique.
Intrathecal Chemotherapy

A controversial issue in the management of PCNSL is the role of i.t. chemotherapy. Historical comparisons have determined that there appears to be no difference in overall survival when i.t. MTX is added to regimens that already include high doses of i.v. MTX [56]. By administering MTX systemically, the risk of Ommaya placement, extra-CSF drug delivery, chemical meningitis, and infection can be avoided. However, as mentioned above, the i.v. dose must be high enough for MTX to penetrate into the CSF and tumor. For patients with concurrent brain and leptomeningeal lymphoma, i.t. chemotherapy is often recommended. Ommaya reservoir placement is the most efficient and safest way to deliver i.t. chemotherapy. Repeated lumbar punctures are uncomfortable for patients and may result in delivery of chemotherapy into the epidural space rather than into the CSF. For patients who require ventricular–peritoneal shunt (VPS) and i.t. chemotherapy, a VPS with an “on–off” valve is an option. Although not systematically studied, these shunts theoretically allow the physician to temporarily halt CSF drainage into the peritoneum after instillation of chemotherapy. Finally, the use of rituximab for PCNSL is increasing and there is debate about the penetration of this large CD20 antibody through the BBB. Early phase I studies have suggested that intrathecal delivery of rituximab may be effective for relapsed disease and circumvent the concern about CNS penetration.

High-Dose Chemotherapy with Stem Cell Rescue

Initial studies of high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) have involved limited numbers of patients and have yielded mixed results likely because of the use of heterogeneous therapies and outcome measures (Table 14.4) [57–61]. However, results are encouraging and it is likely that high-dose chemotherapy with ASCT will assume an increasingly important role in younger patients with PCNSL in the newly diagnosed and relapsed setting. ASCT may be effective in patients with poor prognostic features as well [62]. Neurotoxicity was low in patients < 60 years old in these studies but aggressive induction chemotherapy seems to be necessary.

Salvage Therapy

Despite aggressive treatment, the majority of patients with PCNSL will progress or relapse and require salvage therapy. Optimal management of relapsed or refractory PCNSL has yet to be determined and has only been studied in small patient series or case reports using heterogeneous therapies. In general, prognosis for patients with relapsed or progressive PCNSL is poor with a median survival of approximately 4.5 months [63]. For patients who initially achieved a CR to a chemotherapy
regimen that included MTX, re-treatment with MTX alone may be effective [64]. Temozolomide; topotecan; etoposide (VP-16), ifosfamide, and cytarabine (Ara-C) (VIA); high-dose chemotherapy followed by ASCT; and procarbazine, lomustine (CCNU), and vincristine (PCV) have all been studied in patients with relapsed or refractory PCNSL with varying results as summarized in Table 14.4 [65–68].

Rituximab, a monoclonal antibody to CD20, has been administered in combination with temozolomide in two studies of relapsed or progressive PCNSL, yielding a median survival of 8 and 14 months [69, 70]. Intraventricular rituximab (10–25 mg) was determined to be feasible in a phase I study of patients with relapsed or refractory lymphomatous meningitis but further testing is needed [71]. An unexpected observation from this study was a radiographic response of brain parenchymal lymphoma in one case and two patients with intraocular lymphoma who experienced disease resolution and/or clinical improvement in vision. Further studies are planned with rituximab including patients with brain parenchymal lymphoma.

Radiation as a salvage therapy has also been explored. Following WBRT, 74–79% of patients with relapsed or refractory PCNSL can achieve a radiographic response [72, 73]. Median survival after radiation treatment is 10.9–16 months, with those patients less than 60 years old faring better. These results with WBRT as salvage therapy are comparable to the results when WBRT alone is utilized in the newly diagnosed PCNSL setting.

**Neurotoxicity**

Delayed neurotoxicity is an unfortunate consequence of PCNSL treatment with chemoradiation (WBRT + chemotherapy) or WBRT alone. More commonly associated with patients older than 60 years, it typically presents as a subcortical dementia
with gait ataxia and incontinence. MRI changes associated with neurotoxicity include periventricular white matter abnormalities, cortical atrophy, and ventricular enlargement. Less severely affected patients have problems with attention, executive function, memory (particularly verbal), and psychomotor speed. These changes may appear 6–12 months following WBRT but it is important to note that radiographic changes do not always correlate with clinical symptoms which may appear earlier. Pathological studies have demonstrated demyelination, neuronal loss, gliosis, and rarefaction of the white matter [74]. Large vessel atherosclerosis has been observed as well, implicating vascular injury and resultant tissue ischemia as one possible mechanism for neurotoxicity. Although the pathophysiology of treatment-related neurotoxicity is multifactorial, toxicity to neural progenitor cells is likely to play a pivotal role [75].

Studies examining neurotoxicity have several methodological limitations including lack of baseline evaluations, different definitions of cognitive impairment, and small patient sample sizes [76]. In one study of PCNSL patients, the 5-year cumulative incidence of neurotoxicity was 24% and the use of WBRT was the only significant predictor of development of neurotoxicity on multivariate analysis [77]. This is in contrast to chemotherapy alone in which less decline in cognitive function is observed despite evidence of white matter changes on MRI [76, 78, 79]. One treatment strategy has been to decrease the dose of WBRT to 23.4 Gy in patients who achieved a complete response to induction chemotherapy. In a small study of 12 PCNSL patients who had serial neuropsychological testing up to 24 months after R-MVP chemotherapy followed by low-dose WBRT, there was no significant decline in cognitive function compared to baseline [80]. However, the small sample size and high attrition rate may have limited the ability of the investigators to detect more subtle cognitive changes.

Unfortunately, there is no effective treatment for neurotoxicity, and patients often die from complications of neurotoxicity without evidence of recurrent lymphoma. In order to better assess cognitive function as an endpoint in this patient population, the International PCNSL Collaborative Group (IPCG) has proposed a battery of psychometric tests for inclusion in all prospective PCNSL clinical trials [76].

### Treatment of HIV-Related PCNSL

PCNSL is the second most common mass lesion in the brain of HIV-infected persons after toxoplasmosis. Therefore, the typical approach to an HIV-infected patient with an enhancing brain mass is to initially treat the patient with antitoxoplasmosis drugs for 2 weeks. If the patient fails to improve after 2 weeks, a biopsy is performed to determine if the patient has PCNSL. This approach highlights the importance of withholding steroids for as long as possible since steroids may render a biopsy for PCNSL non-diagnostic because of tumor cell lysis. EBV is closely associated with HIV-related PCNSL leading to interest in a diagnostic test for EBV infection as an alternative to brain biopsy. CSF PCR for EBV is less invasive than a brain biopsy but
the positive predictive value of CSF EBV PCR is only 10–50% and the specificity is 66–90% [81, 82]. Thus, brain biopsy is recommended for definitive diagnosis if other CSF studies are non-diagnostic.

Since the adoption of highly active antiretroviral therapy (HAART), the proportion of HIV-infected patients with PCNSL dropped from 28 to 17% in one study [83]. This is likely because fewer patients are reaching such a severe immunocompromised state, reducing the likelihood of latent EBV reactivation in the CNS. Prior to the introduction of HAART in 1996, median survival of HIV-infected patients with PCNSL was only 2.1–2.6 months with radiation alone [10, 84]. Adding two or more antiretroviral agents to WBRT can prolong survival [12]. Skiest et al. showed that six of the seven PCNSL patients who received HAART were still alive at a median follow-up of 22 months. In this study WBRT prolonged survival but not as much as adding WBRT to HAART. A survival benefit was observed in those patients whose viral load dropped and in those whose CD4 count increased to >50 cells/mm$^3$ with treatment [85]. A significant problem in these studies is the potential for selection bias. Patients who are treated are usually stable enough to undergo WBRT or tolerate HAART and may represent a healthier, more compliant subset of patients.

Chemotherapy has been used in HIV-infected patients as well, despite a concern that it will exacerbate immunosuppression. In ten AIDS patients with histologically confirmed PCNSL treated with MTX (3 g/m$^2$), the median survival was 9.7 months [86]. In another study, thiotepa and procarbazine were added to MTX and this regimen was associated with a median survival of 3.5 months in all patients and 7 months in those patients who completed the entire course of treatment [87]. Considering the association between EBV and HIV-related PCNSL, there has been interest in using EBV-directed therapies in this patient population. Ganciclovir, a nucleoside analog with efficacy against EBV, reduced EBV DNA load in CSF and prolonged survival in HIV-positive patients with PCNSL [88]. Another report of four patients showed promising results with intravenous zidovudine, ganciclovir, and interleukin-2 followed by oral ganciclovir, patient-specific HAART, and subcutaneous interleukin-2 [89]. After 4 years of follow-up, one patient was still in CR. There is a critical need to conduct prospective studies of novel therapeutics to improve survival in patients with HIV-related PCNSL.

References

14 Primary Central Nervous System Lymphoma


Chapter 15
Meningiomas

Marc C. Chamberlain

Keywords  Intradural meningiomas · Surgery · Radiotherapy · Chemotherapy

Historical Perspective and Epidemiology

In 1614, Felix Plater first described a meningioma in an autopsy report [1–3]. A French surgeon, Antoine Louis, published the first report in 1754 that dealt specifically with meningiomas [1–3]. In 1847, Virchow described meningiomas as psammomas (sand-like) due to the presence of tumoral granules. Bouchard, in 1864, termed meningiomas epitheliomas followed by Golgi’s description in 1869 in which he used the term endotheliomas. In 1922, Harvey Cushing first used the term meningioma. Pathologists subsequently demonstrated the origin of meningiomas as arachnoid cap cells commonly found associated with arachnoid villi at the dural venous sinuses and veins [1–3].

Hospital-based brain tumor series indicate that the incidence of meningiomas is approximately 20% of all intracranial tumors (the most common non-glial primary intracranial tumor) whereas autopsy-based studies indicate an overall incidence of 30% [4–7]. In an unselected patient population, the incidence of incidentally discovered meningiomas by cranial MRI is approximately 1%. Furthermore, 2% of autopsies reveal incidental meningiomas. There is an age-dependent incidence of meningiomas with 0.3 cases per 100,000 in childhood and 8.4 per 100,000 in the elderly [4–9]. Intracranial meningiomas are most common in adults in their fourth, fifth, and sixth decades of life and are rare in childhood (2% of all meningiomas present in childhood) [4–9]. Meningiomas are more common in Blacks and in females with a 2:1 female to male ratio in intracranial meningiomas [4–7]. Female preponderance for meningioma correlates with endogenous hormone level and exogenous hormone replacement in postmenopausal women (in whom an increased
incidence of meningioma is seen) as compared to postmenopausal women who have not taken exogenous hormone replacement therapy [4–7, 11–14]. Increased growth of meningiomas during pregnancy as well as during postpartum clinical regression has been reported but remains poorly understood [11–14]. Nonetheless, in a recent case–control study of 151 women with meningiomas, no associations with reproductive or hormonal factors were observed [12, 13]. In addition, the literature does not support any association between the development of meningiomas and oral contraceptives [11].

Clinical Presentation

The clinical presentation of meningiomas (Table 15.1), as is true of all intracranial mass lesions, is dependent upon tumor location (Tables 15.2 and 15.3) [1–3, 10, 15, 16]; 90% of all meningiomas occur in the supratentorial compartment [1–10]. Meningiomas are most often slow-growing tumors, and symptoms at presentation are rarely precipitous but more often insidious in nature. New onset and slowly evolving headache is common and usually unassociated with other symptoms suggestive of raised intracranial pressure, reflecting the slow growth of these tumors. A protracted history of partial seizures for convexity meningiomas is neither uncommon nor is an insidious personality change (easily confused with dementia or depression) in patients with large inferior frontal meningiomas. A number of topographic anatomic tumor syndromes have been defined (Table 15.3); however, these syndromes are not etiologically specific as a variety of focal intracranial lesions (for example, granulomas, gliomas, and cysts) may present in a similar manner [17].

Neuroradiology

Brain imaging with contrast-enhanced computerized tomography (CT) or magnetic resonance imaging (MRI) is the most common method of diagnosing, monitoring, and evaluating response to treatment (Table 15.4). Plain X-rays often obtained for coincidental indications may reveal a number of findings characteristic of meningioma including intratumoral calcifications, bony hyperostosis giving rise to a “sunray effect,” a secondary osteolytic lesion, a dilated middle meningeal artery groove, posterior clinoid erosion, suture separation, and a “beaten brass” appearance of the skull [17].

Although MRI is the imaging technique of choice for glial tumors as it provides more intracranial detail, CT scanning still has an important role in the imaging of meningiomas. The CT scan best reveals the chronic effects of slowly growing mass lesions on bone remodeling. Calcification in the tumor (seen in 25%) and hyperostosis of surrounding skull are features of an intracranial meningioma that can be easily identified on a non-contrast CT scan. Nonetheless, MR imaging reveals a number of imaging characteristics highly suggestive of meningioma and in recent stereotactic
#### Table 15.1  History and physical findings in patients with intracranial meningioma [1, 2, 5, 10, 15, 16]

<table>
<thead>
<tr>
<th>Signs and symptoms</th>
<th>Meningioma</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
<td>Malignant</td>
</tr>
<tr>
<td>Patient history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>70</td>
<td>5</td>
</tr>
<tr>
<td>Personality change/confusion</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>Paresis</td>
<td>37</td>
<td>6</td>
</tr>
<tr>
<td>Generalized seizures</td>
<td>36</td>
<td>1</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td>Focal seizures</td>
<td>29</td>
<td>2</td>
</tr>
<tr>
<td>Ataxia</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>Aphasia</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Decreased level of consciousness</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Diplopia</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Vertigo</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Decreased hearing</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Physical findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresis</td>
<td>57</td>
<td>7</td>
</tr>
<tr>
<td>Normal examination</td>
<td>51</td>
<td>2</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>29</td>
<td>3</td>
</tr>
<tr>
<td>Other cranial nerve deficit</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Visual field deficit</td>
<td>19</td>
<td>3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Aphasia</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Papilledema</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Decreased visual acuity</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Altered level of consciousness</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Decreased hearing</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Radiotherapy articles, MR has been used to operationally define pathology in lieu of surgery [7, 15–22]. These MR findings include a tumor, which is dural-based and isointense with gray matter, demonstrating prominent and homogeneous enhancement (>95%), frequent CSF/vascular cleft(s), and often an enhancing dural tail (60%). However, approximately 10–15% of meningiomas have an atypical MRI appearance mimicking metastases or malignant gliomas [7, 10, 17, 18]. In particular secretory meningiomas may have significant amount of peritumoral edema. Cerebral angiography is occasionally performed, often for surgical planning, as meningiomas are vascular tumors prone to intraoperative bleeding [1, 2, 5, 15–17]. In some instances preoperative embolization is helpful for operative hemostasis management. Angiographic findings consistent with a meningioma include a dual vascular supply with dural arteries supplying the central tumor and pial arteries supplying the tumor periphery. A “sunburst effect” may be seen due to enlarged and
Table 15.2  Location of intracranial meningiomas demonstrated by computerized tomography [1, 2, 5, 10, 15, 16]

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Meningioma</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. (%</td>
<td>No. (%)</td>
<td></td>
</tr>
<tr>
<td>Convexity</td>
<td>60 (34)</td>
<td>7 (50)</td>
<td></td>
</tr>
<tr>
<td>Parasagittal</td>
<td>39 (22)</td>
<td>4 (29)</td>
<td></td>
</tr>
<tr>
<td>Sphenoid ridge</td>
<td>30 (17)</td>
<td>3 (21)</td>
<td></td>
</tr>
<tr>
<td>Lateral ventricle</td>
<td>10 (5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Tentorium</td>
<td>7 (4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Cerebellar convexity</td>
<td>9 (5)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Tuberculum sellae</td>
<td>7 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Intraorbital</td>
<td>4 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Cerebellopontine angle</td>
<td>4 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Olfactory groove</td>
<td>6 (3)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Foramen magnum</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Clivus</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>179</strong></td>
<td><strong>14</strong></td>
<td></td>
</tr>
</tbody>
</table>

Table 15.3  Clinical syndromes of intracranial meningiomas [1, 2, 5, 10, 15–17]

- Parasagittal/parafalcine: Simple partial seizures, paraparesis
- Posterior parasagittal: Homonymous hemianopsia
- Anterior parasagittal: Neurobehavioral syndrome
- Sphenoid wing: Visual loss, trigeminal dysfunction, ophthalmoplegia
- Olfactory groove: Anosmia, dementia
- Suprasellar: Bitemporal hemianopia
- Tentorial: Headache, vertigo, ataxia

multiple dural arteries, and a prolonged vascular stain or so-called blushing can also be seen, which results from intratumoral venous stasis and expanded intratumoral blood volume [17].

There has also been interest in the use of MR spectroscopy (MRS) to assist in the diagnosis of meningiomas. MRS may be particularly useful in patients unable to undergo a surgical procedure for whatever reason. Creatinine-containing peaks in meningioma are 20% that of comparable levels in normal brain [18, 23–25]. An increase in the choline-containing peaks and the alanine peak has been reported as well [25]. A low inositol peak may help distinguish a meningioma from a neurinoma [25]. Buhl reported that greater than 60% of atypical meningiomas had a characteristic lactate peak on preoperative MRS [24].

While positron emission tomography (PET) has not been routinely used in the diagnostic work-up and follow-up of patients with meningiomas it can be useful in cases of skull base meningiomas that are frequently difficult to visualize using
Table 15.4  Computerized tomography (CT) findings in patients with meningioma [1, 2, 5, 10, 16, 17]

<table>
<thead>
<tr>
<th>Finding</th>
<th>Meningioma</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Benign</td>
<td>Malignant</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Midline shift</td>
<td>140</td>
<td>78</td>
<td>12</td>
</tr>
<tr>
<td>Homogenous enhancement</td>
<td>129</td>
<td>72</td>
<td>5</td>
</tr>
<tr>
<td>Non-homogenous enhancement</td>
<td>41</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>No adjacent hypodensity</td>
<td>86</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Mild adjacent hypodensity</td>
<td>55</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>Moderate adjacent hypodensity</td>
<td>10</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Severe adjacent hypodensity</td>
<td>28</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Hyperostosis</td>
<td>32</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Calcification</td>
<td>49</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Fringing (a fringe-like extension</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>from an otherwise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>well-demarcated tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“Mushrooming” (prominent tumor</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>pannus, extending away from the</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>globoid mass)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

standard CT and MRI techniques. Rutten reported that using PET/CT and 2-18F-fluoro-L-tyrosine (18F-TYR), a marker of amino acid transport, may be useful in managing meningiomas [26]. Rutten showed that 18F-TYR uptake completely overlapped with the MR lesion in 54%, extended beyond the MRI lesion in 38%, and was smaller in 8% of the tumors. This technique may be particularly useful in patients who were previously irradiated.

Meningiomas are also known to have high somatostatin cell surface receptor density allowing for the potential use of octreotide brain scintigraphy to help delineate extent of disease or support radiographic diagnosis in lieu of pathological confirmation [27–36]. Octreotide imaging may be particularly useful in distinguishing residual tumor from postoperative scarring in subtotally resected/recurrent tumors and may well be useful as part of imaging surveillance.

Pathology and Molecular Genetics

A number of pathologic subtypes of meningioma have been defined and are outlined in Table 15.5. Notwithstanding the histological variety of meningiomas, treatment is determined primarily by the World Health Organization classification, a three-tiered system comprised of three grades (meningioma 90–95%; atypical meningioma 6–8%; and anaplastic meningioma 1–2%). Histopathology reveals that meningiomas have a characteristic array of immunohistological markers as seen in
Table 15.5 World Health Organization classification of tumors of meningothelial cell origin

1. Meningioma 90–95%
   a. Meningothelial (syncytial)
   b. Transitional
   c. Fibrous
   d. Psammomatous
   e. Angiomatous
   f. Microcystic
   g. Secretory
   h. Lymphoplasmacyte rich
   i. Metaplastic variants (xanthomatous, myxoid, osseous, cartilagenous, etc.)
2. Atypical meningioma 6–8%
   a. Clear cell
   b. Chordoid
3. Anaplastic [malignant] meningiomas 2–3%
   a. Rhabdoid
   b. Papillary

Table 15.6. In addition, meningiomas express a variety of cell surface receptors as seen in Table 15.7.

The primary chromosomal aberration in meningiomas is monosomy or deletion of chromosome 22 [1, 2, 4, 5, 10, 15, 22, 37–39]. The meningioma gene has been mapped to a region between the myoglobin locus and the c-sis proto-oncogene. Loss of one chromosome 22 occurs in 75% of meningiomas and is the sole chromosomal abnormality in 50% [4, 22, 37, 39]. The loss of chromosome 22 is believed to represent the loss of a putative tumor suppressor gene and thereby results in malignant change. In the majority of patients with sporadic meningiomas, the lost tumor suppressor gene appears to be the neurofibromatosis type 2 (NF2) gene, a 595 amino acid-long protein called merlin or schwannomin which belongs to the band 4.1 superfamily of proteins [4, 22, 37, 39]. Merlin appears to function as a molecular switch regulating cell contact by binding to the actin cytoskeleton and cell proliferation by binding to a transcription factor. Conformational changes determine the activity of merlin. In the closed state, merlin is active and functions as a growth suppressor whereas in the open state merlin is inactive and is growth permissive. Loss of expression for merlin varies by histological subtype of meningioma and is highest in fibrous and transitional tumors and lowest in meningotheliomatous types. Recently, loss of another member of the 4.1 family of proteins, DAL-1 (absent in approximately 50% of all meningiomas), has been identified as an important factor.

Table 15.6 Meningioma: immunohistological markers

- Epithelial membrane antigen
- Vimentin
- Laminin
- Fibronectin
- Carcinogenic embryonic antigen
- S-100
- Keratin
Table 15.7 Receptors identified in meningiomas

<table>
<thead>
<tr>
<th>Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgen</td>
</tr>
<tr>
<td>Epidermal-derived growth factor</td>
</tr>
<tr>
<td>Estrogen</td>
</tr>
<tr>
<td>Fibroblast growth factor-1</td>
</tr>
<tr>
<td>Glucocorticoid</td>
</tr>
<tr>
<td>Growth hormone</td>
</tr>
<tr>
<td>Insulin-like growth factors-1, 2</td>
</tr>
<tr>
<td>Interferon-α</td>
</tr>
<tr>
<td>Platelet-derived growth factor</td>
</tr>
<tr>
<td>Progesterone</td>
</tr>
<tr>
<td>Prolactin</td>
</tr>
<tr>
<td>Somatostatin</td>
</tr>
<tr>
<td>Vascular endothelial growth factor</td>
</tr>
<tr>
<td>Transforming growth factor-β</td>
</tr>
</tbody>
</table>

in meningioma tumorigenesis [22, 37, 39]. Aside from loss of chromosome 22q (the NF2 gene), loss of chromosomes 1q, 14q, and 10q occurs in atypical and malignant meningiomas [4, 22, 37, 39]. Additionally, both epidermal growth factor receptor and platelet-derived growth factor receptor are overexpressed in meningioma.

In a recent study, 126 sporadic meningiomas were analyzed with microarray-based comparative genomic hybridization [40]. The frequency of biallelic NF2 inactivation was 52% in fibroblastic compared to 18% in meningothelial tumors, both of which are WHO Grade 1 meningioma subtypes. These data suggest that NF2 inactivation may not be a critical step in the pathogenesis of meningothelial meningiomas. In addition, 51 meningiomas (40%) showed no evidence of chromosome 22q loss and 16 (13%) showed partial chromosome 22q loss that did not involve the NF2 locus. These findings indicate that additional genes on chromosome 22q and elsewhere in the genome have an important pathogenic role in the development of a subset of meningiomas. Candidate genes on chromosome 22q include BCR (implicated in chronic myeloid leukemia), Rgr, an oncogene involved in Ras signaling, and the zinc finger protein encoding gene ZCWC1.

Recurrent meningiomas often have loss of chromosome 14q [39]. Transition to atypical meningiomas (WHO Grade 2) is associated with losses on chromosomes 1p, 6q, 10q, 14q, 18q, and gains on 1q, 9q, 12q, 15q, 17q, and 20q, together with increased telomerase activity and loss of progesterone receptor (PR) expression [22, 39–41]. Malignant meningiomas are associated with gains on 17q, losses on 9p (CDKN2A/B, p14ARF), and further losses on 1p, 6q, 14q, and 18q, as well as loss of PR expression [22, 39–41].

Gene expression profiling studies distinguished WHO Grade 1 meningiomas from atypical and malignant tumors and confirmed previously noted altered expression of growth hormone receptor (GHR), insulin-like growth factor binding protein-7 (IGFBP-7), endothelin receptor A (ET-A), and insulin-like growth factor-2 (IGF-2) [42]. Additional genes were noted to be differentially overexpressed, including genes that encode cathepsin K (a cellular protease associated with an invasive tumor phenotype), midkine (mitogenic and angiogenic factor), and ear-2 (nuclear orphan receptor associated with hormonal gene regulation). Other genes
such as Rad (nm23 metastasis suppressor), BCR, and junB (represses cyclin D and cell proliferation) proved to be downregulated in high-grade meningiomas [42]. More recent microarray studies showed that losses on chromosomes 10 and 14 in high-grade meningiomas were associated with distinct expression profiles including increased expression of several genes related to the insulin-like growth factor (IGF-2, IGFBP3, and AKT3) or wingless (WNT) (CTNNB1, CDK5R1, ENC1, and CCND1) pathways [43]. Proteomic analysis may also help to elucidate the molecular events that underlie the transition from benign to atypical or malignant meningiomas [44].

There are many rare familial conditions that predispose to meningiomas (Table 15.8). Of these familial syndromes, neurofibromatosis type 2 and meningiomatosis, both inherited as autosomal dominant traits, are most common in clinical practice [4, 37, 38].

<table>
<thead>
<tr>
<th>Table 15.8 Familial syndromes: meningiomas [1, 5, 8–10, 22, 39]</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Neurofibromatosis type 2</td>
</tr>
<tr>
<td>■ Gorlin syndrome (nevoid basal cell carcinoma)</td>
</tr>
<tr>
<td>■ Rubinstein–Tabby syndrome</td>
</tr>
<tr>
<td>■ Li–Fraumeni syndrome</td>
</tr>
<tr>
<td>■ von Hippel–Lindau syndrome</td>
</tr>
<tr>
<td>■ Werner syndrome</td>
</tr>
<tr>
<td>■ Gardner syndrome (adenomatous polyposis of the colon)</td>
</tr>
<tr>
<td>■ Melanoma/astrocytoma syndrome</td>
</tr>
<tr>
<td>■ Cowden disease</td>
</tr>
<tr>
<td>■ Multiple endocrine neoplasia type 1</td>
</tr>
</tbody>
</table>

Rarely (<1% of all meningiomas) meningiomas may occur following either low-dose radiotherapy as was once administered routinely for tinea capitis or following high-dose radiotherapy as given for CNS prophylaxis of acute lymphoblastic leukemia (ALL), glioma, or head and neck malignancies [45]. In both instances of radiation-induced meningiomas, long delays (10 or more years) occur between the administration of radiotherapy and meningioma occurrence and not infrequently, multifocal tumors develop.

Pathologically, the biological behavior of meningiomas may be predicted by MIB-1-labeling indices, vascular endothelial growth factor receptor expression, quantitative staining of proliferating cell nuclear antigen, and expression of JAK (Janus tyrosine kinase) and STAT (signal transducer and activator of transcription) proteins [46–51].

Natural History

Several studies have examined the growth rate of incidental meningiomas (meningiomas discovered in an otherwise asymptomatic patient) (Table 15.9) [52–57]. These studies concluded that the majority of asymptomatic meningiomas may be
Table 15.9  Observational studies

<table>
<thead>
<tr>
<th>Author/reference</th>
<th>Cohort</th>
<th>Number observed</th>
<th>% Progressed</th>
<th>Annual growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firsching [53]</td>
<td>52</td>
<td>17 (33%)</td>
<td></td>
<td>3.6%</td>
</tr>
<tr>
<td>Olivero [56]</td>
<td>60</td>
<td>45 (75%)</td>
<td>22% (10)</td>
<td>2.4 mm/year</td>
</tr>
<tr>
<td>Braunstein [52]</td>
<td>100</td>
<td>12 (12%)</td>
<td>8% (1)</td>
<td></td>
</tr>
<tr>
<td>Go [54]</td>
<td>121</td>
<td>35 (29%)</td>
<td>11% (4)</td>
<td>3.6 mm/year</td>
</tr>
<tr>
<td>Niiro [55]</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herscovici [106]</td>
<td>43</td>
<td>43</td>
<td>37% (16)</td>
<td>4 mm/year</td>
</tr>
<tr>
<td>Nakasu [107]</td>
<td>13</td>
<td>13</td>
<td>15%</td>
<td>Three growth patterns</td>
</tr>
<tr>
<td>Hashiba [57]</td>
<td>70</td>
<td>70</td>
<td>65%</td>
<td>Three growth patterns</td>
</tr>
</tbody>
</table>

followed safely with serial brain imaging until either the tumor enlarges significantly or becomes symptomatic. As well, these studies confirm the tenet that many meningiomas grow very slowly (on average 3–4 mm/year) and that a decision not to operate is justified in selected asymptomatic patients. As the growth rate is unpredictable in any individual, repeat brain imaging is mandatory to monitor an incidental asymptomatic meningioma. A recent observational study using serial volumetric assessment classified meningiomas into three growth patterns: no growth, linear growth (mean annual growth 15%), and exponential (mean annual growth 25%) growth [57]. In patients with asymptomatic meningiomas repeat CT/MRI 3 months after the initial study, followed by scans at increasing intervals (i.e., 6 months, 1 year, 2 years) is confirmed over the first 1–2 years appears adequate to assess growth rate and need for intervention.

Treatment

Surgery

The treatment of meningiomas is dependent upon both patient-related factors (symptoms, age, performance status, medical co-morbidities) and treatment-related factors (reasons for symptoms, resectability, and goals of surgery). In patients who are considered surgical candidates (surgically accessible symptomatic meningiomas), the goal of therapy is total surgical excision [1, 5, 10, 15, 16, 22, 58] (Fig. 15.1). As is common with all brain tumors, extent of surgical resection is determined by early (<72 h) postoperative, contrast-enhanced brain imaging utilizing either CT or MRI. MRI following resection and histopathology at time of resection constitutes the basis for the Simpson grading system, a predictive system for meningioma recurrence (Table 15.10). Patients with a Simpson grade 1 meningioma have a 9% 10-year recurrence rate as compared to patients with a Simpson grade 3 meningioma in whom a 29% 10-year recurrence rate is seen. Prognostic variables predictive for survival in patients with meningiomas include the extent of surgical resection, histological grade, age, and tumor location.
M.C. Chamberlain

Fig. 15.1 Newly diagnosed meningioma treatment algorithm

Table 15.10 Meningiomas: Simpson grading system [1, 10, 16, 58]

| Grade 1 | Macroscopic gross total resection (GTR) with excision of dura, sinus, and bone |
| Grade 2 | Macroscopic gross total resection (GTR) with coagulation of dural attachment |
| Grade 3 | Macroscopic resection without resection or coagulation of dural attachment |
| Grade 4 | Subtotal resection |
| Grade 5 | Biopsy |

Mirimanoff reported recurrence-free survival rates following total resection of 93% at 5 years, 80% at 10 years, and 68% at 15 years [58]. By contrast, with partial resection recurrence-free survival rates dropped to 63%, 45%, and 9%, respectively. Jaaskelainen, in a study of patients with benign intracranial meningiomas, found a recurrence rate of 19% at 20 years following complete resection [16]. The same
group reported that in patients with atypical or malignant meningiomas following complete resection, the risk of recurrence was, respectively, 38% and 78% at 5 years.

**Radiotherapy**

Radiation therapy should be considered following partial resection of a meningioma and following resection of atypical or malignant meningiomas [1, 2, 10, 15, 59–61] (Fig. 15.1). Improving upon the recurrence-free survival rates cited by Mirimanoff (see above), Goldsmith found an 89% 5-year progression-free survival (PFS) with adjunct radiotherapy (median dose 54 Gy) in 140 patients with a partially resected benign meningioma [59]. Ten-year progression-free survival was 77%. Although with radiotherapy the PFS rate for a partially resected meningioma can approach that of a gross total resection (GTR) (63–89%), the decision to radiate should be weighed against the potential for symptomatic recurrence (considering the slow growth rate of most meningiomas) in the patient’s lifetime, versus potential side effects of radiation (i.e., leukoencephalopathy and cognitive symptoms, necrosis, and focal neurologic injury).

The use of stereotactic radiotherapy (either single fraction or fractionated) in the management of meningiomas continues to evolve [20, 21, 60–65]. Utilizing the linear accelerator (LINAC radiosurgery), Leksell Gamma Knife™ or Cyberknife™, stereotactic radiotherapy has been administered in lieu of external beam radiotherapy for small (<35 mm) tumors, which are either recurrent or partially resected. In addition, stereotactic radiotherapy has been used increasingly as primary therapy in surgically inaccessible tumors (i.e., skull base meningiomas) or in patients deemed poor surgical candidates such as some elderly patients. Trials using stereotactic radiotherapy for meningioma reported to date involve comparatively small numbers of patients (usually <100) with relatively short follow-up times (usually <10 years). Notwithstanding these caveats, results of stereotactic radiotherapy compare favorably with external beam radiotherapy and surgery in select meningioma patients [20, 21, 60–64]. A majority of patients will obtain disease stabilization with a small minority achieving tumor regression [61, 65]. This is an important point when considering patients for serial observation who will likely need radiotherapy at some juncture for residual/recurrent disease.

**Hormonal Therapy**

Both epidemiological (female predominance) and biochemical evidence (70% of meningiomas are progesterone receptor positive and 30% are estrogen receptor positive) suggest meningioma growth may be hormone dependent [1, 2, 10, 13, 15]. Additionally, approximately 60% of meningiomas show staining for prolactin receptors [66, 67]. As a consequence, a variety of hormonal therapies have been utilized in the treatment of recurrent benign meningiomas not amenable to further surgery or
radiotherapy. The oral progesterone agonist megestrol acetate (Megace) was used in a small trial of nine patients with no observed responses [68]. Subsequently, in a trial of 14 patients, the progesterone antagonist mifepristone (RU-486) was evaluated [69]. Five objective minor responses were seen, though availability of mifepristone limited further study. The Southwest Oncology Group (SWOG) completed a study of mifepristone for unresectable meningiomas (198 total patients, of whom 160 were evaluable) [70]. The results did not support a role for RU-486 as compared to placebo (median progression-free survival was 10 months in the RU-486 arm and 12 months in the placebo arm). In addition, SWOG reported on a phase II trial of 21 meningioma patients treated with oral tamoxifen, an estrogen receptor antagonist [71]. One patient achieved a partial response, two patients had a minor response, and six patients had stable disease for >6 months.

**Biochemotherapy**

Recombinant α-interferon has been found to inhibit the growth of cultured human meningioma cell lines in vitro [72–75]. Four small reports, two in abstract form, have been published [72–75]. In the largest series, 35 patients with recurrent unresectable and previously irradiated meningiomas were treated [75]. Although no radiographic responses were seen, 74% demonstrated stable disease with a median progression-free survival of 7 months (6-month and 12-month PFS were 54% and 31%, respectively). Median overall survival was 8 months (range 3–28 months).

Schrell demonstrated in vitro that hydroxyurea, an oral chemotherapy with a variety of antitumoral effects, was a potent inhibitor of cultured meningioma cells by inducing apoptosis [76]. Several subsequent clinical trials suggest in vivo efficacy with modest and acceptable toxicity [76–79] (Table 15.11). Problematic with the various hydroxyurea trials, however, is that many patients had not failed radiotherapy or that radiotherapy was administered concurrently.

Calcium channel antagonists have a strong inhibitory effect on meningioma growth in culture and are being investigated for their clinical utility in conjunction with chemotherapeutic agents [80]. A recent trial of chronic oral temozolomide for surgical and radiotherapy refractory meningiomas failed to demonstrate activity in

<table>
<thead>
<tr>
<th>Author</th>
<th>Number (# benign)</th>
<th>Prior RT</th>
<th>Response</th>
<th>Median TTP (mns)</th>
<th>Toxicity (≥ Grade 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newton [78]</td>
<td>17 (13)</td>
<td>7</td>
<td>SD (88%)</td>
<td>20</td>
<td>25% (15%)</td>
</tr>
<tr>
<td>Mason [77]</td>
<td>20 (16)</td>
<td>8</td>
<td>SD (60%)</td>
<td>30</td>
<td>15%</td>
</tr>
<tr>
<td>Rosenthal [108]</td>
<td>15 (5)</td>
<td>1</td>
<td>SD (73%)</td>
<td>10</td>
<td>27% (20%)</td>
</tr>
<tr>
<td>Hahn [109]</td>
<td>21 (4)</td>
<td>21 (concurrent)</td>
<td>SD (52%)</td>
<td>14</td>
<td>53% (0)</td>
</tr>
<tr>
<td>Loven [110]</td>
<td>12 (8)</td>
<td>6</td>
<td>SD (8%)</td>
<td>13</td>
<td>33% (25%)</td>
</tr>
</tbody>
</table>

#, number; RT, radiotherapy; SD, stable disease; TTP, time to tumor progression
16 patients [81]. Similarly, a trial of CPT-11 (irinotecan) in 16 patients with refractory meningiomas failed to show significant activity notwithstanding in vitro work suggesting antimeningioma activity [82, 83].

Multidrug chemotherapy trials for recurrent meningiomas whether aggressive, malignant, or refractory to surgery and radiotherapy are scant [84, 85]. The best-documented chemotherapy regimen (cyclophosphamide, adriamycin, and vincristine) has been used primarily in an adjuvant setting for the treatment of malignant meningiomas; however, without a control group, the results are difficult to interpret [84]. Other published regimens do not report response rates, length of response, or toxicity data and therefore should be regarded as investigational [85]. Unpublished data from a small number of patients from a phase II SWOG trial for aggressive meningeal tumors and malignant meningiomas with ifosfamide/MESNA did not show initial promise.

**Targeted Therapy**

In contrast to the increasing understanding of the molecular pathogenesis and biology of systemic malignancies including gliomas, relatively little is known about the molecular pathogenesis of meningiomas and the critical molecular changes promoting meningioma growth [10, 22, 39, 86]. Overexpression of several growth factors (including platelet-derived growth factor [PDGF], epidermal growth factor [EGF], and vascular endothelial growth factor [VEGF]) and their receptors and signal transduction pathways (i.e., the Ras/mitogen-activated protein kinase [MAPK], phosphatidylinositol-3-kinase [PI3K]-Akt, and phospholipase C [PLC]-γ1-protein kinase C [PKC] pathways) has been implicated, but their relative significance is largely unknown [10, 86–90]. As a result, the most important molecular targets for meningioma-targeted therapy remain uncertain.

PDGF is a fundamental driver of cell proliferation in normal development and in a variety of pathological conditions, including cancer. Accumulating evidence suggests that PDGF plays an important role in meningioma growth [87–90]. The majority of meningiomas of all histological grades express PDGF ligands AA and BB and the PDGF-beta (PDGF-β) receptor. Expression levels appear higher in atypical and malignant meningiomas than in benign meningiomas [89]. Laboratory data suggest that an autocrine PDGF loop supports meningioma cell growth and maintenance [87]. These data suggested a sound rationale for testing PDGF inhibitors in meningioma patients. Imatinib is a potent inhibitor of the Bcl-Abl, PDGF-α, and PDGF-β receptors, and c-Kit tyrosine kinases. Its ability to inhibit PDGFR with an IC$_{50}$ of 0.1 μM suggested that it may have therapeutic potential in meningiomas. The North American Brain Tumor Consortium (NABTC) conducted a phase II study of imatinib in patients with recurrent meningiomas [91]. Patients were stratified into two cohorts: (1) benign meningiomas or (2) atypical and malignant meningiomas. As imatinib is metabolized by the cytochrome P450 system, patients could not be receiving enzyme-inducing antiepileptic drugs. Patients initially received 600 mg/day of imatinib; the dose was increased in the second cycle to 800 mg/day.
if no significant toxicity was observed in the first cycle. Twenty-three patients were enrolled into the study (13 meningiomas, 5 atypical meningiomas, and 5 malignant meningiomas). Although the treatment was well tolerated, imatinib had minimal activity. Of the 19 patients evaluable for response, 10 progressed at the first scan and 9 were stable. There were no radiographic responses. Overall median progression-free survival (PFS) was 2 months (range 0.7–18 months); 6-month PFS was 29.4%. For benign meningiomas, median PFS was 3 months; 6-month PFS was 45%. For the atypical and malignant meningiomas, median PFS was 2 months; 6-month PFS was 0%.

The EGF receptor (EGFR) is overexpressed in more than 60% of meningiomas [89–94]. EGF and transforming growth factor-alpha (TGF-α) activate these receptors and stimulate meningioma growth in vitro, supporting the concept that activation of EGFRs in human meningiomas by autocrine/paracrine stimulation may contribute to their proliferation [92–98]. Increased TGF-α immunoreactivity in meningiomas has been associated with aggressive growth [86, 96]. The NABTC has conducted two trials of EGFR inhibitors in recurrent meningiomas using either gefitinib (Iressa; 500 mg/day) or erlotinib (Tarceva; 150 mg/day) [98]. A total of 25 patients were entered on trial. In both studies, the drugs were well tolerated; the main toxicities were the expected adverse effects of rash and diarrhea. Nonetheless, there were no objective responses and PFS-6 was 25%. Based on the results of this study, neither EGFR inhibitors appear to have significant activity against recurrent meningioma.

Many tumors express somatostatin receptors, providing a molecular rationale for utilizing long-acting somatostatin analogs for therapeutic and diagnostic purposes [27–36]. Somatostatins, also known as somatotropin release-inhibiting factors (SRIFs), form a family of cyclopeptides that bind to G-protein coupled receptors. SRIFs act as neuromodulators and neurotransmitters as well as potent inhibitors of various secretory processes and cell proliferation. 111Indium-DTPA octreotide is a useful ligand for in vivo imaging of somatostatin receptor positive neuroendocrine tumors as well as meningiomas [27–36]. Among brain tumors, meningiomas show the highest frequency of somatostatin receptor expression [29, 30]. The largest study comprising 52 patients with intracranial meningiomas studied by somatostatin scintigraphy indicated a 90% positive rate of detection [31, 33]. In another study by the same group, postoperative somatostatin scintigraphy was complimentary to cranial MRI and in many instances (>50% of cases) suggested residual tumor not evident by MRI [31, 33]. A previous study evaluated as a treatment escalating doses of a long-acting octreotide analog in three patients with unresectable meningiomas [34]. No objective radiographic response was demonstrated; however, therapy was limited to a median of 7 weeks. A second report, communicated in letter format, described relief of headache in three patients with unresectable meningiomas [35]. A final paper described objective visual improvement, without radiographic tumor shrinkage in a patient with a sellar meningioma [36]. Somatostatin receptors, especially the sst2A subtype, are present on most meningiomas, although their functional role remains unclear [29]. The addition of somatostatin inhibits meningioma growth in vitro in most studies, but increases meningioma proliferation in some. In the largest trial of somatostatin use in meningiomas, 16 patients with recurrent
Meningiomas (progressive after prior surgery and radiotherapy) shown to overexpress somatostatin receptors by octreotide scintigraphy were treated with monthly long-acting somatostatin [27]; 31% of patients demonstrated a partial radiographic response and 44% achieved progression-free survival at 6 months with minimal toxicity. New somatostatin analogs with higher affinity may offer a novel, relatively non-toxic alternative treatment for patients with recurrent meningiomas. SOM230C (pasireotide) is an intramuscularly administered, long-acting somatostatin analog with a wider somatostatin receptor spectrum (including subtypes 1, 2, 3, and 5) and higher affinity (particularly for subtypes 1, 3, and 5) than the sustained-release somatostatin described above. A phase II trial for patients with recurrent or progressive meningiomas has just opened and is accruing patients.

Meningiomas are highly vascular tumors that derive their blood supply predominantly from meningeal vessels supplied by the external carotid artery, with additional supply from cerebral pial vessels [17]. Inhibition of angiogenesis has become an increasingly important approach to treating cancer [99]. VEGF plays a central role in tumor angiogenesis, and there is increasing evidence that inhibition of VEGF or VEGF receptors (VEGFRs) can lead to significant antitumor effects [96]. Inhibition of VEGF with the anti-VEGF antibody bevacizumab (Avastin®) has significantly improved survival in several malignancies including colorectal, lung, and breast cancers [100]. Inhibitors of VEGFRs such as sorafenib (Nexavar®) and sunitinib (Sutent®) have also prolonged survival in renal cell carcinoma and gastrointestinal stromal tumors [100]. Both VEGF and VEGFR are expressed in meningiomas, and the level of expression increases with tumor grade [49, 50, 101, 102]. VEGF expression is increased twofold in atypical meningiomas and tenfold in malignant meningiomas compared to benign meningiomas [49, 50]. VEGF also plays an important role in the formation of peritumoral edema which adds to the morbidity of these tumors [101, 102]. Inhibitors of VEGF and VEGFR are promising agents in recurrent meningiomas, with the potential not only to inhibit angiogenesis, but also to decrease peritumoral edema. Studies to date evaluating inhibitors of angiogenesis in meningiomas are, however, limited. Two small trials reported in abstract utilized small molecule inhibitors for recurrent meningioma [103, 104]. In one, sunitinib, a multifunctional tyrosine kinase inhibitor with antivascular endothelial growth factor receptor activity, reported a 30% (3/10 patients) stable disease best response in an ongoing trial [103]. In a second trial of 15 patients, utilizing PTK787 (vatalanib), another multifunctional tyrosine kinase inhibitor with antivascular endothelial growth factor receptor activity reported 25% stable disease as best response [104]. This trial is as yet incomplete and continues to accrue patients.

Conclusions

In summary, meningiomas are benign extra-axial CNS tumors, which when symptomatic are typically treated with definitive surgical resection (Fig. 15.1). However, small asymptomatic meningiomas may be observed and followed by sequential
MR/CT imaging (Fig. 15.1). Radiation is suggested for residual and recurrent disease following surgery and for symptomatic meningiomas in surgically hazardous locations (for example, the cavernous sinus) (Figs. 15.1 and 15.2). In elderly patients or high-risk surgical patients small meningiomas are increasingly being treated primarily with stereotactic radiotherapy. Several trials of chemotherapeutic and hormonal agents for progressive or recurrent disease have been reported and are ongoing [105]. The abovementioned studies should be interpreted with caution, as neither large cohorts have been studied nor has the therapy have been shown to cause regression of disease, and stability (defined clinically and radiographically) must be scrutinized carefully, given the inherent slow rate of growth of these tumors. As well, these studies have not consistently treated patients with recurrent meningiomas having failed both surgery and radiotherapy. Another underappreciated aspect of recurrent meningioma is the potential for CSF dissemination and pulmonary metastases, issues that need be considered when planning treatment [27, 111]. Clearly there is a need to develop new biologic and chemotherapeutic options for recurrent meningiomas when surgical and radiation treatment options are exhausted. Future treatments will be based upon an improved understanding of the molecular biology of meningiomas, better in vitro models and novel therapeutics including chemotherapeutic agents based on specific mechanisms of action, monoclonal antibodies targeted to meningioma cell surface receptors, and targeted therapies that either antagonize surface receptors or ligands involved in cell growth or small molecules that interfere with cell signaling.
References


Chapter 16
Pituitary Adenomas

Gabriel Zada, Whitney Woodmansee, Ursula Kaiser, and Edward R. Laws

**Keywords** Pituitary adenoma · Transsphenoidal craniotomy · Prolactinoma · Cushing’s disease · Acromegaly · Cabergoline

Neoplasms of the pituitary gland and sellar region constitute a unique crossroads in medicine. The clinical manifestations of pituitary tumors are defined by their relationship with the intricate anatomy and functional physiology of the pituitary gland and its surrounding structures, including the infundibulum, hypothalamus, cavernous sinuses, optic complex, and Circle of Willis. Pituitary tumors are relatively commonly occurring lesions, and optimization of care for patients with these lesions mandates an interdisciplinary approach with a thorough understanding of the anatomic, physiologic, endocrinologic, pathologic, and surgical aspects of the disease. The wide variability in the clinical presentation and pathological subtypes of pituitary tumors requires familiarity with the various nuances of the current medical and surgical management, so that the appropriate management can be tailored for patients with each subtype and size (stage) of lesion and its associated clinical conditions. The differential diagnosis of sellar lesions is broad, and practitioners should be mindful of the wide variety of neoplastic and cystic lesions that may arise in this region (Table 16.1). The current review will focus on the clinical diagnosis and management of pituitary adenomas, which are the most commonly encountered lesions in the sellar and parasellar region.

**Epidemiology**

Tumors of the pituitary gland are among the most commonly occurring neoplasms of the central nervous system, comprising approximately 15% of newly diagnosed
Table 16.1  Differential diagnosis of sellar lesions

<table>
<thead>
<tr>
<th>Primary diagnosis</th>
<th>Cystic lesions</th>
<th>Rathke cleft cyst</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary hyperplasia</td>
<td>Arachnoid cyst</td>
<td>Epidermoid/dermoid tumor</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>Epidermoid/dermoid tumor</td>
<td>Colloid cyst</td>
</tr>
<tr>
<td>Null cell</td>
<td>Lymphocytic hypophysitis</td>
<td>Neurosarcoidosis</td>
</tr>
<tr>
<td>Gonadotropin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH-secreting</td>
<td></td>
<td></td>
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<tr>
<td>Prolactinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH-secreting</td>
<td>Lymphocytic hypophysitis</td>
<td>Neurosarcoidosis</td>
</tr>
<tr>
<td>TSH-secreting</td>
<td></td>
<td></td>
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<tr>
<td>Inflammatory lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atypical pituitary adenoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary Carcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other neoplasms</td>
<td>Meningioma</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Meningioma</td>
<td></td>
<td>Invasive fungal disease</td>
</tr>
<tr>
<td>Cranioopharyngioma</td>
<td></td>
<td>Pituitary abscess</td>
</tr>
<tr>
<td>Gangliocytoma</td>
<td></td>
<td>Neurocysticercosis</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td></td>
<td></td>
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<tr>
<td>Pituicytoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metastatic tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chordoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrasellar aneurysm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathogenesis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary brain lesions [1]. However, autopsy studies of the sellar region and pituitary gland have reported a prevalence of 11–25% of incidental pituitary tumors in the general population, with the majority being microadenomas measuring less than 10 mm in diameter and causing no clinical symptoms [2–4]. A recent meta-analysis of autopsy and magnetic resonance imaging (MRI) studies reported an overall prevalence of 16.7% in the general population [5]. The reported incidence of pituitary tumors is approximately 2 per 100,000 people per year [6–8].

Pituitary adenomas occur infrequently in children, with an increasing incidence observed throughout adolescence and adulthood [9]. Pituitary adenomas are detected more frequently in the seventh and eighth decades of life [10]. Overall, there appears to be a slight preponderance of pituitary adenomas in women, especially for tumor subtypes such as prolactinomas and adrenocorticotropic hormone (ACTH)-secreting adenomas [11].

**Pathogenesis**

Tumors of the pituitary gland have several properties that make them a distinct model for neoplastic development. Pituitary adenomas do not follow the typical paradigm observed in the tumorigenesis and proliferation of many other neoplasms, in which a progression from initiation/transformation to hyperplasia, to benign and later aggressive adenoma, and ultimately carcinoma occurs [12]. Pituitary adenomas rarely metastasize. In this regard, they are generally considered to progress
along a unique pathway guided by distinct genetic and molecular dynamics. It has been demonstrated by several studies that pituitary adenomas arise from genetic mutations in a single cell prior to proliferation and are therefore thought to have a monoclonal cellular origin [13–16].

Several genes have been implicated in the transformation and progression of pituitary adenomas. Although these tumors arise sporadically in the majority of cases, various hereditary conditions have provided some insight into the genetic transformations underlying their development. It is estimated that 5–15% of pituitary adenomas occur as a result of a familial disorder, most commonly associated with multiple endocrine neoplasia type 1 syndrome (MEN-1), Carney Complex, or McCune–Albright Syndrome [17]. In MEN-1, pituitary tumors are often identified along with tumors of the parathyroid gland and/or pancreas, due to mutations in the \(MEN-1\) gene. Such lesions comprise approximately 2.7% of surgically resected adenomas and have a greater tendency to be functional tumors [18]. In Carney Complex, mutations have been identified in the gene encoding the regulatory subunit of protein kinase A. In the absence of these genetic disorders, several additional familial settings of pituitary adenomas have been identified and are collectively known as familial isolated pituitary adenomas (FIPAs) [19]. At the time of diagnosis, patients with FIPAs have a tendency to be younger and have larger tumors. From a molecular standpoint, a significantly higher proportion of FIPAs have mutations in the aryl hydrocarbon receptor-interacting protein (\(AIP\)) gene [19, 20].

In contrast to familial pituitary adenomas, no single oncogene or tumor suppression marker has been identified as a sole contributor to the formation of sporadic pituitary adenomas [21, 22]. It is generally accepted that tumorigenesis and proliferation of pituitary adenomas require activation of a single oncogene followed by a complex interplay of various intrinsic transcription and growth factors that subsequently promote tumor proliferation [21, 23]. Additionally, tumor proliferation and progression have been linked to defects in cell cycle regulators, including G-proteins, pituitary tumor-transforming gene (\(PTTG\)), and CDK inhibitors [24, 25]. Because the genetic contributions to the development of pituitary tumors are likely to be multifactorial, it has been suggested that there is also a significant epigenetic contribution to their progression. For example, variations in gene silencing due to aberrations in methylation may contribute to the formation or progression of these tumors [12].

**Classification**

Pituitary adenomas may be classified according to several characteristics, including tumor size, degree of invasion of surrounding structures, functional hormonal activity, and immunohistochemical properties. Microadenomas are defined as lesions with a diameter of less than 10 mm, whereas macroadenomas are those with a diameter of 10 mm or greater. The degree of local tumor invasion is an important factor in predicting the likelihood of total resection and remission associated with surgical resection [26]. The Hardy classification (as modified by Wilson) characterizes four
stages of pituitary adenomas: Stage I refers to microadenomas with normal sellar volume; Stage II includes macroadenomas with increased sellar volume; Stage III includes invasive adenomas with erosion of the sellar floor; Stage IV includes locally invasive tumors with more than one direction of dural penetration [27, 28]. More recently, a radiologic classification scale for pituitary adenomas was developed based on MRI findings, including the degree of cavernous sinus invasion and encasement of the internal carotid artery [29]. Furthermore, evidence of microscopic dural invasion has been reported to occur in 50–85% of pituitary adenomas according to some series and is found more frequently in macroadenomas and the silent ACTH cell, GH cell, and prolactinoma subtypes [30, 31].

From a pathological standpoint, immunohistochemical staining remains the gold standard in the diagnosis and subtyping of pituitary adenomas. Immunohistochemical assays are routinely utilized in order to identify a potential tumor origin from each cell type of the adenohypophysis, including lactotroph, somatotroph, corticotroph, gonadotroph, and thyrotroph cells. From their stem cell origins in Rathke’s pouch, anterior pituitary cells can differentiate along three initial pathways based on the influence of various transcription factors [32, 33]. Somatotroph stem cells differentiate under the influence of Pit-1 and may later differentiate into thyrotroph cells, lactotroph cells, or somatotroph cells. The transcription factors Tpit and Neuro D1/β2 promote differentiation of primary pituitary stem cells into corticotroph cells. Finally, gonadotroph cells develop under the influence of the SF-1 and GATA-2 transcription factors. Because of these distinct pathways in differentiation, pituitary adenomas have a tendency to maintain particular properties of immunoreactivity and functional hormonal secretion (Table 16.2). The cellular origin and functional properties of adenomas therefore tend to remain confined to cell types within one of these lineages. Because lactotrophs and somatotrophs differentiate along a similar cellular pathway under the expression of Pit-1, adenoma subtypes such as mammosomatotrophs and “lactotrophs with GH reactivity” are commonly encountered. In contrast, it is not common to see crossreactivity for cell types from different developmental lineages, such as gonadotroph and corticotrophs [32].

Approximately two-thirds of pituitary adenomas are hormonally functional and may produce any of the hormones normally secreted by the anterior pituitary gland, including prolactin (from lactotrophs), growth hormone (somatotrophs), adrenocorticotropic hormone (corticotrophs), thyroid-stimulating hormone (thyrotrophs), and the gonadotropins, luteinizing hormone, and follicle-stimulating hormone (gonadotrophs). Prolactinomas are the most commonly occurring functional adenomas, followed by GH-secreting and ACTH-secreting adenomas and finally TSH-secreting and functional gonadotropin-secreting adenomas [7, 34].

Nonfunctional, or endocrine-inactive, adenomas are those not secreting any functional hormones and comprise approximately 25–33% of all surgically resected pituitary tumors [1, 35, 36]. In many cases of nonfunctional adenomas, immunostaining demonstrates positivity for a particular cell subtype, yet the tumor lacks the ability to secrete a biologically functional protein. For example, nonfunctional pituitary adenomas demonstrate immunoreactivity for gonadotropin subunits in
### Table 16.2 Histopathological classes of pituitary adenomas based on lineage, transcription factors, immunohistochemical analysis, functional production, and clinical presentation

<table>
<thead>
<tr>
<th>Adenoma class</th>
<th>Subtypes</th>
<th>Transcription factor(s)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Hormonal secretion</th>
<th>Clinical/radiologic characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null cell adenomas</td>
<td>n/a</td>
<td>None</td>
<td>None</td>
<td>Often macroadenomas</td>
</tr>
<tr>
<td>Gonadotroph adenoma</td>
<td>n/a</td>
<td>SF-1, GATA-2</td>
<td>None α-Subunit, LH, FSH</td>
<td>Rare lesions may have ovarian overstimulation (women) or testicular excess (men)</td>
</tr>
<tr>
<td>ACTH-secreting adenoma</td>
<td>Densely or sparsely granulated ACTH adenoma</td>
<td>Tpit</td>
<td>ACTH</td>
<td>Cushing’s disease</td>
</tr>
<tr>
<td></td>
<td>Crookes’ cell adenoma</td>
<td></td>
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<tr>
<td></td>
<td>Silent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GH-secreting adenoma</td>
<td>Densely or sparsely granulated GH adenoma</td>
<td>Pit-1</td>
<td>GH</td>
<td>Acromegaly</td>
</tr>
<tr>
<td></td>
<td>GH with PRL reactivity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>GH-plurihormonal adenoma (rare)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>Densely or sparsely granulated prolactinoma</td>
<td>Pit-1</td>
<td>Prolactin</td>
<td>Oligomenorrhhea/galactorrhea in women. Sexual dysfunction and decreased libido in men</td>
</tr>
<tr>
<td>TSH-secreting adenoma</td>
<td>n/a</td>
<td>Pit-1, TEF, GATA-2</td>
<td>TSH, α-subunit</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>Plurihormonal</td>
<td>n/a</td>
<td>Multiple</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Refers to transcription factor(s) associated with development of a particular cell lineage
Adapted from Al-Brahim et al. [33]
approximately 40–50% of cases, although it is exceedingly uncommon for them to secrete functional FSH and LH that cause clinically apparent changes [37–39]. Lesions with immunoreactivity for one cell type yet with no functional hormonal excess are known as “silent” adenomas, with a corresponding tumor classification for each of the classes of functional tumors. Silent ACTH tumors are nonfunctional tumors demonstrating strong immunoreactivity for corticotroph cells, yet rarely cause hormonal excess of ACTH or cortisol. These lesions deserve special attention because they are typically aggressive macroadenomas with a high likelihood of local invasion and recurrence [40]. True “plurihormonal” tumors with functional production of multiple hormones are the exception, comprising 10–15% of all functional pituitary adenomas [41]. These tumors occur more frequently in younger patients and are more likely to have a GH-secreting component [41]. On the contrary, completely negative immunoreactivity occurs in approximately 35% of nonfunctional adenomas; these tumors are classified as “null cell” adenomas [7, 42].

Recently, the World Health Organization (WHO) created a subclass of pituitary adenomas based on structural and immunohistochemical features in order to identify atypical tumors, thought to be more aggressive neoplasms at higher risk for local invasion, recurrence, or malignant transformation [43]. This designation may serve as an intermediary between typical adenomas and pituitary carcinomas, which are malignant tumors defined by the presence of metastases either within or out of the central nervous system, making up less than 0.2% of all surgically resected pituitary tumors [7, 44]. Tumor characteristics consistent with the WHO atypical classification include increased tumor proliferation and mitotic activity, a MIB-1-labeling index greater than 3%, and extensive p53 immunoreactivity. MIB-1 is a monoclonal antibody that detects Ki-67, a protein that is expressed in proliferating cells. The MIB-1-labeling index (proportion of cells expressing MIB-1) is often used as a measure of cellular proliferation. In pituitary tumors, the MIB-1-labeling index has independently been reported to correlate with the rate of tumor growth, degree of local invasion, and risk of recurrence [6, 7, 45, 46].

**Clinical Presentation**

Pituitary adenomas can present clinically with mass effect on surrounding structures or as one of several distinct clinical syndromes based on the particular hormone(s) secreted in excess. Not infrequently, both scenarios are encountered concurrently. Typical symptoms and signs associated with local mass effect from pituitary adenomas include headaches, visual deficits, and hypopituitarism. In many cases, visual loss occurs secondary to mass effect on the optic chiasm from below, resulting initially in a superior bitemporal quadrantanopsia that often progresses to a classic bitemporal hemianopsia [47]. In a minority of cases, larger or more invasive pituitary adenomas may present with more pronounced neurological deficits such as cranial nerve deficits, motor deficits, seizures, or hydrocephalus.
Nonfunctional adenomas (NFAs), by nature of being hormonally inactive, are more likely to present secondary to features of mass effect on surrounding structures and are larger at the time of diagnosis. Symptoms including headache, visual deficits, decreased libido, and other features of panhypopituitarism are typically associated with nonfunctional adenomas. The most frequent hormonal abnormalities associated with NFAs are hypogonadism and mild hyperprolactinemia, followed by growth hormone deficiency and hypothyroidism [48]. NFAs frequently cause elevated serum prolactin levels due to a phenomenon known as the “stalk effect.” In the normal state, the hypothalamus inhibits the tonic secretion of prolactin from the adenohypophysis via dopamine release in the communicating portal system, which is a unique phenomenon among all the hypothalamic–pituitary hormonal axes. Any lesion causing compression and subsequent dysfunction of this communication may result in hypersecretion of prolactin, typically in the range of 30–100 ng/mL.

In a minority of patients, an event corresponding to intratumoral hemorrhage, known as pituitary apoplexy, may result in an acute clinical scenario consisting of headaches, visual deficits, and/or endocrinopathy. Pituitary apoplexy is more likely to occur in patients with nonfunctional adenomas, those receiving anticoagulant therapy, and those undergoing surgical procedures [49, 50]. The majority of patients presenting with this condition have no known history of a pituitary tumor, and many patients are initially misdiagnosed with other entities, such as subarachnoid hemorrhage [51, 52]. Although supporting evidence for intratumoral hemorrhage is often provided by MR imaging, the diagnosis of pituitary apoplexy remains a clinical one, usually requiring urgent neurosurgical attention and hormonal replacement.

Functional Pituitary Tumors

Taken collectively, functional pituitary tumors constitute the majority of pituitary adenomas and are further subdivided according to the hormone(s) produced in excess, the resulting clinical syndrome, and immunohistochemical staining properties of the tumor.

Although prolactinomas are the most commonly occurring functional adenoma subtype, they typically comprise a smaller proportion of surgically resected pituitary tumors because medical management results in successful outcomes in the majority of patients. In women, an excess of serum prolactin may result in oligomenorrhea, amenorrhea, and/or galactorrhea. Additionally, chronic excess of serum prolactin can result in hypoestrogenism and predispose to the development of osteoporosis [53]. In men, the most common presenting symptom associated with hyperprolactinemia is decreased libido and sexual dysfunction. In men, prolactinomas are often large tumors at the time of diagnosis and may be associated with anemia and osteopenia.

Adenomas that secrete growth hormone (GH) result in the clinical syndromes of gigantism and acromegaly. Acromegaly is the more commonly observed clinical
scenario, in which post-pubertal adult onset of GH excess causes significant changes in acral growth patterns as well as systemic and metabolic dysfunction. GH excess results in increased downstream production of insulin-like growth factor-I (IGF-I), which mediates the systemic effects of GH. Multiple physical and pathological features are associated with acromegaly, including increased soft tissue edema, frontal bossing, coarse features, prognathism, acral growth, diabetes mellitus, hypertension, carpal tunnel syndrome, sleep apnea, skin tags, hyperhydrosis, cardiac hypertrophy, and cardiomyopathy among others. Uncontrolled acromegaly is a life-threatening condition that has been associated with decreased longevity, which frequently occurs secondary to cardiac and respiratory complications [54]. The weighted mean standardized mortality ratio of patients with acromegaly, according to one meta-analysis, was 1.72 [55]. It has also been reported that acromegalic patients may have an increased risk of colon cancer. Therefore, routine colonoscopy screening is recommended for all acromegalic patients [56].

Pituitary adenomas that secrete ACTH result in Cushing’s disease or Nelson’s syndrome. Cushing’s disease needs to be differentiated from Cushing’s syndrome, which pertains simply to excess serum cortisol, requiring initial exclusion of a source other than an ACTH-secreting pituitary adenoma. Cushing’s disease is a life-threatening condition if left unchecked and is associated with characteristic systemic manifestations including hypertension, diabetes mellitus, obesity, hypokalemia, osteoporosis, as well as progressive renal and cardiac disease. Physical characteristics of chronic cortisol excess may include hirsutism or hair loss, moon facies, lipodystrophy, abdominal striae, and thinning of the skin, among numerous others. Furthermore, many psychological disturbances, including anxiety, depression, insomnia, psychosis, and euphoria, may occur in patients with Cushing’s disease. Nelson’s syndrome is also caused by supraphysiologic levels of ACTH, typically in the setting of an ACTH-secreting adenoma following bilateral adrenalectomy, wherein negative feedback from adrenal corticosteroids is lost. Patients with Nelson’s syndrome frequently present with cutaneous hyperpigmentation. Because of improvements in the diagnosis and management of ACTH-secreting tumors and more stringent indications for performing bilateral adrenalectomies, Nelson’s syndrome has become a relatively uncommon entity [57, 58].

TSH-secreting adenomas are uncommonly encountered lesions, comprising approximately 1–2% of all pituitary adenomas [7, 59]. These tumors can result in the classic symptoms and signs associated with hyperthyroidism, including weight loss, tachycardia, palpitations, hypertension, intolerance to heat, tremor, loss of libido, nausea/vomiting, and diarrhea. In the past, TSH-secreting adenomas have been frequently misdiagnosed as primary hyperthyroidism, with a significant proportion of patients undergoing thyroid ablation procedures prior to the diagnosis of a pituitary adenoma [59]. The diagnosis of a TSH-secreting adenoma is supported by elevated thyroid hormone levels and inappropriately elevated or normal TSH levels.

Gonadotroph-secreting adenomas with production of functional levels of FSH and LH are rarely encountered [60]. These lesions can result in an ovarian hyperstimulation syndrome in women or testicular hypertrophy in men.
Diagnosis

Endocrine Testing

In the clinical setting of a suspected endocrinopathy, a variety of routine and dynamic screening and confirmatory tests can be obtained to establish a diagnosis. The advent and evolution of specific radioimmunoassays for various hormones has enabled practitioners to quantifiably diagnose and monitor the progress of various neuroendocrine disorders caused by the wide spectrum of pituitary pathology [61]. Typically, a thorough endocrine evaluation is performed if any abnormal sellar or pituitary pathology is present or suspected, especially in the face of clinical symptoms. A standard screening endocrine panel might include serum prolactin, fasting morning cortisol, ACTH, GH, IGF-I, TSH, free T4, and possibly LH, FSH, and testosterone levels. If diabetes insipidus is suspected, a serum sodium and osmolality level as well as urinalysis may be obtained.

An elevated serum prolactin level of >200 ng/mL is typically indicative of a prolactin-secreting adenoma [62]. Moderately elevated prolactin levels less than 200 ng/mL require correlation to the size of the tumor, as they may represent a stalk compression effect rather than a prolactinoma. Microprolactinomas may also have prolactin levels in the 30–200 ng/mL range [34]. Furthermore, it should be noted that various physiological states, such as pregnancy and breast feeding, as well as a wide variety of medications, such as antiemetics or antipsychotics, may elevate the serum prolactin level. Clinicians must beware of a phenomenon known as the hook effect, in which an excessively high serum prolactin level results in a laboratory value that is significantly lower than the actual value, secondary to the presence of excessive antigen [63]. This phenomenon can be avoided if appropriate serial dilution testing of serum samples is carried out for all macroadenomas that are suspicious for prolactinomas.

If clinical suspicion of Cushing’s syndrome exists, screening for hypercortisolism should be performed. Recommended initial screening tests with high diagnostic accuracy include nighttime salivary cortisol, a 24-h urinary-free cortisol, 1 mg overnight dexamethasone suppression test (DST), or a longer low-dose DST (0.5 mg every 6 h for 48 h) [64]. To confirm a diagnosis of Cushing’s syndrome, a second test for hypercortisolism should be performed. Once hypercortisolism is confirmed, a serum ACTH level can subsequently be drawn to differentiate between ACTH-dependent and ACTH-independent hypercortisolism. Following the laboratory diagnosis of ACTH-dependent Cushing’s syndrome, an MRI of the sella should be performed. If an MRI is negative, yet a strong suspicion for Cushing’s disease exists, a high-dose dexamethasone suppression test and/or inferior petrosal sinus sampling (IPSS) may then be performed. IPSS is an angiographic procedure in which serial venous sampling of ACTH is performed from the inferior petrosal sinuses during administration of corticotropin-releasing hormone (CRH) and may help differentiate Cushing’s disease from an ectopic source of ACTH secretion. IPSS offers a sensitivity and specificity of 92–100% for the diagnosis of Cushing’s disease [65–67] and has been reported to have an accuracy of 60–84% for predicting
the laterality of the microadenoma, if one side demonstrates an ACTH level 1.4 times higher than the other side [68].

If clinical suspicion of acromegaly is present, an initial screening test consisting of an IGF-I level may be obtained. Because GH is secreted in a pulsatile fashion with random daily levels reaching a peak of 5–30 μg/L, a relatively high level is not sufficient to confirm the diagnosis of acromegaly. A serum IGF-I level provides a better correlation with the disease state in acromegaly, and normalization of IGF-I correlates with restoration of normal life expectancy [69]. IGF-I levels are age-specific and sex-specific, requiring appropriate correlation with the particular laboratory’s normal ranges. An oral glucose tolerance test (OGTT) is a dynamic study that can be administered to confirm the diagnosis of acromegaly, when necessary. In an OGTT, an oral glucose load of 75 g is given and serum GH levels are subsequently monitored for up to 120 min afterward. A nadir GH level of >1 μg/L during an OGTT is consistent with a diagnosis of acromegaly. However, this value depends on the specificity of the particular immunoassay utilized [69, 70].

**Imaging**

Standard imaging for the diagnosis and assessment of pituitary tumors includes pre-gadolinium and post-gadolinium contrast MRI of the sellar region. The coronal, sagittal, and axial planes are all of importance in assessing the location and extent of invasion of pituitary lesions. In a typical non-contrast MRI, the pituitary gland is isointense to brain parenchyma and tumors are typically isointense or hypointense to the gland. The posterior pituitary gland may demonstrate higher intensity than the anterior gland, a finding known as the “posterior pituitary bright spot,” which is usually not identifiable in the setting of a pituitary macroadenoma [71]. In post-gadolinium sequences, the gland typically enhances more avidly than the tumor. Typical characteristics of pituitary adenomas that may be assessed on MR imaging include tumor diameter (microadenoma vs. macroadenoma), location of the normal or compressed pituitary gland, deviation of the infundibulum (frequently away from the side of the adenoma), and degree of invasion of the tumor into surrounding structures (Fig. 16.1). Particular attention should be paid to extension into the suprasellar region and possible compression of the optic apparatus, infrasellar invasion into the sphenoid sinus, lateral invasion into the cavernous sinuses and the tumor relationship to the internal carotid arteries, or bony invasion into the clivus or dorsum sellae. Additional noteworthy features that may be evident within tumors are cyst formation, hemorrhage, or calcification (Fig. 16.2). In advanced cases, large or giant pituitary adenomas may extend superiorly into the third or lateral ventricles or laterally into the middle fossa (Fig. 16.3). Important radiological considerations for neurosurgeons on pre-operative imaging include the location and separation of the carotid arteries, location of the optic complex relative to the tumor, and the anatomy of the sellar floor and sphenoid sinus.
Fig. 16.1 Sagittal (a) and coronal (b) gadolinium-enhanced MR imaging demonstrating a large, invasive pituitary macroadenoma. There is clear evidence of suprasellar and left cavernous sinus invasion. The normal pituitary gland (arrow) is deviated to the right and compressed. The tumor extends into the frontal lobe.

In some cases, especially in patients with Cushing’s disease, a microadenoma may exist yet is not evident on standard sellar MR imaging (Fig. 16.4). In such situations, high-resolution MR imaging or dynamic MR imaging may aid in revealing the location of the tumor within the gland [72]. As mentioned, inferior petrosal sinus sampling may be required to establish a diagnosis of Cushing’s disease and as an attempt to ascertain the laterality of the microadenoma within the gland as a guide for surgical management.

**Medical Therapy**

**Pituitary Hormone Replacement**

Because of advances in recombinant therapy over the last several decades, the majority of pituitary hormones and/or the hormones secreted by their target glands can be synthesized and administered to patients with primary or post-operative dysfunction of a single hypothalamic–pituitary axis or panhypopituitarism. Patients with macroadenomas or pituitary apoplexy will often have panhypopituitarism upon presentation, requiring primary correction of several hormonal axes before surgical treatment is initiated. Replacement of the ACTH–cortisol axis is typically achieved with hydrocortisone or prednisone; once or twice daily dosing at physiological levels is generally sufficient. Oral *levo*-thyroxine is typically used to replace thyroid hormone deficiency. The GH axis can be replaced in the form of a daily injection of recombinant human growth hormone. Multiple testosterone replacement preparations are available including intramuscular injections, buccal mucosal patches, and topical patches or gels. Estrogen replacement therapy is also available in multiple
Fig. 16.2 Noncontrast (a and b) and gadolinium-enhanced (c and d) sagittal (a and c) and coronal (b and d) MR imaging demonstrating a hemorrhagic pituitary adenoma in the context of pituitary apoplexy. There is evidence of intratumoral hemorrhage and sphenoid sinus mucosal thickening (arrows).

formats. Finally, patients with diabetes insipidus from stalk or posterior gland dysfunction may require oral or intranasal synthetic vasopressin (DDAVP), although this entity occurs much more commonly in a transient setting following surgical treatment for pituitary lesions.

If the diagnosis of a prolactinoma is made, medical therapy is frequently initiated in the form of an oral dopamine agonist. The standard agents used are bromocriptine and cabergoline. Because it is more potent, cabergoline offers the benefit of less frequent dosing rather than the daily dosing required with bromocriptine. Dopamine agonist therapy is successful in the reduction or normalization of prolactin levels in 85–90% of patients [34, 73, 74]. A subset of patients, comprising
approximately 6–10% of those with prolactinomas, demonstrate evidence of resistance to dopamine agonists [75]. Furthermore, some patients are unable to tolerate dopamine agonists due to various psychological or systemic side effects associated with these agents, including dizziness, nausea, and other gastrointestinal disturbances. Cystic prolactinomas may not respond to medical therapy by decreasing in size. Invasive prolactinomas, on the other hand, may shrink so significantly that a cerebrospinal fluid leak can occur. The effectiveness of dopamine agonist therapy has been tested in nonfunctioning adenomas and GH-secreting adenomas as well, with only marginal responses [76].

Medical treatment for acromegaly typically consists of somatostatin receptor ligands, the most widely used being octreotide. This class of medications has been reported to normalize GH and IGF-I levels in 34–70% of patients over a 10-year
period and may result in significant tumor volume reduction in 50–75% of patients [70, 77]. However, octreotide may cause side effects such as cramping and diarrhea. In patients with GH-secreting adenomas refractory to somatostatin analogs, especially those with mammosomatotroph subtypes, dopamine agonists may provide normalization of the IGF-I level in 35–50% of patients receiving combination therapy, consisting of cabergoline and a somatostatin analog [70]. A newer agent in the management of acromegaly is the GH-receptor antagonist pegvisomant, which acts by inhibiting the production of IGF-I. This agent offers a new and efficacious tool in the treatment of refractory acromegaly, with a reported success rate of 80–97% [70, 78]. Liver dysfunction may occur in approximately 25% of patients receiving pegvisomant and this requires serial monitoring [77]. Furthermore, it has been reported that patients may develop increases in the size of a GH-secreting adenoma following administration of pegvisomant, due to compensatory somatotroph hypertrophy from reduction of systemic IGF-I in the feedback mechanism [79]. More recently, combination therapy with somatostatin analogs and pegvisomant has proven to be more effective in many cases [80]

Effective medical therapy for Cushing’s disease is limited, with the most effective intervention for this condition remaining primarily surgical. Inhibitors of adrenal steroid synthesis, such as the antifungal agent ketoconazole, have been utilized with reduction of serum cortisol levels in approximately 70% of patients [81, 82]. However, significant side effects including gastrointestinal distress, gynecomastia, decreased libido, and impotence may occur. Hepatotoxicity occurs in up to 12% of patients receiving these medications, mandating frequent laboratory assessments of liver function [81]. Second-line adrenal enzyme inhibitor agents available for refractory Cushing’s disease include metyrapone and mitotane. The dopamine agonist bromocriptine has also been given in an attempt to treat ACTH-secreting adenomas, with only limited success [82]. Finally, cortisol receptor antagonists such as mifepristone (RU-486) are currently being evaluated in the treatment of Cushing’s disease, although the long-term efficacy of this class of medication is undetermined. Bilateral adrenalectomy remains a viable option for patients with refractory Cushing’s disease. One study reported improved quality of life in 89% of patients following bilateral adrenalectomy for Cushing’s Disease, with undetectable cortisol levels in almost 80% of patients [83]. In this study, the short-term incidence of symptomatic Nelson’s syndrome was 8.3% in patients following bilateral adrenalectomy.

**Surgical Treatment**

Many patients diagnosed with pituitary adenomas do not require surgical treatment. Some pituitary tumors, especially prolactinomas, can be managed effectively with medical treatment. Furthermore, in many patients with incidentally discovered lesions, and some with clinically nonfunctional microadenomas exerting little or no mass effect, observation with serial imaging, endocrine, and visual field testing can be performed to monitor for interval tumor growth.
Indications for surgical resection of a pituitary adenoma include significant mass effect causing symptoms such as headache or visual loss, especially those not treatable with medical therapy. A clinical diagnosis of pituitary tumor apoplexy usually requires urgent neurosurgical evaluation and intervention. In patients with acromegaly or Cushing’s disease, surgery remains the primary treatment option, in that a successful surgical procedure may provide long-term remission and significantly improve patient survival. Prolactinomas may require surgical resection in patients with dopamine agonist resistance or intolerance, in large tumors with significant mass effect or major cystic components, or in women who hope to achieve fertility and desire a curative procedure. In larger or more invasive pituitary tumors that may not be completely resectable, surgical debulking of tumor may be indicated prior to the initiation of medical or radiosurgical treatment. As in any clinical situation, the patient’s overall condition and additional medical and social factors must always be considered in the decision for or against surgical intervention.

Historically, tumors of the pituitary region have been treated via a variety of surgical approaches, although the transsphenoidal approach has been the predominant approach for the past four decades. The first transsphenoidal operation for a pituitary tumor was performed by Schloffer in 1907 [84], although the procedure did not evolve as the primary treatment for pituitary tumors until the 1960s [85]. Since that time, the transsphenoidal approach has demonstrated excellent rates of safety and efficacy in the management of pituitary tumors [26]. The approach can be performed via a sublabial incision, an endonasal method, or in recent decades, via an endoscopic approach. The efficacy of transsphenoidal surgery in achieving long-term remission of pituitary adenomas depends on several factors, including the tumor subtype, tumor size, degree of local invasion, and histopathological markers for tumor aggressiveness. Larger tumors with invasion into the cavernous sinuses are known to have a lower rate of remission following surgery than microadenomas or intrasellar macroadenomas [6, 7]. Although the transsphenoidal route is a minimally invasive approach that can be performed quite safely in the hands of an experienced surgeon, it carries its own profile of associated risks. The risks associated with the transsphenoidal approach include infection, visual loss, panhypopituitarism, diabetes insipidus, cerebrospinal fluid leak, and a small risk of carotid artery injury.

In a small proportion of patients harboring pituitary adenomas, a transsphenoidal craniotomy is not the preferred method for optimal surgical resection. Some patients may require a standard craniotomy via a pterional, subfrontal, or interhemispheric approach. Factors that may lend preference to a more invasive craniotomy include larger tumor size with significant suprasellar or middle fossa extension, the tumor relationship to the optic nerves and arteries of the Circle of Willis, or firm tumor consistency. In some cases, combined or staged transsphenoidal and supratentorial craniotomies are required to achieve adequate surgical debulking [86].

The definition of successful outcomes following surgical treatment for pituitary adenomas depends on the tumor subtype (functional vs. nonfunctional) and extent of invasion. For nonfunctional adenomas, a “surgical cure” implies a gross total resection, although adjunctive radiosurgery may be utilized post-operatively to achieve
long-term tumor control, especially in the case of locally invasive adenomas. For larger or invasive nonfunctional macroadenomas, reported total resection rates have generally been between 35 and 60%, depending on the size and degree of surrounding tumor invasion [26, 48, 87]. Surgery has demonstrated higher rates of total resection for intrasellar macroadenomas, ranging between 80 and 95% [26].

In the case of functional pituitary tumors, a surgical success is typically defined as achieving biochemical remission based on a hormone-specific assay. In acromegaly, the widely accepted definition of remission is a normalized IGF-I level obtained 2–3 months following surgery and a nadir GH level of <1 μg/mL during an OGTT. A post-operative day 1 serum GH level of ≤2 μg/mL serves as an early predictor of long-term remission in acromegaly, although it does not currently serve as the gold standard test for surgical remission [88]. For GH-secreting tumors confined to the intrasellar space, reported surgical long-term remission rates have ranged between 75 and 95% [77, 89]. For invasive GH-secreting macroadenomas, tumor remission rates have been reported to be 40–60% [26, 89].

In patients with Cushing’s disease, successful surgical remission is predicted by a normal or preferably subnormal post-operative 24-h urinary-free cortisol level. During the first week following surgical resection, fasting morning cortisol levels are typically evaluated on a daily basis until discharge, and replacement therapy is initiated in cases where post-operative hypocortisolemia is apparent [90]. A post-operative day 3 overnight low-dose dexamethasone suppression test with a cortisol level of <3 μg/dL has also been reported to serve as a predictor of remission in over 90% of patients [91]. Rates of remission following transsphenoidal surgery for ACTH-producing tumors have been reported in 70–90% of patients with noninvasive microadenomas and approximately 25–50% in patients with invasive macroadenomas [26, 58, 92, 93].

In patients with prolactinomas, post-operative remission corresponds to normalization of the serum prolactin level. A post-operative day 1 prolactin level of <10 ng/mL in patients is a highly predictive indicator of long-term remission [94]. Reported surgical outcomes for prolactinomas are 50–60% for all lesions and 80–90% for microprolactinomas [26, 94, 95]. However, medical management remains the primary treatment for the majority of prolactinomas.

Radiation Therapy and Radiosurgery

In the past, residual or recurrent pituitary adenomas have been successfully managed with localized external beam radiation. This adjunctive modality is effective in achieving long-term tumor control in greater than 90% of patients, according to multiple series, yet poses a substantial risk for panhypopituitarism [96–100]. Additional risks including visual loss, secondary brain tumors, cerebral infarction, and cognitive deficits have also been reported in major series of radiotherapy for residual pituitary adenomas [96, 101, 102]. Adjunctive radiotherapy has demonstrated some benefit following subtotal resection of pituitary adenomas, yet is not ordinarily recommended following an initial gross total removal [87].
In the past several decades, standard fractionated radiotherapy has fallen out of favor in many medical institutions and has been replaced by stereotactic radiosurgery [103, 104]. As compared to standard external beam therapy, stereotactic radiosurgery (SRS) offers the benefits of improved accuracy in targeting tumors, with minimized risk to surrounding structures, as well as the potential for single-dose unfractionated treatment. SRS can be used to effectively target residual or recurrent pituitary adenomas, with reported rates of long-term tumor control being greater than 90% in most major series [105–111]. Radiosurgery is frequently employed following surgical debulking of a pituitary adenoma, especially in those with invasion of the cavernous sinus that cannot be completely resected surgically. Primary treatment of pituitary adenomas using SRS has been reported, yet the long-term outcomes of this strategy remain to be determined [112, 113]. Varying doses of radiation can be administered, depending on whether the lesion is functional or nonfunctional and whether the treatment is fractionated or given as a single session. In general, prescription doses of 14–16 Gy are used for nonfunctional tumors and doses of 18–22 Gy are used for functional tumors [108, 114]. However, the maximal prescription dose to the tumor depends significantly on tumor proximity and peripheral isodose radiation to the pituitary gland and optic apparatus, which must be carefully assessed in each case. As a guideline, tumors within 3 mm of the optic chiasm or nerves are not amenable to treatment with single fraction radiosurgery [115]. However, fractionated SRS can be an equally safe and effective modality for the treatment of residual or recurrent perioptic pituitary adenomas [116]. Intraoperative transposition of the pituitary gland away from the residual tumor burden has been reported as a method of reducing the risk of hypopituitarism associated with subsequent radiosurgery for pituitary tumors [117].

**Prognosis**

**Quality of Life**

Following multimodality treatment of pituitary adenomas, patients frequently benefit from improvements in vision, headaches, and normalization of excess hormone levels. Although quality of life may improve in many patients following transsphenoidal surgery for functional and nonfunctional pituitary tumors, it has been demonstrated that quality of life remains diminished in many patients as compared to age-matched and sex-matched controls, even despite long-term endocrine remission [118–122]. One factor contributing to this finding is hypopituitarism, which has independently been correlated with diminished quality of life and patient survival [123–126]. Despite undergoing multimodality treatment, patients with Cushing’s Disease may have long-term physical impairment and anxiety, and those with acromegaly may suffer from increased bodily pain and physical impairment [118]. Finally, patients with GH deficiency are known to have a diminished quality of life...
as compared with age-matched and sex-matched controls and may benefit from GH replacement therapy [127, 128].

Long-term neuroimaging and biochemical monitoring following surgery for pituitary adenomas are mandatory. Recurrence rates for both functional and non-functional tumors following multimodality therapy with initial remission range between 9 and 19%, with the usual time to first recurrence reported as 5–9 years [48, 87, 93, 129]. Following surgery, MR imaging of the sellar region is recommended at 3 and 6 months, then at a yearly interval for a minimum of 5 years in order to identify interval tumor growth or recurrence. Patients with any initial endocrinopathy should be followed by an endocrinologist with twice yearly or yearly biomarkers for detection of potential recurrence and to ensure optimization of hormonal replacement. Recurrence of a pituitary adenoma may be treated by surgical, medical, or radiosurgical options, depending on the endocrinological and radiologic features of the recurrent tumor burden.

Conclusions

Patients with pituitary adenomas may present with a wide variety of clinical and endocrinological manifestations. In order to optimally manage the various aspects of pituitary tumors, an interdisciplinary effort is required to address the complex and dynamic medical, surgical, endocrinological, radiosurgical, pathological, and ophthalmic issues encountered in patients with these lesions. For many patients, a diagnosis of a pituitary tumor is a chronic disease that requires long-term monitoring, reassessment, and possibly re-treatment in order to reduce the burden of disease and maximize quality of life and longevity.

References


Chapter 17
Vestibular Schwannomas

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Keywords Acoustic neuroma · Vestibular schwannoma · Stereotactic radiosurgery · Fractionated stereotactic radiotherapy · Neurofibromatosis · Surgery

Abbreviations
CPA Cerebellopontine angle
IAC Internal acoustic canal
FSRT Fractionated stereotactic radiotherapy
GKS Gamma Knife radiosurgery
NF2 Neurofibromatosis type 2
SDT Speech discrimination testing
SRS Stereotactic radiosurgery
VS Vestibular schwannoma

Introduction

Vestibular schwannomas (VSs) are tumors that arise from the vestibular branch of the eighth cranial nerve. They originate along the zone of transition between the central and peripheral myelin located near the medial aperture of the internal acoustic canal (IAC). They grow in an expansile fashion, displacing rather than invading surrounding structures. They are nearly always histologically benign, with a few case reports of malignant dedifferentiation [1]. Despite their mainly benign character, they grow within a confined space and are surrounded by several critical structures including cranial nerves and the brainstem; unchecked growth therefore eventually causes severe morbidity. Active treatments for vestibular schwannoma are primarily
intended to prevent this eventuality, because most VSs present with relatively minimal symptoms and active treatment only rarely reverses deficits that are present at diagnosis.

The apparent incidence of VS is increasing, which has been largely attributed to the increased use and enhanced resolution of magnetic resonance imaging (MRI) scanning [2]. Clinical presentation can vary from smaller incidental lesions to symptomatic lesions of varied size. Coupled with significant improvements in both surgical (refined surgical techniques and cranial nerve monitoring) and non-surgical treatment approaches (stereotactic radiosurgery techniques and dose tolerance determinations), as well as increased acceptance of an initial watch-and-wait strategy for many patients, this creates the challenge of elucidating the optimal management algorithm for a heterogeneous patient population.

VSs comprise about 6–8% of intracranial neoplasms. More than 90% of VSs are sporadic and unilateral [3]. Typical symptomatic presentation occurs in the fifth or sixth decades of life and unilateral sensorineural hearing loss in the most frequent presentation. Bilateral VS is essentially pathognomonic for neurofibromatosis type 2 (NF2) [4], a dominantly inherited tumor suppressor gene syndrome described elsewhere in this book. When associated with NF2, VSs have a significantly earlier symptomatic presentation, often in the second or third decades of life. Risk factors associated with the development of sporadic vestibular schwannomas include exposure to loud noise, NF2, and prior exposure to radiation. There have been several conflicting studies on the role of electromagnetic field radiation in the form of cellular telephone use as either causing VS or leading to its progression.

Although VSs arise from the vestibular portion of the eighth cranial nerve, cochlear symptoms predominate, with two of the most common being hearing loss and tinnitus. Progressive or sudden unilateral hearing loss along with ipsilateral tinnitus represents the most common presenting auditory symptoms of VS. Loss of balance (unsteadiness) and, less often, vertigo are the most common vestibular symptoms. If tumors are large enough to grow out of the IAC into the cerebellopontine angle, trigeminal compression with consequent facial numbness or (less often) trigeminal neuralgia are typically the next symptoms. With growth to much larger sizes, impingement on the brainstem or cerebellum can eventually cause ipsilateral ataxia. In the modern era, tumors large enough to cause facial weakness, swallowing difficulty, or hemiparesis are quite unusual in developed countries.

MRI with and without contrast with thin cuts (no greater than 3 mm slice thickness, no gap) through the internal auditory canal (IAC) is the diagnostic study of choice. The typical appearance of a VS is a gadolinium-enhancing mass located along the course of the eighth cranial nerve with variable intracanalicular and extra-canalicular components (Fig. 17.1). Early growth is usually within the IAC, which is characteristically dilated by the growth; this can help distinguish VS from meningioma, which can have a similar appearance but rarely enlarges the IAC. Other than meningioma, MRI can typically distinguish VS from other cerebellopontine angle (CPA) lesions such as epidermoid cysts, arachnoid cysts, and, rarely, lipomas based on signal characteristics.
Hearing status in both ears is important in decision-making for patients with VS, and pure tone and speech audiometry should also be evaluated to quantitatively assess hearing loss. Air and bone conduction are measured by playing sounds at varying intensities and frequencies. Hearing loss is typically more pronounced at higher frequencies, with both air and bone transmissions affected. Speech discrimination testing (SDT) is more predictive of functional hearing and supplements pure tone testing. The degree of speech discrimination loss is often disproportionately worse than the pure tone hearing loss. This accounts for difficulty using the telephone with the ipsilateral ear as a common presenting sign of VS.

Management of VS centers on achieving local control with minimal critical tissue toxicity, namely, preservation of function in adjacent cranial nerves (especially the auditory, facial, and trigeminal nerves). Factors that typically influence the choice between observation or some form of active treatment (surgery or radiotherapy) include tumor size, patient age, the presence and severity of symptoms, genetic predispositions (such as NF2), the status of contralateral hearing, and patient preference. Currently, three management options exist for VS: observation, surgery, and radiotherapy. However, medical treatments for VS are being developed.

**Observation**

VSs are typically slow-growing lesions, with characteristic annual growth rates of 1–2 mm in diameter when growth can be detected [3]. This “average” growth rate belies a wide variation in individual tumor growth rates; some tumors display continuous growth and others can have growth arrest or even regression. Distinguishing progressive from non-progressive lesions is critical. Aggressively growing tumors...
will require active treatment (surgery or radiotherapy), while indolent tumors can be managed conservatively. This, coupled with the increased incidence of small, asymptomatic VS promotes active surveillance as a standard management alternative – in fact, one that is appropriate at first diagnosis for the majority of patients, at least those with small tumors. The protocol for observation of VS generally consists of annual or semi-annual clinical and MRI follow-up [5], with audiometry in those patients who have useful hearing at presentation. Many clinicians consider observation to be the favored approach for non-progressive VSs that are not causing brainstem compression at presentation, due to the risks inherent in active intervention. Patient compliance with the recommended follow-up is important, because many VSs will grow significantly without causing new symptoms; this leads to elevated surgical or radiotherapy risk when patients return with larger tumors.

Several attempts have been made to characterize the natural history of VS and identify predictive factors for tumor growth. In the largest prospective trial assessing conservative management to date, 552 patients were followed over a variable period [6]. The data indicate that tumor growth is most likely to occur in the first 5 years of follow-up. Moreover, 83% of intrameatal tumors remained intrameatal, and 70% of extrameatal tumors grew less than 2 mm in largest diameter over the course of the follow-up period. These results suggest that the majority of VSs are non-progressive. Other studies have confirmed and extended these findings [5, 7–14]. A systematic review of 26 studies including 1,340 patients showed that the overall frequency of VS growth was 46% and regression occurred in 8% [15]. These data suggest that a large proportion of VSs remain without growth for a significant period of time. Interestingly, annual growth rates of VSs also appear to decrease as a function of time. This suggests that tumors that show initial growth (which informs the current clinical threshold for intervention) are not likely to maintain a similar growth rate over time; some tumors may reach plateau phase of growth and possibly even regress. However, the tendency of tumors that show initial growth to continue growing leads many practitioners to advise a shift from observation to active treatment when growth is first detected [16].

Besides tumor growth, a second event that is frequent during observation of VS is loss of hearing in the ipsilateral ear. Almost half of patients with useful hearing at the start of observation will lose hearing during follow-up, with or without a measurable increase in tumor size [10, 17]. Whether earlier active treatment can prevent such loss is not known.

Successful implementation of the surveillance strategy depends on the ability to identify those patients not suitable for continued observation. Patient and tumor factors that have been proposed as favoring intervention include larger tumor size, rapid rate of growth, younger age, extrameatal extension, and symptomatic progression. Several retrospective single-institution studies and prospective trials have attempted to identify factors predictive of growth [5–7, 11, 12, 14, 17–24]. The rates of intervention varied widely from institution to institution suggesting a lack of standardized approach to VS management in current clinical practice. Several of these trials identified putative predictors of growth including tumor growth in the first year, larger initial tumor size (>2 cm in size), presence of disequilibrium, and
extrameatal versus intrameatal tumors [6, 20, 21, 24]. Cystic tumors also characteristically grow more rapidly. These data suggest that asymptomatic patients with lesions less than 2 cm in size represent the best candidates for active surveillance. Further studies are needed to confirm these findings.

**Surgical Resection**

Surgical resection was the first effective treatment for VS and is still the primary treatment for many VS patients. In the 1970s, essentially all diagnosed VSs were resected. Since then both observation and radiotherapy have become the primary means of management for many VS patients because of the lower risks of early morbidity with these treatments. The advent of safe and effective radiotherapy for VS has also made subtotal resection a consideration when complete resection appears to pose an unacceptable risk of postoperative facial weakness. Surgery is used as primary management for tumors that are too large for safe or effective radiotherapy, tumors that are causing symptomatic brainstem or trigeminal compression, and in other situations primarily due to patient preference.

There are three standard surgical approaches for VS removal: middle fossa [25], translabyrinthine [26], and suboccipital (also called retromastoid) [27]. Hearing preservation is possible only through the middle fossa and suboccipital approaches, because the translabyrinthine approach critically damages inner ear structures. Most groups consider the middle fossa approach suitable only for smaller tumors (intracanalicular or with a small CPA extension), while the other approaches are suitable for tumors of any size. Most VSs are eligible for two approaches or for all three; the likelihood of hearing preservation and the prior experience of the specific surgical team are important factors in the decision. For small tumors, hearing preservation may be slightly more likely with the middle fossa approach (compared with suboccipital). For larger tumors, the suboccipital approach is used when hearing preservation will be attempted; other outcomes (among which facial nerve function is paramount) are similar between the translabyrinthine and suboccipital approaches in experienced hands.

All modern surgery for VS includes intraoperative monitoring of facial nerve function, unless the facial nerve is surgically absent because of prior operations. Monitoring of trigeminal nerve motor function and of hearing (through brainstem auditory-evoked potential recording) is also used when appropriate.

Complete tumor removal while preserving facial nerve function and, when applicable, hearing are the goals of surgery. Patients usually consider good postoperative facial function to be most important, followed by complete tumor removal and hearing preservation in that order. The risk of postoperative facial weakness is strongly dependent on tumor size. Other factors leading to difficulty preserving facial function, such as the degree of adherence between the facial nerve and the tumor surface, the degree of nerve thinning and distortion by the tumor, and the length of the nerve–tumor interface to be dissected, are not apparent until during surgery. Postoperative
Table 17.1  House–Brackmann facial nerve grading scale [28]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal facial function in all muscles</td>
</tr>
</tbody>
</table>
| II    | Mild dysfunction  
Slight weakness only noticeable on close inspection  
Rest: normal symmetry and tone  
Motion: no or minimal synkinesis; no contracture or hemifacial spasm |
| III   | Moderate dysfunction  
Obvious but not disfiguring weakness; no functional impairment  
Rest: normal symmetry and tone  
Motion: noticeable but not severe synkinesis; contracture or spasm may be present |
| IV    | Moderately severe dysfunction  
Obvious weakness; disfiguring asymmetry; functional impairment  
Rest: normal symmetry and tone  
Motion: obvious synkinesis or mass action; hemifacial spasm |
| V     | Severe dysfunction  
Only barely perceptible motion  
Rest: asymmetry with droop of corner of mouth and decreased nasolabial fold  
Motion: synkinesis, contracture, and hemifacial spasm usually absent |
| VI    | Total paralysis  
No motion  
Rest: no tone; asymmetry; no synkinesis, contracture, or hemifacial spasm |

Facial function is usually graded using the House–Brackmann scale [28]; normal facial function is grade 1 on this scale and complete paralysis is grade 6 (Table 17.1).

When the risk of a complete removal appears too high during surgery, a small tumor remnant can be left attached to the facial nerve, brainstem, or both. Such remnants are commonly observed postoperatively rather than proceeding directly to radiotherapy, because of the increased risk of irradiating a surgically compromised facial nerve [29] and the low tendency of such remnants to grow after surgery [30]. Occasionally a planned subtotal resection is done because of patient request or in elderly patients who require tumor debulking because of brainstem compression from a large tumor.

Hearing preservation is unusual after surgery in tumors larger than 2 cm and when preoperative hearing speech discrimination is lower than 60%. Complete tumor removal usually takes precedence over hearing preservation unless there is no useful hearing in the contralateral ear. Hearing loss from VS resection is usually complete hearing loss and such patients do not benefit from standard hearing aids. Hearing status in VS patients is most often graded using a specific scale based on pure tone audiometry and speech discrimination, with grade A hearing being best and grade D hearing being worst [31] (Table 17.2).

Facial nerve outcomes after surgery are usually reported as 1-year postoperative results, because temporary postoperative facial weakness has typically resolved
Table 17.2 American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) Committee on hearing and equilibrium guidelines for reporting of hearing preservation in acoustic neuroma surgery [31]

<table>
<thead>
<tr>
<th>Class</th>
<th>PTA (dB hearing loss)</th>
<th>Word recognition score (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>≤30 dB</td>
<td>≥70</td>
</tr>
<tr>
<td>B</td>
<td>&gt;30 but ≤50 dB</td>
<td>≥50</td>
</tr>
<tr>
<td>C</td>
<td>&gt;50 dB</td>
<td>≥50</td>
</tr>
<tr>
<td>D</td>
<td>Any level</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

by this time. Outcomes are strongly dependent on tumor size. For intracanalicular tumors or those with less than 1.5-cm intracranial extension, House–Brackmann grade 1 or 2 (no or minimal weakness) results at 1 year are typically 95–100% regardless of approach [32–34]. For tumors between 2 and 3 cm, approximately 75% House–Brackmann grade 1 or 2 results are achieved [33, 34]. For tumors larger than 3 cm, about 50–60% House–Brackmann grade 1 or 2 results are reported [33, 35]. When the entire tumor is not removed, facial nerve results tend to be better. In a series of 70 patients with less-than-total resection, with a median tumor size of 3 cm, 93% had House–Brackmann grade 1–2 results [36].

Hearing preservation is less common after surgery than good facial nerve results and depends on both tumor size and preoperative hearing status. About half to three-quarters of patients with preoperative Class A hearing will retain useful hearing postoperatively, with a slight advantage in hearing preservation for the middle fossa approach [32, 37, 38].

Tumor recurrence after a complete surgical removal is an uncommon event [39]. The risk of facial weakness after a second resection is high [40], thus, radiotherapy is often used to manage the recurrence if the tumor is reasonably small.

Radiotherapy

Radiotherapy treatments for VS include stereotactic radiosurgery (SRS) and fractionated radiation therapy. SRS involves the delivery of high-dose radiation therapy in a single treatment, and technique options include Gamma Knife radiosurgery (GKS), LINAC-based SRS, or proton SRS. Fractionated radiation therapy is most commonly delivered by fractionated stereotactic radiotherapy (FSRT), utilizing an external stereotactic coordinate system to improve localization of the small tumor target. The majority of the reported radiotherapy experience is with SRS. In the early experiences, single-institution case series demonstrated excellent local control rates (>90% at 10 years) with SRS [41]. The principal report establishing SRS as an alternative to microsurgery was the University of Pittsburgh case series which consisted of 162 consecutive patients treated with GKS to a mean marginal dose of 16 Gy [41]. The dose delivered to the tumor margin in this series varied; the initial dose of 20 Gy was derived from the first report of SRS in VS in the seminal Swedish study [42], but dose was later decreased due to a higher than expected cranial nerve morbidity. The tumor control rate in this series was an impressive 98%;
however, normal facial and trigeminal function was preserved in only 79 and 73% of patients, respectively. Due to the unacceptable cranial nerve morbidity in this and other series, the marginal prescription dose of SRS was subsequently lowered to 12–13 Gy. Results from the decreased prescription dose maintained a low rate of subsequent tumor growth, along with a concomitant decrease in the risk of facial weakness (1%); hearing preservation improved to 71% [43]. These results were confirmed with longer follow-up, although other groups have reported increased rates of tumor growth after treatment with comparable doses, with 90% progression-free survival 10 years after treatment with a median marginal dose of 13 Gy in one study [44].

Surgery and radiotherapy represent the two primary treatment options for VS. Most studies comparing these modalities are either retrospective case series or opinions [45]. Five retrospective case–control series have shown early posttreatment outcomes including improved cranial nerve function, better cost-effectiveness, and less impact on patients’ activities of daily living for patients having radiosurgery. A prospective cohort study compared surgical resection to SRS [46]. A total of 82 patients with unilateral VS of <3 cm were enrolled; 36 underwent surgical resection and 46 underwent radiosurgery. There was no difference noted in tumor control (100% surgery vs. 96% SRS, $P < 0.50$). Normal facial movement was more frequent in the SRS group at 3 months (100% vs. 61%, $P < 0.001$), 1 year (100% vs. 69%, $P < 0.001$), and at last follow-up (96% vs. 75%, $P < 0.01$) compared to the surgical group. Hearing preservation was greater in the SRS group at 3 months (77% vs. 5%, $P < 0.001$), 1 year (63% vs. 5%, $P < 0.001$), and at last follow-up (63% vs. 5%, $P < 0.001$) compared to the surgical group. These results suggest markedly superior outcomes for VS patient having SRS compared to surgical resection. Another prospective study also demonstrates decreased morbidity with SRS compared to surgery [47]. These studies, however, have a limited mean follow-up period (24–42 months). Tumor control, late radiation toxicity, and secondary malignancy rates may increase over time. Therefore, longer term follow-up that correlates with the expected life expectancy of these patients (20–25 years) is needed. Despite this, the best-quality evidence shows superior early outcomes for VS patients with tumors < 3 cm having stereotactic radiosurgery compared to surgical resection [45]. However, patients whose VSs grow after radiotherapy are a challenge to manage. Complete surgical removal after radiation treatment has high rates of postoperative facial palsy [48], and results of reirradiation are not well established, although small series have been reported.

The risk of treatment-induced cranial neuropathy is directly related to the volume of the lesion, the dose given, and the length of nerve irradiated. Approximate single-fraction tolerance doses are 12 Gy for brainstem and 15 Gy for the facial nerve [49], which are attainable with current dose regimens. Hearing preservation rates are lower than facial nerve preservation, largely attributed to the proximity of the cochlea to the treatment volume. Single-fraction cochlear tolerance is unknown, although recent studies suggest that a dose of less than 4.2 Gy to the central cochlea leads to significantly improved hearing preservation rates [50, 51]. Another approach to minimize toxicity is the use of fractionation, which takes
advantage of the radiobiological differences between VS and surrounding normal tissue structures. In a comparison of SRS (10–12.5 Gy in a single fraction) with hypofractionated treatments (20–25 Gy in four to five fractions), local control rates, hearing preservation, and facial nerve function were not statistically different, but there was a fourfold increase in trigeminal nerve complications with single-fraction treatment compared to fractionated radiation (8% vs. 2%) [52]. Comparison of other fractionated treatment schedules (50 Gy in 25 fractions) to SRS in prospective trials showed similar tumor control rates and a statistically significant difference in retention of useful hearing (81% vs. 33% at 1 year) in favor of fractionated treatment [53]. Similar rates of tumor control and hearing preservation have been reported in other single-institution experiences [54–56]. Therefore, fractionated treatment appears to provide similar tumor control rates with reduced cranial neuropathy compared to SRS. Despite the demonstrated benefits with fractionated therapy, the reduced neuropathy rates appear modest and decrease over time. Therefore, the potential benefit obtained by FSRT must be considered in the context of patient pretreatment functional hearing, tumor size, and the logistics of providing 25–30 treatments, compared to the convenience of a single treatment from both a patient and institutional perspective.

Chemotherapy

Patients with NF2 develop bilateral VS at an early age, putting them at high risk for complete hearing loss during their lifetime. NF2-related VSs have typical growth rates of around 2 mm per year which is similar to sporadic tumors [57]. Unfortunately, long-term growth data over a time span appropriate for NF2 patients (i.e., decades) are not available; unlike sporadic tumors, it does not appear that tumor growth is most likely to occur in the first 5 years of follow-up. Tumor regression (defined as shrinkage of >2 mm) can occur in NF2 patients, but clinically significant shrinkage (>5 mm) is not observed during long-term follow-up [57]. Clinical experience shows that in most patients NF2 is a progressive disorder in which VS growth over decades results in complete hearing loss, often followed by other serious morbidity from tumor growth of VS (or other tumors such as meningiomas) or from the sequelae of tumor treatment.

Patients with NF2 who lose hearing in one ear after resection or after irradiation of a VS represent a unique management challenge. If the contralateral tumor begins to grow or hearing declines in the contralateral ear, treatment with surgery or radiation is likely to result in complete hearing loss. These patients represent a subgroup in which medical treatments for VS are urgently needed. A recent report suggests that treatment with the antivascular endothelial growth factor (VEGF) antibody bevacizumab may improve hearing function and reduce tumor volume in NF2 patients with progressive VSs [58]. In this study, ten patients with NF2 and progressive VSs were treated with bevacizumab for a median of 12 months (range 3–19 months). Before treatment, the median annual volumetric growth rate for ten
VSs was 62%. After treatment, the median best response was a volumetric reduction of 26%. Six of ten patients experienced a radiographic response and four of seven patients experienced hearing improvement. Additional studies are underway to determine the optimal drug regimen, duration, and adverse-effect profile for long-term anti-VEGF therapy for VS associated with NF2, as well as the effects of other molecularly targeted agents on these tumors [59]. If a non-toxic therapy can be identified in the NF2 population, it may eventually be possible to treat patients with sporadic VS tumors that progress during observation using medical therapy instead of surgery or radiotherapy.

**Conclusion**

We propose the following VS management algorithm based on the best currently available data (Fig. 17.2). Tumors larger than 3 cm are candidates for surgical resection, as this allows for the greatest probability of tumor control and is clearly indicated if the tumor abuts the brainstem. Tumors of 2–3 cm in size are candidates for surgery, SRS, or FSRT, with decisions made after weighing the multiple clinical factors, treatment resources, and patient preferences. In tumors of <2 cm in size, patient hearing status and other symptoms must be assessed. If the patient is asymptomatic with intact hearing, a strategy of conservative management could be considered. If the patient has hearing loss, they are likely to continue to experience hearing loss and early radiotherapy intervention should be used to maximize hearing preservation (FSRT or SRS, depending on pretreatment hearing preservation). In the elderly with co-morbid disease, one can consider observation regardless of tumor size.

![Fig. 17.2 Management algorithm for vestibular schwannoma](image)

**References**


Chapter 18
Medulloblastomas

Alba A. Brandes and Enrico Franceschi

Keywords  Adult medulloblastoma · Surgery · Radiotherapy · Chemotherapy

Introduction

Medulloblastoma, a highly cellular malignant embryonal neoplasm classified as a primitive neuroectodermal tumor (PNET) [1], is the most common malignant brain tumor in children, accounting for 15–25% of all childhood primary central nervous system (CNS) neoplasms [2]. By definition, medulloblastoma arises in the posterior fossa, usually from the cerebellar vermis in the roof of the fourth ventricle (Fig. 18.1). Medulloblastomas have a marked tendency to spread by seeding along the cerebrospinal fluid (CSF) pathways; evidence of this metastatic process is found in up to 35% of cases at diagnosis (Fig. 18.2).

Incidence

Medulloblastomas are rare tumors. The European annual incidence (world-standardized) is about 1.1 per million in the male and 0.8 per million in the female adult population [3]. These neoplasms are typically seen in children, about 70% of all cases being diagnosed in patients below 15 years of age. The incidence peak is highest among children between ages 3 and 6, with only 25% of cases diagnosed in patients between 15 and 44 years of age [2]. In Europe, a rise in the incidence of PNETs has been recorded in children and adolescents; the rates increased on
average by 1.3% during the period 1978–1997 [2]. Worldwide, epidemiologic differences can be seen, with a high incidence (more than 1 million year) in Columbia (Cali), Australia (Victoria), Denmark, Canada, Israel, and the Netherlands.

**Survival**

Survival data for patients with medulloblastoma are available in the population-based cancer registries of about 20 European countries in the EUROCASE study
The survival analysis covered 867 adults diagnosed with PNETs of the brain during the period 1995–2002. In the patients, who had a follow-up until 2003, the relative survival (calculated as the ratio of absolute survival of patients with cancer to the expected survival of a group of people of the corresponding sex and age in the general population) analysis was 78% at 1 year, 61% at 3 years, and 52% at 5 years, and no gender-related differences were recorded. The 5-year relative survival decreased with age: from 56% in the younger (15–44 years) age group to 9% in the older group (45 years and over). The 5-year survival rates analyzed in 1,050 European patients diagnosed during 1987–2002 showed no significant change over the same timespan.

**Risk Factors**

The causes of medulloblastoma have not yet been clearly established. Some of the genetic syndromes known to greatly increase the risk of developing PNET include Turcot syndrome (in association with familial polyposis colon cancer) and nevoid basal cell carcinoma syndrome (associated with \textit{PTCH} germline mutations) \cite{5}. These mutations are rare and account for fewer 5% of all cases. Ionizing radiation \cite{6} is also known to increase the risk of brain tumors. Low-dose radiotherapy for tinea capitis and skin disorders in children increases the risk of CNS tumors well into adulthood, as does radiotherapy for childhood cancers and leukemia. Few epidemiological studies have addressed the potential role of viruses in causing brain malignancies. Polyomaviruses, including JC virus (JCV), BK virus (BKV), and simian virus 40 (SV40), have attracted much attention in the past decade, since they have been isolated from various human tumors, including those originating in the central nervous system (CNS). JCV DNA sequences have been isolated from a number of human CNS tumors, including medulloblastoma \cite{7}.

**Pathology and Biology**

The histogenic origin of medulloblastoma is a controversial issue. Histological variants of medulloblastoma are classic, desmoplastic, large cell, with extensive nodularity. However, nearly all (>95%) medulloblastomas are classic or desmoplastic tumors, and neither classic nor desmoplastic medulloblastomas are uniform entities; both show a range of architectural and cytological features. The desmoplastic variant appears to arise from specific cerebellar progenitor cells. These are often correlated with a higher expression of neurotrophin receptor p75NTR, which is rarely observed in classical childhood medulloblastoma, suggesting that the tumors may have different origins \cite{8}. Additionally, other molecular genetic investigations indicate that these tumors do not share a common pathogenesis \cite{9, 10}. In particular, amplification and overexpression of MYC and MYCN occur in 5–10% of medulloblastomas. Some authors have examined the expression of MYC mRNA...
and related it to clinical outcome; increased levels of MYC expression appear to be a significant predictor of worse outcome [11, 12]. Other frequent genetic abnormalities in medulloblastomas are chromosomal alterations, in particular on chromosome 17. Deletions of the short arm of this chromosome occur in up to 40–50% of primary tumors. Several authors have observed that chromosome 17p deletion is correlated with a worse prognosis, even if this correlation has not always attained statistical significance [13–15]. Other frequent non-random chromosomal abnormalities detected in medulloblastomas include gains of chromosomes 1 and 7 and loss of 1p, 3q, 6q, 9q (locus of *PTCH* gene), 11p, 11q, and 16q [16]. Moreover, loss of heterozygosity (LOH) for a specific region in chromosome 9q has been found in medulloblastomas with a desmoplastic phenotype [17]. The hedgehog (Shh) pathway is an essential embryonic signaling cascade that regulates stem cell and progenitor cell differentiation in multiple developmental processes. In the absence of Shh, patched (*PTCH*), the receptor protein, suppresses the signaling activity of another membrane protein, smoothened (SMO). When Shh binds to *PTCH*, it allows SMO to transduce a signal into the cytoplasm. This signal leads to the breakdown of a large protein complex formed by Fused, Sufu, and GLI in the cytoplasm and releases the GLI transcription factors. The released GLI transcription factors translocate into the nucleus resulting in transcriptional activation of specific target genes. This signaling is involved in diverse functions in mammalian development such as patterning in the central nervous system, cell fate determination, proliferation, differentiation, and survival. The role of Shh–GLI signaling as a mediator in proliferation and survival of various cancers including medulloblastoma has been proposed, as well as it has been recognized in granule-cell precursors during cerebellar maturation. Recently, an interesting but transient response to a Shh-targeted small molecule inhibitor (GDC-0449) has been described [18]. The tendency for metastatic spread is somewhat lower in adults than in children (8 and 13%, respectively) [19, 20]. However, late relapses are common, as shown in the series reported by Frost et al. in which the 5-year relapse rate (62%) was clearly higher than the 10-year relapse rate (41%). Likewise, Chan et al. observed a 5-year overall survival of 83%, which decreased to 45% at 8 years [21]. Metastatic spread outside the CNS is rare. Bone is the most common site of metastasis in adults and children, accounting for 80% of metastases found outside the CNS [22]. Lung metastases appear to be more frequent in adults than in children, whereas metastasis to the liver occurs more frequently in children [22]; the interval between diagnosis and treatment of metastases is shorter in children (20 months) than in adults (36 months). Ray et al. [23] showed that expression of MYC, p53, PDGFR-α, ErbB2, MIB-1, and TrkC combined with clinical characteristics could accurately predict relapse risk in pediatric medulloblastoma patients.

Pomeroy et al. studied the gene expression profile in pediatric medulloblastoma using oligonucleotide microarrays and demonstrated that the expression profile of eight genes helped to predict outcomes. Patients with a good prognosis pattern had a 5-year overall survival of 80% compared with 17% for those with a poor prognosis pattern [24]. In another study of gene expression profiles, the PDGFR-α and the Ras/mitogen-activated protein (MAP) kinase pathway genes were significantly upregulated in metastatic tumors but not in non-metastatic medulloblastomas.
This finding suggests that the PDGFR-α and Ras/MAP kinase signal transduction pathway may be rational therapeutic targets for metastatic disease [64].

**Diagnosis**

Medulloblastomas of the fourth ventricle and vermis frequently present with signs and symptoms of increased intracranial pressure, especially when the tumor obstructs CSF flow and causes hydrocephalus. Nausea and vomiting are common. Ataxia, which may also be present, is often underestimated. Cranial nerve palsies may indicate infiltration of the floor of the fourth ventricle. Spinal metastases tend to cause neurological deficits related to the sites of the lesions. Nystagmus and abnormalities in extraocular muscle movement are also common findings. Diplopia generally signifies involvement of the fourth or sixth cranial nerves. Other focal neurologic deficits such as hemiparesis, hearing loss, and seventh cranial nerve palsies are less frequent.

**Staging**

Accurate staging is indispensable for distinguishing between standard-risk and high-risk patients, because modern treatment concepts are based on the prognoses of these different patient groups; this applies to both children and adults. Magnetic resonance imaging (MRI) should be performed before surgery in order to clearly delineate the tumor. CSF cytology and MRI of the spinal canal are required in order to detect possible metastatic spread. Surgical information and imaging data allow staging to be carried out according to the Chang staging system (Fig. 18.3). Computerized tomography (CT) can be performed for staging purposes if MRI is unavailable or is contraindicated due to the patient’s condition.

**Prognosis**

The prognosis for adults with medulloblastoma is mainly based on the extent of disease spread. Risk factors include primary tumor size, brainstem infiltration, postoperative residual tumor and metastatic disease, but the definitions of standard-risk (or average) and high-risk groups, respectively, have been shown to be of controversial clinical utility. Some authors consider that patients with residual tumor of <1.5 cm² and no metastatic disease are at average risk [25, 26] whereas others also incorporate T stage in the risk assessment, and include patients T1–T2 and T3a tumors in the average-risk group [16]. In their analysis of 47 patients, Prados et al. found a 5-year progression-free survival for average-risk patients of 54%, compared to 38% for high-risk patients [27]. The influence of metastatic disease is unclear. Frost et al. reported a 5-year progression-free survival of 42% in patients
<table>
<thead>
<tr>
<th>Tumor size and extent of disease</th>
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<tbody>
<tr>
<td>T1</td>
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<tr>
<td>T2</td>
</tr>
<tr>
<td>T3a</td>
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<td>T3b</td>
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<td>T4</td>
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<tr>
<td>M0</td>
</tr>
<tr>
<td>M1</td>
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<tr>
<td>M2</td>
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<tr>
<td>M3</td>
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<tr>
<td>M4</td>
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</table>

Fig. 18.3 Chang classification system for medulloblastoma

without metastatic disease whereas none of the patients with metastases survived [19]. In the series reported on by Chan, the 5-year progression-free survival was 47% in patients with M1–M3 disease but 59% in patients without metastatic disease [21]. Although preliminary, data reported in the prospective series of Brandes et al. suggest that patients without metastases have a significantly better outcome than those with metastatic spread (75% progression-free survival at 5 years, compared to 45%, respectively) [16]. More recent data on the same population, after a median follow-up of 7.6 years, showed that this difference was not maintained, progression-free survival at 5 years being 61 and 78% in metastatic and non-metastatic patients, respectively, which did not achieve statistical significance [28]. These data were consistent with those reported by Carrie et al., who detected no impact from metastatic disease on prognosis [20]; in this study, the 5-year survival rates were 51% for patients with metastases and 58% for metastases-free patients, and this difference was not statistically significant.

The prognostic relevance of postoperative residual disease is also a controversial issue. Carrie et al. analyzed 156 patients and found that residual tumor had no impact on survival [20]. The 5-year progression-free survival rate was 59% in 109 patients without residual disease, compared with 64% in 50 patients with residual tumor. By contrast, Chan observed a 5-year progression-free survival rate of 86% in 17 patients without residual tumor compared to 27% in patients with residual tumor [21]. In their large retrospective series of 253 patients, Padovani et al. found that brainstem and fourth ventricle involvement and the dosage of radiotherapy to the posterior cranial fossa were negative prognostic factors on multivariate analysis [29].

Data from the updated analysis performed by Brandes et al. showed that postoperative residual disease did not impact significantly on the 5-year progression-free survival.
Table 18.1 Univariate analysis showing correlation between radiotherapy parameters and progression-free survival rates in 63 children with supratentorial PNET (HIT 88/89 and 91) [31]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients</th>
<th>3-Year progression-free survival</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>7</td>
<td>14.3</td>
<td>0–40.2</td>
<td>0.0012</td>
</tr>
<tr>
<td>Local + CSI</td>
<td>54</td>
<td>43.7</td>
<td>30.3–57.1</td>
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<tr>
<td>None</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose, local</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt;54 Gy</td>
<td>10</td>
<td>10.0</td>
<td>0–28.6</td>
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<td>≥54 Gy</td>
<td>53</td>
<td>44.7</td>
<td>31.1–58.2</td>
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<td>Dose, CSI</td>
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<td></td>
<td>0.0051</td>
</tr>
<tr>
<td>≥35 Gy</td>
<td>48</td>
<td>49.3</td>
<td>35.6–63.7</td>
<td></td>
</tr>
</tbody>
</table>

In supratentorial PNETs, despite the employment of the same treatments as those used for medulloblastoma, the survival rate following combined radiochemotherapy is 20–30% less than that obtained in patients with tumors within the posterior fossa [30]. In the HIT 88/89 and 91 trials, a progression-free survival at 3 years of 39.1% was achieved in 63 children. Radiotherapy with a sufficient dosage to the primary tumor site (≥54 Gy) and craniospinal (≥35 Gy) is crucial for obtaining an optimal outcome. Interestingly, in 48 patients receiving treatment according to the protocol guidelines, the 3-year progression-free survival increased to 49.3% (Table 18.1) [31]. In the HIT 88/89 and 91 studies, after a median follow-up of 31 months, the local recurrence rate was 71%, indicating that local tumor control is of particular importance. Some authors suggest that local dose escalations appear conducive to achieving the highest possible rate of local tumor control. However, the series reported on are too small for reliable conclusions to be drawn. Of five patients treated by Halperin et al. with this approach, four have complete remission, and the other patient is alive with stable disease [32]. This concept is currently under investigation in Germany [33].

Treatment

In the past it was assumed that medulloblastomas in adults had the same properties as those in children. Adult patients therefore were frequently treated with pediatric protocols, with simple variations in drug dosages and schedules. There is a paucity of prospective controlled trials in adults, and current experience is based exclusively on small retrospective studies investigating a variety of different treatments. Moreover, several of the studies available were conducted when diagnostic procedures, neurosurgical skills, and radiation therapy techniques were considerably different from those used at present. Due to the paucity and heterogeneity of data
the identification of prognostic factors and the definition of standard treatment are, at present, impossible to achieve.

**Neurosurgery**

The role of surgical resection in patients with medulloblastoma is now well established [34]. Findings made in several recent studies confirm the prognostic importance of achieving a total or near-total surgical excision [35]. For this reason, neurosurgeons, aided by modern technological devices, make considerable efforts to achieve complete or near-complete resection. Today, developments in neurosurgical skills have increased the proportion of tumors falling into this category, and peri-operative or postoperative complications and neurological deficits following surgery are now rare occurrences. However, as yet in the literature little information has been reported on the side effects of surgery, and no large prospective studies have been conducted to investigate the sequelae in patients following a standard therapeutic strategy.

**Radiation Therapy**

Postoperative radiotherapy, which is standard treatment, became widely accepted as the most effective treatment available when, in 1930, Cushing first reported its role in the management of medulloblastoma [36]. In 1953, Paterson pointed out the need for craniospinal irradiation, with accurate coverage of the target volume [37]. Craniospinal irradiation is followed by a boost to the posterior fossa, which nowadays is performed using three-dimensional treatment planning systems, in order to spare normal tissue from unnecessary damage. Over the past 40 years treatment outcomes have progressively improved, and the current long-term survival rates are 60 and 70% in children and adults, respectively. In adults, surgery alone is associated with a high recurrence rate, thus calling for adjuvant radiotherapy. Hubbard et al. reported six spinal recurrences in eight patients who underwent surgery alone [38]. In his analysis on 32 patients Ferrante et al. demonstrated that additional radiotherapy was followed by an increase in survival (of 6.5 months to 6.6 years) [39]. The dose–response relationships for treatment of tumors within the posterior fossa have been clearly documented [40–42]. Berry et al. observed a 10-year disease-free survival of 77% with a dose to the posterior fossa of more than 52 Gy. Lower doses were associated with a 5-year survival rate of 47%. In adults, Hazuka et al. observed tumor control of 75% in the posterior fossa after a dose of 55 Gy or more, compared to 40% with doses of less than 50 Gy [43]. Abacioglu et al. confirmed these observations, reporting a 5-year control rate of 33% following doses of less than 54 Gy, compared to 91% in patients given higher doses [44]. Dose reductions in the adjacent areas of the neuraxis appear to be of critical importance. According to the CCSG (Children’s Cancer Study Group)-experience
dose reductions from 36 to 23.4 Gy were associated with a significantly increased risk of recurrence outside the posterior fossa [45]. If combined with chemotherapy, however, these dose reductions appear to be feasible [46] and active with a 5-year progression-free survival rate of 79%. The only study available with data on adults, by Bloom, reports an increase in the recurrence rate after dose reductions (32–35 Gy reduced to 15–25 Gy) [40]. In their study, Packer et al. showed an encouraging event-free survival (EFS) rate for children with non-disseminated medulloblastoma who received reduced-dose radiation (craniospinal irradiation, 23.4 Gy with a boost of up to 55.8 Gy to the posterior fossa) followed by adjuvant chemotherapy (lomustine, cisplatin, and vincristine; or cyclophosphamide, cisplatin, and vincristine) [47].

The findings made in an updated French series in adults showed that radiotherapy at reduced doses in conjunction with chemotherapy yielded results identical to those achieved with standard-dose radiotherapy alone [29]. A French phase II study investigated radiotherapy alone using hyperfractionation followed by a dose-escalating boost in children and achieved results similar to those obtained with conventional dose prescription combined with chemotherapy [47, 48]. At a median follow-up of 45.7 months, the overall survival and progression-free survival rates at 3 years were 89 and 81%, respectively [48]. However, because of the differences in terms of long-term toxicity between adult and children, this approach has not been proposed for adult patients. It has yet to be established whether adjuvant chemotherapy should be administered together with radiotherapy in average-risk adults, because 70–80% of these patients are progression free at 5 years with radiotherapy alone, and hematological toxicity in adult patients can be consistent [49, 50].

**Quality of Radiation Therapy**

The quality of radiotherapy has an impact on treatment outcome (Table 18.2). The progress made in modern technology and the introduction of quality assessment programs have highlighted the need for accurate and reproducible irradiation schedules in the treatment of medulloblastoma. Grabenbauer et al. observed that an increase has been achieved in survival rates in recent decades and concluded that the use of modern techniques has contributed to the improvements made in overall radiotherapy management [51]. In their analysis of the precision of treatment techniques and their impact on survival, Miralbell et al. found that inadequate field alignment in whole brain irradiation was associated with a significantly worse survival [52]. In their detailed analysis of treatment techniques, Carrie et al. paid special attention to the coverage of a clinical target volume in SFOP (French Society of Pediatric Oncology) protocols [53] and found that the risk of relapses increased proportionally to an increasing frequency of protocol violations. In the German HIT study, detailed radiotherapy guidelines for the treatment protocol were given. An analysis of radiotherapy records revealed both a high degree of adherence to the guidelines and consistency between the recommendations and the actual treatment delivered.
### Table 18.2 Impact of quality of radiotherapy on outcome in childhood medulloblastoma

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>“Low quality”</th>
<th>“High quality”</th>
<th>Outcome</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Packer et al. [65]</td>
<td>108</td>
<td>Radiotherapy 1975–1982; n = 67 (62%)</td>
<td>Radiotherapy 1983–1989; n = 41</td>
<td>5-Year progression-free survival; 49% vs 82%</td>
<td>0.004</td>
</tr>
<tr>
<td>Grabenbauer et al. [51]</td>
<td>40</td>
<td>Radiotherapy pre-1980</td>
<td>Radiotherapy post-1980</td>
<td>5-Year overall survival; 64% vs 80%</td>
<td>0.02</td>
</tr>
<tr>
<td>Miralbell et al. [52]</td>
<td>77</td>
<td>Inadequate “helmet-technique;” n = 36 (47%)</td>
<td>Adequate “helmet-technique;” n = 41 (53%)</td>
<td>5-Year progression-free survival; 94% vs 72%</td>
<td>0.016</td>
</tr>
<tr>
<td>Carrie et al. [53]</td>
<td>169</td>
<td>Minor violations: n = 67 (40%) Major violations: n = 53 (31%)</td>
<td>No violations: n = 49 (29%)</td>
<td>3-Year recurrence rate One major violation: 17% Two major violations: 67% Three major violations: 78%</td>
<td>0.04</td>
</tr>
<tr>
<td>Packer et al. [46]</td>
<td>63</td>
<td>Violations: n = 20 (32%)</td>
<td>No violations: n = 43 (68%)</td>
<td>5-Year progression-free survival; 81% vs 70%</td>
<td>0.42</td>
</tr>
</tbody>
</table>

It was concluded that high-quality treatment was a major contributory factor in the overall outcome, which was in the region of 80% for standard-risk patients [33, 54].

### Chemotherapy

#### Standard-Risk Medulloblastoma

In the recently published SIOP III trial (Société Internationale d’Oncologie Pédiatrique), the addition of chemotherapy to radiotherapy achieved a statistically significant improvement in the event-free and overall survival [55]. By contrast, the role of chemotherapy in adults is far from clear. The 5-year overall survival rates in retrospective studies range from 26 to 83%, irrespective of the use of adjuvant chemotherapy (Table 18.3). In addition, the impact of chemotherapy in high-risk patients is unknown, and it has yet to be established whether intensive regimens can ameliorate the widely acknowledged poor outcome. In a large French retrospective...
### Table 18.3 Medulloblastoma in adults: treatment outcome in retrospective studies

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Age (years)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farwell and Flannery [66]</td>
<td>44</td>
<td>60% of patients had surgery and radiation</td>
<td>No</td>
<td>&gt;20</td>
<td>5-Year OS: 26% Systemic metastasis rate: 27%</td>
</tr>
<tr>
<td>Carrie et al. [20]</td>
<td>156</td>
<td>$n = 154$ (99%); CSI (35/55 Gy)</td>
<td>$n = 75$ (48%); multiple regimens</td>
<td>&gt;18</td>
<td>5-Year EFS: 61% 10-Year EFS: 48% No significant benefit from chemotherapy</td>
</tr>
<tr>
<td>Peterson and Walker [67]</td>
<td>45</td>
<td>CSI</td>
<td>Yes</td>
<td>&gt;15</td>
<td>50% recurred 10–76 months after initial treatment</td>
</tr>
<tr>
<td>Prados [27]</td>
<td>47</td>
<td>CSI</td>
<td>$n = 32$ (68%)</td>
<td>&gt;15</td>
<td>5-Year OS: 81% (low risk) vs 58% (high risk); $p = 0.03$ 5-Year DFS: 54% (low risk) vs 38% (high risk); $p = 0.05$</td>
</tr>
<tr>
<td>Frost et al. [19]</td>
<td>48</td>
<td>CSI ($n = 46$) Local ($n = 2$)</td>
<td>No</td>
<td>&gt;16</td>
<td>5-Year OS: 62% 10-Year OS: 41%</td>
</tr>
<tr>
<td>Giordana et al. [68]</td>
<td>44</td>
<td>n.d.</td>
<td>n.d.</td>
<td>&gt;18</td>
<td>5-Year OS: 40% 10-Year OS: 36%</td>
</tr>
<tr>
<td>Giordana et al. [69]</td>
<td>45</td>
<td>n.d.</td>
<td>n.d.</td>
<td>&gt;15</td>
<td>5-Year OS: 70%</td>
</tr>
<tr>
<td>Chan et al. [21]</td>
<td>32</td>
<td>CSI (36/55 Gy)</td>
<td>$n = 24$ (75%)</td>
<td>&gt;15</td>
<td>5-Year DFS: 57% 8-Year DFS: 40% 5-Year OS: 83% 8-Year OS: 45%</td>
</tr>
</tbody>
</table>
Table 18.3 (continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Radiotherapy</th>
<th>Chemotherapy</th>
<th>Age (years)</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greenberg et al. [50]</td>
<td>17</td>
<td>CSI + local boost</td>
<td>Packer regimen (n = 10)</td>
<td>&gt;17</td>
<td>Median recurrence-free survival/median OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pediatric oncology group regimen (n = 7)</td>
<td></td>
<td>Packer: 26/36 months</td>
</tr>
<tr>
<td>Coulbois et al. [70]</td>
<td>22</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>POG: 48/57 months</td>
</tr>
<tr>
<td>Louis et al. [71]</td>
<td>24</td>
<td>CSI + local boost</td>
<td>(n = 6) (25%)</td>
<td>&gt;16</td>
<td>5-Year recurrence-free survival: 63%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-Year OS: 81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-Year OS: 82%</td>
</tr>
<tr>
<td>Brandes et al. [16]</td>
<td>36</td>
<td>CSI + local boost</td>
<td>“High-risk” patients only</td>
<td>&gt;18 years</td>
<td>5-Year PFS: M0 75% vs M + 45%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-Year PFS: “standard risk” 76% vs “high risk” 61%</td>
</tr>
<tr>
<td>Kühl (2002, personal communication)</td>
<td>46</td>
<td>CSI + local boost</td>
<td>(n = 36) (78%)</td>
<td>&gt;15</td>
<td>5-Year PFS: 63%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5-Year PFS: M0 71% vs M3 45%</td>
</tr>
</tbody>
</table>

OS: overall survival, PFS: progression-free survival, DFS: disease-free survival, EFS: event-free survival, CSI: craniospinal irradiation, n.d.: no data
analysis the 5-year and 10-year overall survival rates for patients without additional chemotherapy were 57 and 43%, respectively, compared to 66 and 52% with chemotherapy; these differences are not statistically significant [20]. Brandes et al. reported 36 adult patients with average-risk or high-risk medulloblastoma treated prospectively with a protocol consisting of pre-irradiation chemotherapy (cisplatin, etoposide, cyclophosphamide) followed by standard-dose radiotherapy. The median time to progression was 81 months and the 5-year event-free and overall survival rates were 65.4 and 75.3%, respectively. Patients with a high-risk profile receiving additional chemotherapy had a 5-year progression-free survival of 61% [16]. In Germany, an analysis was conducted on 56 patients given additional chemotherapy according to the German HIT’91 protocol. Patients treated according to the protocol achieved a 5-year event-free survival of 67%, compared to 48% in those treated without any strict adherence to the protocol guidelines. The overall 5-year event-free survival was 59%. Sixteen patients who received maintenance chemotherapy had a 5-year progression-free survival of 78%, compared to 62% for 20 patients receiving chemotherapy before and after radiotherapy (sandwich chemotherapy). In M3 disease, the outcome appeared to be worse (54%) than in M-negative disease (71%) (Kühl, Rutkowski, personal communication). In adults, however, maintenance chemotherapy appears difficult to apply due to the increased toxicity [50]. Yet the updated data reported by Brandes et al., after a median follow-up of 7.6 years, demonstrated that the risk of recurrence increased markedly after 7 years of follow-up in low-risk patients. In the same analysis, the authors found no significant differences between the progression-free and overall survival of low-risk patients treated with radiotherapy alone and high-risk patients treated with radiotherapy and chemotherapy (upfront and adjuvant), thus raising the issue of a role for chemotherapy in average-risk patients [28]. Furthermore, in their study reporting retrospective data from patients with long-term follow-up, Padovani et al. suggested that in the average-risk subgroup of patients, there was no overall survival difference between patients treated with axial doses of >34 Gy and those treated with craniospinal doses of <34 Gy plus chemotherapy.

**High-Risk Medulloblastoma**

Metastatic disease, as described by Chang’s classification [56] (Fig. 18.3), appears rare in adults, unlike in children. In one French series, for example, medullary metastases were detected in 4–6% of cases, and positive CSF was found in 6–7% of cases. The positivity of CSF did not appear to be of prognostic significance, with a 10-year overall survival of 33% compared with 59% in CSF-negative patients. On the contrary, spinal involvement was of important prognostic influence. The 10-year overall survival was 24% in patients with spinal metastases, compared to 58% in patients without metastatic deposits. The poor outcome, in spite of intensive chemotherapy regimens, is well known in children. In the early CCSG trial reported by Evans et al., patients with metastatic disease had a 5-year event-free survival of 36% and those with M0 disease 59%; the overall survival of both groups was similar. In this study, adjuvant chemotherapy given as a maintenance regimen
achieved a marked improvement, with 5-year event-free survival of 46% compared to 0% for patients treated with radiotherapy alone [57]. In the HIT’91 study, the 3-year progression-free survival for patients with M2/M3 disease after radiotherapy followed by maintenance chemotherapy was 30%, compared with 83% for patients without metastasis [33]. No significant difference in outcome was found between patients receiving sandwich chemotherapy and those on maintenance chemotherapy. The efficacy of adjuvant chemotherapy in adults appears to be similar to that in children. In one series, none of the patients treated with postoperative radiotherapy alone survived [19]. In the series reported on by Chan, adjuvant chemotherapy yielded a 5-year progression-free survival rate of 47% [21]; in the series reported on by Prados et al., a 5-year disease-free survival rate of 38% was achieved following the administration of adjuvant chemotherapy. Brandes et al. achieved a 1-year progression-free survival rate of 45% in patients with M-positive disease. In the HIT study, patients with M3 disease had a 5-year progression-free survival rate of 45% (Kühl, Rutkowski, personal communication). Because of the heterogeneity of patients and protocols, one regimen cannot be considered preferable to another. Nor is there yet any evidence that more intensive chemotherapeutic approaches yield a better outcome.

**General Recommendations for the Management of Medulloblastoma**

To date, treatment recommendations for the management of medulloblastoma in adults are essentially based on experience gained in children. There is a lack of prospective trials, although retrospective data do indicate that irradiation of the craniospinal axis followed by a boost to the posterior fossa, with appropriate conventional doses as used in the pediatric population, is required for an optimal outcome. The prognostic factors in adults appear to be similar to those in children, but differences in, for example, tumor location and histological subtype suggest the presence of specific biological properties which might have an additional influence. The advantage of additional chemotherapy in standard-risk patients is a controversial issue. A major point of concern is the acute toxicity of chemotherapy given after radiation therapy. In the pediatric population, it is necessary to dose-reduce chemotherapy in up to 60% of cases. Although the experiences for young adults were very promising in Germany the feasibility of this approach in older patients and in a larger cohort is not well understood. However, it is known that the tolerance for chemotherapy given for diseases other than medulloblastoma gradually decreases with increasing age. Chemotherapy must therefore be investigated in a phase I/II study in order to reliably assess the toxicity that it incurs and its feasibility. In conclusion, the recommendation for average-risk patients is surgery followed by postoperative radiotherapy (craniospinal followed by a boost to the entire posterior fossa) using conventional doses (without dose reductions). Adjuvant chemotherapy
cannot be recommended since its effect and possible toxicity when administered for this disease are, as yet, unknown. For high-risk patients, it is impossible to establish detailed treatment recommendations. In adults, as in children, conventional treatment schedules are associated with a poor outcome; consequently, novel approaches are required. These rare cases should be discussed on an individual basis with a medical oncologist, radiation oncologist, and pediatric oncologist, and the national medulloblastoma working groups should be contacted each time a new case is diagnosed. Data from the prospective trial conducted by Brandes et al. suggest that upfront chemotherapy followed by radiotherapy is feasible and provides long-term outcomes similar to those obtained with radiotherapy alone in standard-risk patients [28].

Late Sequelae

Long-Term Sequelae

Cognitive and focal neurological deficits may have a great impact on long-term survivors of brain tumors, regardless of their histology and grade. Memory loss, apathy, concentration difficulties, and personality changes may have a profound effect even in patients who appear to have a Karnofsky Performance Status of 100. Surgery in the so-called silent areas may contribute to cognitive deficits. The late effects of radiation therapy on cognitive function are less clearly understood. Radiotherapy is known to cause not only an early somnolence syndrome but may also have late sequelae, in particular a delayed leukoencephalopathy with cognitive dysfunction and radiation necrosis [58–60]. In individual patients, it is difficult to untangle the direct effects of the tumor on cognition from the late effects of treatment. A recent survey on cognitive deficits in progression-free survivors of low-grade glioma failed to confirm the generally assumed relationship between radiotherapy and cognitive deficits [61]. Only in patients treated with a fraction size of more than 2 Gy evidence of cognitive dysfunction increased. The only other association with cognitive deficits was treatment with anti-epileptic drugs. Prior studies suggested that whole brain radiotherapy may be associated with more cognitive deficits than involved field irradiation, but today involved field radiotherapy is standard practice [62]. Radiation therapy may also affect cranial nerves or induce endocrine dysfunction even in tumors distant from the hypothalamus–pituitary region [63]. Apart from cognitive deficits, a risk of death of 2.5% at 2 years has been reported for doses of 50.4 Gy. A risk of radionecrosis of up to 5% in 5 years may occur after 60 Gy to one-third or 50 Gy to two-thirds of the brain volume or with 50–53 Gy to the brainstem. A similar risk of blindness was shown with 50 Gy delivered to the optic chiasm. Also chemotherapy may induce late sequelae, such as lymphoma, leukemia, solid tumors, lung fibrosis, infertility, renal failure, and neurotoxicity.
Follow-Up

No general guidelines for follow-up can be defined, since it should be tailored for the individual patient while taking into account tumor grade and previous and remaining treatment options. However, rough guidelines are that brain MRI may be repeated every 3 months and spinal MRI may be repeated every 6 months in standard risk, for the first 2 years; both examinations may then be repeated every 6 months for up to 5 years, after which they can be performed annually. In high-risk medulloblastomas, a brain and spinal MRI may be performed every 3 months for the first 2 years, as MRI is a more reliable tool in making a further diagnosis during follow-up than waiting until signs and symptoms develop; after this period, it can be performed every 6 months. Of course, unexpected new signs or symptoms may also call for imaging or patient restaging.

References


Chapter 19
Pineal Region Tumors

Harry C. Brastianos, Priscilla K. Brastianos, and Jaishri Blakeley

Keywords Pineal region tumor · Germinoma · Non-germinomatous germ cell tumor · α-Fetoprotein · Human chorionic gonadotropin · Pineocytoma · Pineoblastoma · Pineal Parenchymal tumor of intermediate differentiation

Introduction

Brief History of the Pineal Gland

The pineal gland was first discovered in 300 B.C. by Herophilus [1]. The first pineal tumor was reported in a 20-year-old woman in 1717 by Charles Drélincourt [1] and the first reported attempt at a pineal tumor resection was in 1910 by Hosley [2]. Since then, there has been ongoing debate about optimal management of pineal tumors.

Anatomy and Physiology of the Pineal Gland

The pineal gland is an endocrine organ named because of its resemblance to a pine cone (Latin pineas). It is located at the posterior roof of the third ventricle dorsally and the tectum of the midbrain caudally [3]. This gland is either circular or oval in shape, is on average $7 \times 7 \times 2$ mm, and is mostly covered by pia mater [2]. Arterial supply to the pineal gland is via the posterior choroidal arteries, and venous drainage is provided by the internal cerebral veins [2, 3]. Both sympathetic and parasympathetic nerves provide innervations to the pineal gland. Histologically, the pineal

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body is mostly glandular and is composed of both pinealocytes and astrocytes. Pinealocytes, the main cells of the pineal gland, produce melatonin [3].

Unlike most endocrine organs which are regulated by other hormones, the pineal gland is regulated by light in the environment. It secretes its main product, melatonin, at night [4]. Melatonin is a highly lipophilic molecule that is biosynthesized from tryptophan [5]. This hormone directly affects circadian rhythms and blood pressure and is thought to have antioxidant properties and influence on various growth hormones [6].

**Overview of Tumors of the Pineal Region**

Multiple tumor types can occur in the pineal region (Table 19.1). The most commonly encountered tumor type is a germ cell tumor, which accounts for 50–75% of all pineal body tumors [7]. These tumors arise from primitive embryonal tumors rather than from cells of the pineal gland. Pineal parenchymal tumors (arising from pinealocytes) are the second most common pineal tumors. The presence of astrocytes in the pineal body allows gliomas to form within the pineal body, although rarely. Other tumor types found in this region include meningiomas, choroid plexus papillomas, and ependymomas from the third ventricle. Metastases, lymphomas, and neuronal tumors are uncommon in the pineal region [8].

<table>
<thead>
<tr>
<th>Table 19.1 Pineal region tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germ cell tumors</td>
</tr>
<tr>
<td>Germinomatous</td>
</tr>
<tr>
<td>Germinoma</td>
</tr>
<tr>
<td>Non-germinomatous</td>
</tr>
<tr>
<td>Teratoma</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
</tr>
<tr>
<td>Yolk sac tumors</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
</tr>
<tr>
<td>Pineal parenchymal tumors</td>
</tr>
<tr>
<td>Pineocytoma</td>
</tr>
<tr>
<td>Pineoblastoma</td>
</tr>
<tr>
<td>Pineal parenchymal tumor of intermediate determination</td>
</tr>
<tr>
<td>Gliomas</td>
</tr>
<tr>
<td>Tectal glioma</td>
</tr>
<tr>
<td>Thalamic glioma</td>
</tr>
<tr>
<td>Pineal glioma</td>
</tr>
<tr>
<td>Meningioma</td>
</tr>
<tr>
<td>Ependymoma</td>
</tr>
<tr>
<td>Metastases, lymphoma, neuronal tumors</td>
</tr>
<tr>
<td>Papillary tumors of the pineal region</td>
</tr>
</tbody>
</table>
Presentation of Pineal Tumors

Tumors in the pineal region share a similar presentation due to tumor involvement of neighboring brain structures. The most common presentation is headache, nausea, vomiting, and dizziness, due to compression of the cerebral aqueduct, which results in obstructive hydrocephalus and elevated intracranial pressure [9]. Less common presentations include oculomotor and vision abnormalities consistent with Parinaud syndrome (light near dissociation, convergence retraction nystagmus, and vertical gaze palsy) secondary to dorsal midbrain compression. Compression of the superior cerebral peduncle may cause dysmetria and ataxia. A rare clinical manifestation is hearing loss due to compression of the inferior colliculi [10, 11].

As a consequence of the secondary effects of hydrocephalus or multifocal involvement including the suprasellar region (most commonly with germ cell tumors), pituitary and hypothalamic axis irregularities may be present. The most frequently linked endocrine abnormality is diabetes insipidus [12]. In rare cases, pseudoprecocious puberty can occur, which is due to germ cell tumors secreting β-human chorionic gonadotropin (β-HCG) [7, 11]. Malignant tumors of the pineal gland can destroy the gland and lead to decreased levels of melatonin. Reduced levels of melatonin may cause sleep irregularities [13, 14]. Measuring levels of melatonin can be a diagnostic tool for patients with pineal region tumors. Furthermore, melatonin replacement therapy may be beneficial for some patients [13].

Germ Cell Tumors: Pathology and Diagnosis

Germ cell tumors (GCTs) are hypothesized to be derived from the primordial germ cells residual from embryogenesis. The most common location for an intracranial germ cell tumor is the pineal region (45%), but these neoplasms can involve other regions of the brain including the third ventricle, suprasellar cistern, thalamus, and basal ganglia [15]. GCTs are classified as germinomatous (germinomas) or non-germinomatous germ cell tumors (NGCTs) (Table 19.1). The NGCTs are further subdivided into teratomas, embryonal carcinomas, yolk sac tumors, and choriocarcinomas [15].

The incidence of these tumors varies by geographic location. In Asia, GCTs account for 2.8% of all primary brain tumors and are predominantly germinomas [16, 17]. The incidence of GCTs in Europe and the United States is much lower at 0.5%; however, NGCTs are more likely to be encountered in Western than in Asian countries [15].

Imaging

Diagnosis is initially made with magnetic resonance imaging (MRI) or computed tomography (CT). Distinguishing between the different types of pineal tumors
by imaging is difficult (Table 19.2). With the exception of teratomas, GCTs are mildly hypointense on T1-weighted MRI and mildly hyperintense on T2-weighted sequences. A “butterfly” sign indicative of a calcified pineal gland centrally with symmetric “wings” of tumor may be present on CT or MRI, which is suggestive but not diagnostic of a germinoma. Teratomas generally do have unique imaging features including heterogeneous, multilocular, or ring-enhancing lesions secondary to a combination of cystic, fatty, and calcified areas [18].

**Pathology and Immunohistochemistry of Germ Cell Tumors**

**Germinomas**

Germinomas are typically well-circumscribed lesions composed of soft and solid components, often associated with small cysts. These tumors are rarely associated with necrosis or hemorrhage. They are made up of large cells with round nuclei, prominent nucleoli, and glycogen-rich cytoplasm. Around the vascular stroma, T-helper and T-cytotoxic lymphocytes are present. B-lymphocytes, plasma cells, and syncytiotrophoblastic cells may also be detected [19]. Immunohistochemically, germinomas may stain positively for placental alkaline phosphatase (PLAP) and OCT4 [20]. Immunopositivity for the proto-oncogene c-kit appears to be specific for germinomas [21]. When present, syncytiotrophoblastic cells stain for β-HCG [22]. β-HCG can be seen both in germinomas and NGCTs; however, intense staining is highly suggestive of NGCT.

**Teratomas**

Teratomas are composed of cells from the ectoderm, endoderm, and mesodermal cell lines and are subdivided into mature and immature types. Immature teratomas are the most common lesions in the central nervous system (CNS). They are usually composed of primitive mesenchyme, which is a mitotically active component derived from spindle cells and neuroectodermal tissue, histologically resembling neural tubes or ependymal rosettes. Mature teratomas are comprised of fully differentiated tissue components with an absence of necrosis and mitotic activity [19].
Both mature and immature teratomas are immunoreactive for $\alpha$-fetoprotein (\(\alpha\text{FP}\)) [23].

**Yolk Sac Tumor**

Yolk sac tumors are highly aggressive germ cell malignancies that resemble normal yolk sac structures. Histologically, they consist of cuboidal to columnar epithelial cells, organized in papillary, reticular, and endothelial sinus patterns [19]. A histopathological hallmark of these tumor types is the presence of a “glomerular-like” structure comprised of a perivascular epithelial-lined space called Schiller–Duval bodies. These tumors stain positively for $\alpha$FP and may stain for PLAP and cytokeratin [24, 25].

**Embryonal Carcinomas**

Pure embryonal carcinomas are rare intracranial tumors. Histologically, cells have larger nuclei and very prominent nucleoli and grow in alveolar or tubular patterns. Eosinophilic hyaline droplets may be found in the cytoplasm. Many mitotic figures, as well as necrotic foci are often present [19, 22]. Immunohistochemical staining is positive for cytokeratin, OCT4, and frequently PLAP. Cells may also stain positively for $\alpha$FP and $\beta$-HCG [25].

**Choriocarcinomas**

Choriocarcinomas arise as an extraembryonic differentiation of malignant germ cells and are a rare, but aggressive tumor type. These tumors are associated with hemorrhagic necrosis, often resulting in intracranial hemorrhage. There are two cell types that comprise these tumors, the cytotrophoblastic cells and the syncytiotrophoblastic giant cells (STGCs). STGCs stain positively for human placental lactogen, $\beta$-HCG, and cytokeratin. Choriocarcinoma neoplasms may also stain positively for cytokeratin and PLAP [22].

**Genetics of Germ Cell Tumors**

GCTs present most commonly in adolescence and appear to affect males more frequently than females [17, 26]. Interestingly, both mediastinal and intracranial GCTs may be associated with Klinefelter syndrome (47 XXY), particularly in children who present with precocious puberty [27, 28]. Intracranial germinomas have been associated with Down’s syndrome and neurofibromatosis type 1; however in both diseases, the most common site of the tumor is the basal ganglia and not the pineal gland [29, 30]. Rare cases of pineal yolk sac tumors have been reported in patients with Down’s syndrome [31]. GCTs are associated with specific chromosomal imbalances. Gains on 12p, 12q, 8p, and 1p and deletions on 18q, 16p, and 13q are most common [32, 33].
CSF and Serum Analysis of Germ Cell Tumors

Elevations in serum and cerebrospinal fluid (CSF) tumor markers, β-HCG and αFP, aid in the diagnosis of pineal germ cell tumors (Table 19.3). CSF levels of β-HCG and αFP are far more sensitive measures of disease and these studies are helpful both for the diagnosis of GCT and for monitoring treatment response. Choriocarcinomas have elevated levels of CSF β-HCG, while αFP is a sensitive marker of yolk sac and embryonic tumors. β-HCG may also be mildly elevated in some germinomas; however, significant elevations in CSF β-HCG and αFP are more diagnostic of NGCT [16]. Elevated levels of both of these tumor markers are correlated with more aggressive tumors and portend worse prognosis. Increased levels of CSF and serum PLAP are associated with germinomas [7, 11, 19].

Table 19.3 Key CSF markers for pineal germ cell tumors

<table>
<thead>
<tr>
<th>Germ cell tumor type</th>
<th>CSF marker</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germinomas</td>
<td>PLAP, +/- β-HCG</td>
</tr>
<tr>
<td>Germinomas with STGC</td>
<td>β-HCG, PLAP</td>
</tr>
<tr>
<td>Teratoma</td>
<td>αFP</td>
</tr>
<tr>
<td>Yolk sac tumor</td>
<td>αFP</td>
</tr>
<tr>
<td>Choriocarcinomas</td>
<td>β-HCG</td>
</tr>
<tr>
<td>Embryonal carcinoma</td>
<td>αFP, β-HCG</td>
</tr>
</tbody>
</table>

Prognosis of Germ Cell Tumors

The histological subtype is an important prognostic indicator for GCTs [11]. Germinomas have the most favorable prognosis, as they are extremely radiosensitive and can be treated with radiotherapy alone with a 5-year survival of 65–100% [34–36]. Mature teratomas also have a good prognosis when complete surgical resection is possible. The 10-year survival rate has been reported as ranging from 78 to 93% [23, 35]. Immature teratomas have an intermediate prognosis with a 5-year survival rate of 45–86% [34–36]. NGCTs traditionally carry the worst prognosis as these tumors have an estimated 5-year survival rate of roughly 20–45% [23, 35, 36]. However, more recent studies have suggested improved survival with multimodality approaches including high-dose chemotherapy, radiation therapy (RT), and surgery.

Pineal Parenchymal Tumors: Pathology and Diagnosis

Pineal parenchymal tumors (PPTs) are subdivided into the pineocytomas (PCs), pineoblastomas (PBs), and pineal parenchymal tumors of intermediate differentiation (PPTID) [9]. These tumors are infrequent, accounting for <1% of primary
brain tumors and roughly 10–30% of pineal region tumors. Median age of patients with these tumors ranges from 10 to 65 years, and they appear to affect both sexes equally. PCs account for approximately 14–60% of PPTs and affect mainly adults. These tumors are slow growing and consist of small mature cells that are histologically similar to normal pineal cells. PBs, the most aggressive of the PPTs, make up roughly 40% of all PPTs. They are composed of immature pineal cells. Children and adults in the first two decades of life are more likely to be affected by PB. PPTIDs are of intermediate malignancy and comprise approximately 20% of all PPTs [7, 37].

**Imaging**

Attempting to differentiate between the different forms of PPT on MRI is challenging. PCs may have higher signal intensity on T2-weighted sequences than PBs. PCs are also more likely to have a cystic component (Fig. 19.1). PBs are usually isointense on T2-weighted images. The highly malignant components of PB may be characterized by surrounding brain edema and signs of invasion. There have not been any distinguishing radiological traits that allow for characterization of PPTIDs from the other PPDs [18].

![Fig. 19.1 Example of pineocytoma histology. Note the prominent fibrillary zones (pineocytomatous rosettes) separating rests of cells](image)

**Pathology of PPTs**

**Pineocytomas**

PCs are benign, well-circumscribed tumors consisting of pineal parenchymal cells. They become symptomatic via growth into the posterior portion of the third ventricle, constricting the colliculi and the cerebral aqueduct leading to hydrocephalus. Histologically, PCs are characterized by a lobular structure lined by rows of pineocytes called pineocytomatous pseudorosettes [37]. Tumor cells exhibit darkly staining nuclei and have a round to oval shape. It is uncommon for
necrosis or mitoses to be present [19]. Eosinophilic cytoplasmic material makes up the center of these tumors. The rosettes are immunopositive for synaptophysin and neurofilaments. Other neuronal markers include class III $\beta$-tubulin and chromogranin A [37].

**Pineoblastomas**

Pathologically, PBs appear as grayish masses that contain areas of necrosis and hemorrhage. They consist of masses of pleomorphic cells. The tumors cells contain large hyperchromic nuclei, and mitotic activity is frequent (Fig. 19.2). Both Homer–Wright rosettes and Flexner–Wintersteiner rosettes have been observed. Immunohistochemical studies reveal reactivity to synaptophysin, neurofilaments, class III $\beta$-tubulin, chromogranin, and retinal S-antigen [19, 37]. Other primitive neuroectodermal tumors such as medulloblastoma and retinoblastomas are clinically and histologically similar to PB. In a retrospective analysis, it was reported that pineoblastomas with mutations of the $RB1$ gene (the gene associated with retinoblastoma) represent a subset of more aggressive lesions [38].

**Fig. 19.2** Example of pineoblastoma histology. Note the marked hypercellularity with large, hyperchromic nuclei and eosinophilic cytoplasm with Homer–Wright rosettes

**Pineal Parenchymal Tumor of Intermediate Differentiation**

PPTIDs are histologically divided into two subtypes. The first type consists of cells characterized by poorly differentiated PB-like cells and well-differentiated PC-like cells. PPTIDs of the second subtype are composed of cells with histological features of both pineocytoma and pineoblastoma. Immunohistochemical studies show that these tumors stain positive for synaptophysin. Some staining has also been observed with neurofilaments, chromogranin A, and retinal S-antigen [19, 22].
Genetics of PPTs

Comparative genomic hybridization studies have revealed that the most common chromosomal imbalance in PB is the loss of chromosome 22. In PPTIDs, comparative genomic hybridization has shown gains in 4q and 12q and losses in chromosome 22 [39]. Microarray analysis of PCs revealed a high expression of TPH and HIOMT. These genes are important in melatonin synthesis. PCs also display high expression of genes related to phototransduction in the retina (OPN4, RGS16, and CRB3) [40].

Prognosis

PCs are slow-growing tumors and are rarely invasive. With resection or RT, the 5-year survival rate is found to be 80–90% [7, 41]. As PCs can recur with distant metastases, long-term follow-up with serial MRI scans of the neuraxis is required. In contrast, PB is a World Health Organization (WHO) grade IV tumor which is highly invasive and malignant. With maximal treatment, the 5-year overall survival is a disappointing 10–51%. Without treatment, survival is on the order of months. PPTID is closest in behavior to PB and had only a 15-month median survival in patients with local or spinal recurrence [41].

Miscellaneous Tumor Types

Glioma

Gliomas of the pineal region most commonly arise from the dorsal midbrain and are referred to as tectal gliomas. Tectal gliomas are a distinct form of brainstem glioma that occur in both adults and children. Regardless of age at presentation, tectal gliomas appear to have a benign course in 80% of cases [42, 43]. On MRI, their appearance is characterized as exophytic masses that extend from the quadrigeminal plate into the periaqueductal areas with variable contrast enhancement. The clinical significance of contrast enhancement is a matter of debate. Some studies have shown that contrast enhancement corresponds to higher grade histology [44, 45]. Other reports suggest that benign-behaving tumors may also demonstrate contrast enhancement [42, 45]. The histological subtypes that make up pineal body gliomas include fibrillary astrocytomas, pilocytic astrocytomas, anaplastic astrocytomas, glioblastomas, oligodendrogliomas, ependymomas, and choroid plexus papillomas. Astrocytomas are the most common tectal gliomas [19]. Glioblastomas are rare tumors of the pineal region, with only 19 reported cases in the literature. As one would expect, these tumors have a poor prognosis with survival ranging from
2 to 11 months and they are often associated with leptomeningeal dissemination [46, 47].

**Meningioma**

Pineal meningiomas are rare neoplasms that make up less than 1% of all intracranial meningiomas and 8% of pineal region tumors. The average age of diagnosis is 40 years with a female predominance [48]. For pineal meningiomas that do not have a dural attachment, the average age of diagnosis is 28 years [49, 50]. The origin of these tumors is thought to be at the velum interpositum. On MRI, meningiomas are found to be round, homogeneous, and slightly hyperintense on T1-weighted images. Contrast enhancement is pronounced and homogeneous [18]. On CT, calcifications may also be present [49]. Although imaging may be suggestive, accurate diagnosis requires tissue for histopathological analysis [48].

**Papillary Tumor of the Pineal Region**

The papillary tumor of the pineal region is a recently reported neoplasm, first described in 2003 [51]. Since then, there have been 52 reports of this tumor in the literature [52]. In a study of 31 patients, the 5-year survival and progression-free survival were 73 and 27%, respectively [40]. Fourteen men and 17 women were included in this study with an age range of 5–66 years [53]. Pathological analysis reveals a neuroepithelial tumor with papillary features [54]. These tumors are hypothesized to be derived from the specialized ependyma of the subcommissural organ. MRI reveals a mixed solid and cystic tumor that may obstruct the third ventricle. The tumors are typically hypointense on T1-weighted images and hyperintense on T2-weighted images [52]. Tumors with cystic features are often heterogeneously enhancing [52]. Morphologically, these tumors are similar to choroid plexus tumors and papillary ependymomas. They are defined histologically by an epithelial-like pattern where vessels are coated by tumor cells creating perivascular pseudorosettes [53]. These tumors demonstrate immunopositivity toward the broad spectrum anti-CK antibody KL1. Chromogranin A, synaptosin, and S-100 are also expressed by the tumor cells [40].

**Metastases to the Pineal Gland**

Metastases to the pineal region are uncommon, but do occur. In a study of 7,807 patients with intracranial metastatic tumors, only 0.3% were present in the pineal region [55]. The most common primary tumors that metastasize to the pineal gland include carcinomas of the lung, breast, stomach, esophagus, rectum, and kidney [56]. There have also been reports of melanoma, leukemia, and pancreatic adenoma
metastasizing to the pineal region [56, 57]. Leptomeningeal seeding is frequently observed concurrently with pineal metastases [58]. This is probably due to the close proximity of the pineal gland to the CSF pathways in the third ventricle and quadrigeminal cistern [58].

**Treatment of Pineal Region Tumors**

**Treatment of Hydrocephalus**

Between 58 and 90% of patients with pineal region tumors will need an intervention to relieve hydrocephalus due to compression of the cerebral aqueduct [9, 59]. In patients that have mild symptoms of hydrocephalus and in whom tumor resection is feasible, resection will likely treat the hydrocephalus. In more severe cases, the obstruction often needs to be treated with either ventricular shunting or endoscopic ventriculostomy [9]. Ventricular shunting is the more definitive approach. However, ventricular shunting may be associated with complications including shunt failure, infections, intracranial hypotension, subdural hematomas, and in rare cases, peritoneal metastases. Ventriculostomies via neuroendoscopy are less invasive than ventricular shunting and have fewer complications [7]. Furthermore, fenestrations can be made simultaneously in tumor-related cysts which allow for tissue and fluid sampling. However, if symptoms persist, and the obstruction is not relieved, shunts will need to be placed later [59, 60]. It should also be noted that having small ventricular spaces interferes with tumor debulking. Hence, if possible, permanent CSF diversion should be performed after tumor debulking or when tumor debulking is not feasible [9]. Should an urgent shunt be necessary, programmable or temporary externalized shunts should be considered so that ventricular size can be manipulated during debulking.

**Treatment of Germ Cell Tumors**

**Germinomas**

Germinomas are best treated by radiotherapy following a biopsy. Tissue is desirable to confirm diagnosis; however, there is no additional survival benefit from maximal surgical resection of germinomas. This is because germinomas are extremely radiosensitive, with 10-year survival rates of 87–91% with RT alone [7, 11, 16]. Although RT is the preferred treatment for germinomas, there is ongoing debate about the optimal field and dose of radiation. Craniospinal RT is thought to be the most comprehensive and most likely to prevent late recurrences, however, there are long-term risks including cognitive deficits, endocrinopathies, secondary malignancies, growth arrest, and marrow suppression. In a retrospective study, patients with local germinomas were treated post-operatively with extended focal irradiation to the third and lateral ventricles, the sella and pineal region without craniospinal RT
The 10-year survival rate in these patients was 92.7% [23]. In another retrospective study, in patients for whom craniospinal RT was included upfront, the 10-year survival rate was approximately 90% [61]. Hence, the data suggest that there is no clear benefit for including craniospinal RT for localized germinoma. However, since as many as 2–37% of germinomas will have distant metastases after apparent local cure, many specialists continue to recommend upfront craniospinal RT [61]. The dose of RT is also debated. It is not clear that there was improved outcome from standard dose RT (50 Gy) versus reduced dose RT (30–40 Gy) [7].

Chemotherapy was hypothesized to play a role in the treatment of intracranial germinomas based on the success of platinum-based therapy in patients with systemic GCT [62]. However, in a study conducted by the international CNS GCT study group, the survival rate was only 84% at 2 years with chemotherapy alone, suggesting that RT is required in some form [63]. To better define the optimal use of chemotherapy and RT for germinomas, the Children’s Oncology Group (COG) investigated upfront chemotherapy followed by RT for both germinomatous and non-germinomatous GCTs in a phase II trial for children and young adults. The RT dose was determined by response to chemotherapy and field determined by evidence of CNS dissemination. Low-risk patients were defined as those with pathology showing pure germinoma and normal αFP and β-HCG (β-HCG < 50 mIU/ml) in serum and CSF. These patients received four courses of etoposide and cisplatin alternating with cyclophosphamide and vincristine for a total of 12 weeks of chemotherapy. At 12 weeks, patients were evaluated for response with craniospinal MRI.

In low-risk patients with complete response, 30.6 Gy was given to the primary tumor site. In patients with less than complete response, 50.4 Gy was given to the primary site. In low-risk patients with central nervous system (CNS) dissemination, the primary site was treated with 30.6 or 50.4 Gy (based on response as above) and the neuroaxis was treated with 30.6 Gy in patients with complete response and 36 Gy in patients without response.

High-risk patients were defined as having tumors with mixed pathology or malignant variants or patients with elevated tumor markers in CSF and serum. The same agents were used as in the low-risk group (etoposide, cisplatin alternating with cyclophosphamide, vincristine), but with doubled doses of cisplatin and cyclophosphamide. For high-risk patients with complete response, the primary site received 50.4 Gy and the neuroaxis received 30.6 Gy. In patients who did not respond, the local radiation dose was 54 Gy and the neuroaxis was treated with 36 Gy.

With this approach, 11/12 germinoma patients were free from progression at 66 months. One patient with complete response (CR) to chemotherapy declined RT early, but received it at the time of recurrence with stable disease at 56 months follow-up. In the high-risk group (NGCTs), 2/14 patients had CR, 3 had partial response, and 7 had stable or unevaluable disease. At 58 months follow-up, 11/14 patients were free from progression. Two patients had progressive disease after chemotherapy and both died. In conclusion, 91% of patients with germinoma and 55% of NGCTs showed response with encouraging long-term responses [64].
Non-germinomatous Germ Cell Tumors

In contrast to the germinomas, NGCTs are far less radiosensitive. In a study of 216 patients treated with RT alone, the 5-year survival was only 30–40% [65]. Hence, RT is part of a multimodality approach to treat NGCTs, which includes neoadjuvant chemotherapy and surgical resection. Among 11 patients with NGCTs (yolk sac tumor, embryonal carcinoma, and immature teratoma) who received combined platinum-based chemotherapy and RT followed by surgical excision, a survival rate of 90% was observed at a mean of 96 months [66]. The international CNS GCT study group also showed promising results for NGCTs with multimodality therapy. NGCT patients were treated with two courses of cisplatin, etoposide, cyclophosphamide, and bleomycin (Regimen A). If the patients achieved CR, they were then treated with two courses of carboplatin, etoposide, and bleomycin (Regimen B) followed by an additional course of each regimen. For those patients not in CR, second-look surgery was followed by either RT or no RT. The overall 5-year survival and event-free survival were 75 and 45%, respectively [67]. Subsequently, the COG assessed the efficacy of chemotherapy followed by modified RT in patients with NGCTs based on response. As detailed above, patients received high-dose cisplatin and cyclophosphamide and standard-dose vincristine and etoposide alternating every 3 weeks for a total of 12 weeks. Based on response, patients were treated with high-dose or low-dose RT to the area of involvement (local or CNS dissemination). Of the 14 patients treated with this regimen, 11 children survived without a recurrence with a median follow-up of 58 months, including children who did not have gross total resection [64]. Collectively, these studies suggest that real progress has been made with the application of multimodality therapy in NGCTs, steadily improving both response and survival.

Unique to the NGCTs, mature teratomas can be cured with complete surgical resection [9, 35]. However, a mature teratoma is rare and is often part of a mixed GCT that may be composed of a germinoma as well as an immature teratoma. Following the resection of a mature teratoma, a complete histological analysis should be performed to ensure that there is no immature teratoma or other malignant components [68]. There is some debate whether adjuvant therapy is required for mature teratomas. Some groups support the use of adjuvant chemotherapy as a safeguard against potential sampling error during histopathologic analysis. Unfortunately, this method may also expose patients to harmful chemotherapeutic agents [68].

Treatment of Pineal Parenchymal Tumors

Pineocytomas

Surgery is first-line therapy for pineocytomas, which can be cured with radical resection, with or without adjuvant RT [7]. However, surgical resection of pineal parenchymal tumors remains a challenge due to their deep location and proximity
to critical structures. The role of RT remains poorly defined but is emerging. RT is delivered by either fractionated external beam radiation, Gamma Knife radiosurgery, or brachytherapy. Review of several small series suggests that there is no significant benefit to post-operative RT (in any form) for PC patients, as all patients have good long-term outcomes regardless of RT [7]. Exceptions to this rule are children diagnosed with PC or patients with an incomplete resection of their tumor or recurrent tumors. These patients may need post-operative RT [69, 70]. Nine patients with recurrent PC were treated with surgical resection followed by either Gamma Knife radiotherapy or conventional RT. Patients who underwent RT were stable or had reduced local disease at a follow-up of 19.3 months [69].

Some small retrospective studies have looked at radiosurgery as a primary treatment modality for pineocytomas. Among six patients with pineocytomas treated with radiosurgery alone and another two with radiosurgery following a partial resection, all were alive after a mean follow-up period of 32 months [71]. In a recent retrospective analysis, 13 patients with PC were treated with stereotactic radiosurgery as their primary therapy. These patients showed 1-, 3-, and 5-year survival of 100, 92.3, and 92.3%, respectively [72]. Although encouraging, findings from these retrospective analyses should be interpreted with caution as they are susceptible to various biases.

**Pineoblastomas**

Surgical resection of PBs plays a critical role in their treatment. First, tissue is important to confirm the tumor type. Second, surgery may relieve a symptomatic mass effect. Finally, surgical resection allows tumor debulking prior to RT and chemotherapy. Reports have shown that the 5-year survival rates for patients with all forms of PPT who underwent maximal surgical resection were 70% versus 30% in patients who had partial resections or biopsies [9]. In adult patients, there was 100% 10-year survival for adult patients with malignant PPT without residual disease compared to 40% for patients with minor residual disease and 15% for patients with major residual disease after treatment [41]. The greatest predictors of survival in adult patients with PB were degree of resection and RT. In a recent retrospective study of 11 pediatric patients (mean age 8 years 8 months) with PB, 3 had undergone gross total resection followed by chemotherapy and craniospinal RT. All three were alive after follow-up. The remaining eight underwent a subtotal resection or a biopsy followed by chemotherapy and RT. Of these patients, four of them are deceased and the remaining four are alive and free of disease [73]. Based on these reports, standard treatment for PBs consists of maximal resection followed by chemotherapy and RT.

Although RT is an essential part of PB management, these tumors are somewhat resistant to RT and hence higher doses are required. Moreover, these tumors have a high propensity for CSF shedding. Hence, it is standard of care to treat these tumors with upfront craniospinal RT following surgery. This is followed by adjuvant chemotherapy in virtually all cases. Craniospinal RT appears to prevent distant metastases and increase disease-free survival [41, 70, 74].
However, there is great concern for the long-term sequelae of craniospinal RT in children and hence, alternative treatments have been explored. Efforts to delay RT using upfront chemotherapy (cyclophosphamide, vincristine, cisplatin, and etoposide) in infants with PB had poor results, with all 11 patients progressing on chemotherapy and subsequently failing salvage RT [75]. Therefore, debate continues about the optimal approach for young pediatric patients with PB. In older children and adults, craniospinal RT with adjuvant chemotherapy is recommended for PB and PPTID [7].

As most PBs are chemosensitive, chemotherapy plays a central role in their treatment. The optimal regimen or timing of chemotherapy is still being investigated. Chemotherapeutic regimens that have been studied include single-agent cyclophosphamide or methotrexate and multidrug regimens containing two to eight drugs, such as etoposide, cisplatin, carboplatin, vincristine, and vinblastine [41, 70]. Similar to GCT, platinum-based therapies appear to have the best efficacy. Recent studies have focused on the use of high-dose chemotherapy in the form of various combinations of cyclophosphamide, melphalan, or busulfan followed by autologous stem cell rescue [76, 77]. Four of seven (57%) PB patients in a series of pediatric patients with recurrence responded to high-dose chemotherapy and autologous stem cell rescue. Another series reported even more promising results with 9 of 12 patients (75%) with PB achieving a median survival of 62 months [77]. As mentioned, upfront chemotherapy with delayed RT in infants with PB had 100% treatment failure [75]. Similarly, in a prospective trial, 11 children with PB were treated with chemotherapy followed by RT based on response. Five children older than 3 years were given ifosfamide, etoposide, methotrexate, cisplatin, and cytarabine followed by RT. Five out of six patients were still alive with a median overall survival of 7.9 years [78]. Children under 3 years of age were treated with three cycles of chemotherapy consisting of cyclophosphamide and methotrexate followed by methotrexate and vincristine and then etoposide, carboplatin, and methotrexate. Children who did not achieve remission were treated with additional chemotherapy if <18 months old or with RT if >18 months old. Unfortunately, all of these children died with a median overall survival of 0.9 years [78]. Hence, delayed RT has not yet proved successful in young children with PB. Current treatment of PPT requires surgery, RT, and adjuvant chemotherapy, but there is no evidence of any single agent being optimal for these tumors.

One new approach being explored is stereotactic radiosurgery as a primary treatment modality. In a recent retrospective study, seven patients with PB or mixed PPT underwent stereotactic radiosurgery. Their 1-year, 3-year, and 5-year survival were 85.7, 57.1, and 28.6%, respectively [72]. In another retrospective study, all four patients with PB died (range 7–56 months after diagnosis) when radiosurgery was used as an adjuvant or sole treatment for PB [79]. An alternative approach being studied is $^{125}$I brachytherapy. In a case study of two patients with PB, the patients were treated with CT and image fusion-guided $^{125}$I brachytherapy. There was no active tumor at 53 months and 56 months follow-up [80]. These approaches may increase the diversity of therapies available for PB, but their exact role in primary management has not yet been defined.
Pineal Parenchymal Tumors of Intermediate Differentiation

Pineal parenchymal tumors of intermediate differentiation are rare, and little is known about their treatment and management. One case report described the use of neoadjuvant chemotherapy and craniospinal radiotherapy as a treatment for PPTID. The patient survived 6 years after treatment without relapse [81]. Another report described a patient treated by surgical resection, followed by adjuvant Gamma Knife radiotherapy [82]. The patient was still alive at 1-year follow-up. A third reported patient had a partial resection of the tumor performed followed by adjuvant chemotherapy (carboplatin and etoposide) and linear accelerator radiosurgery. The patient was alive at 2 years follow-up [83]. These reports suggest that a multimodality approach may be effective for PPTID, but studies are needed to define the optimal treatment plan.

Pineal Gliomas

The optimal approach for the treatment of pineal region gliomas is still a matter of debate. Some authors support observation alone and only performing surgery if needed for management of hydrocephalus, as long as the tumors are small, localized to the tectal region, and do not have contrast enhancement [84, 85]. This approach has been explored in both adults and pediatric patients. In a study of ten pediatric patients with tectal tumors, the median progression-free survival was 6.5 years with management of hydrocephalus alone [45]. Other authors support surgical resection of the tumor followed by RT. Stereotactic biopsy is considered when there is a widely infiltrative tumor and a histological diagnosis is necessary [7]. Should the tumor invade beyond the tectum or becomes symptomatic, RT is considered appropriate therapy. However, radiographic assessment of this region of the brain is difficult, and radiographic growth does not always correlate with clinical symptoms. Hence, some experts believe that close observation alone is reasonable [44, 86]. Chemotherapy regimens can also be considered for tectal gliomas if RT is for some reason undesirable. Currently, there is little data on which chemotherapeutic agents are effective, but agents such as temozolomide and carmustine, which are partially active in gliomas elsewhere in the brain, could be explored in tectal gliomas [7]. When there is confirmed recurrent or progressing glioma, RT or chemotherapy is recommended.

Meningiomas

For meningiomas of the pineal region, surgical resection can provide definitive therapy. In a study that examined ten cases, all but one patient had stable disease without recurrence at 3 years follow-up after surgical resection [49].
**Ependymomas**

Surgery is the treatment of choice for ependymomas. The degree of resection is the main prognostic factor for survival. The next mode of treatment is currently heavily debated. Some experts advocate deferring radiotherapy until the tumor recurs, while some prefer to give adjuvant radiotherapy following tumor resection [87, 88].

**Conclusion and Future Directions**

Pineal region tumors are comprised of a diverse collection of tumors with varying clinical presentations, histologies, and prognoses. Evaluation of pineal gland tumors involves a combination of CSF analysis, imaging, and histological analysis. The utility of serum melatonin levels as a marker for pineal gland tumors has not been fully explored and deserves more attention in future studies as a potential marker of disease and response to therapy. Germinomas are a subtype of germ cell tumors that have a favorable prognosis due to their radiosensitivity. However, the optimal dose and volume of radiation remain a matter of debate. Chemotherapy may also be effective in treating germinomas; however, more studies are needed to find the optimal combination and timing of radiation with or without chemotherapy to prevent recurrences of germinomas in young and older children as well as adults. With the exception of mature teratomas, NGCTs have a poor prognosis even when treated with a multimodal approach. Identification of novel therapies for these tumors is required, but is difficult to study due to the relative rarity of NGCTs. PCs, which tend to have an excellent prognosis, are treated with surgical resection with or without RT. Some studies have shown that stereotactic radiosurgery may be an alternative to surgical resection, but prospective data are lacking. PBs follow a more malignant course and are treated using a multidisciplinary approach including surgery, chemotherapy, and RT. It is possible that advances in therapeutics specific to the underlying genetic mutations for medulloblastoma and retinoblastoma will also lead to new therapeutics for PB. In the interim, maximal surgical resection and rapid initiation of chemotherapy and RT are required for hopes of favorable outcomes.

In conclusion, tumors of the pineal region are rare and require detailed and thoughtful diagnostic procedures including MRI of the neuraxis, CSF, and serum studies and in most cases, tissue sampling for histology. Effective treatment strategies that better match the risk of toxicity to degree of disease have been established for germinoma, the most common pineal region tumor. Advances are being made in improving both response and survival in the most threatening of the pineal region tumors including NGCTs and PBs. However, these tumors remain very difficult to treat in the youngest patients and gains are needed in effective therapies with fewer long-term sequelae.

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References

Chapter 20
Genetic Syndromes

Mikael L. Rinne and Scott R. Plotkin

Keywords
Brain tumor · Genetic syndrome · Neurofibromatosis 1 · Neurofibromatosis 2 · Tuberous sclerosis · Von Hippel–Lindau syndrome · Cowden syndrome · Hemangioblastoma · Li–Fraumeni syndrome · Gorlin syndrome · Turcot syndrome

Introduction

Nervous system tumors most often arise sporadically, but in rare cases tumor formation is the result of inherited cancer predisposition. A diverse group of familial syndromes with multi-organ involvement is recognized to impart an increased risk for the development of benign and malignant tumors of the central and peripheral nervous systems (Table 20.1). These tumor predisposition syndromes are generally inherited in an autosomal dominant fashion with high penetrance and variable expressivity. The majority result from an inactivating germline mutation in a tumor suppressor gene. A subsequent somatic mutation leads to tissue-specific tumor formation in accordance with Knudson’s “two-hit” hypothesis [1].

Though inherited syndromes only underlie a minority of nervous system tumors, insights gained from these disorders have led to an understanding of the molecular pathways involved in tumorigenesis. This knowledge has shed light on the etiology and behavior of sporadic tumors and has set the stage for the development of molecularly targeted cancer therapeutics.

The recognition of these syndromes can be challenging because of their marked variability and multi-organ presentation. The diagnosis should be considered in patients presenting with multiple tumors, particularly at a young age or when there is a strong family history of cancer. Establishing the diagnosis of a tumor predisposition syndrome is important in order to initiate directed tumor screening.

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Table 20.1  Summary of clinical features associated with tumor predisposition syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
<th>Mutation</th>
<th>Nervous system tumor</th>
<th>Other common features</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF1</td>
<td>Dominant</td>
<td>17q11.2 Neurofibromin</td>
<td>Neurofibromas</td>
<td>Café-au-lait macules</td>
</tr>
<tr>
<td></td>
<td>50% sporadic</td>
<td></td>
<td>Gliomas (OPG, brainstem, hemispheres)</td>
<td>Skin-fold freckling</td>
</tr>
<tr>
<td></td>
<td>1/3,000</td>
<td></td>
<td></td>
<td>Lisch nodules</td>
</tr>
<tr>
<td>NF2</td>
<td>Dominant</td>
<td>22q12.2 Merlin</td>
<td>Schwannomas (CNVII)</td>
<td>Juvenile cataracts</td>
</tr>
<tr>
<td></td>
<td>50% sporadic</td>
<td></td>
<td>Meningioma</td>
<td>Epiretinal membranes</td>
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<tr>
<td></td>
<td>1/25–40,000</td>
<td></td>
<td>Spinal ependymoma</td>
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<td></td>
<td></td>
<td>Spinal astrocytoma</td>
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<tr>
<td>Tuberous sclerosis</td>
<td>Dominant</td>
<td>9q34 Hamartin</td>
<td>Cortical tubers</td>
<td>Facial angiofibromas</td>
</tr>
<tr>
<td></td>
<td>2/3 sporadic</td>
<td>16p13.3 Tuberin</td>
<td>Subependymal nodules</td>
<td>Shagreen patch, Ash leaf</td>
</tr>
<tr>
<td></td>
<td>1/6,000</td>
<td></td>
<td>SEGA</td>
<td>Ungul fibromas</td>
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<td>Lymphangiomiyomatosis</td>
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<td>Renal angiomiyolipoma</td>
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<td></td>
<td></td>
<td>Cardiac rhabdomyoma</td>
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<tr>
<td>Von Hippel–Lindau</td>
<td>Dominant</td>
<td>3p25 pVHL</td>
<td>Hemangioblastoma</td>
<td>Retinal hemangioblastoma</td>
</tr>
<tr>
<td></td>
<td>20% sporadic</td>
<td></td>
<td></td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>1/40,000</td>
<td></td>
<td></td>
<td>Pheochromocytoma</td>
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<td></td>
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<td></td>
<td></td>
<td>Endolymphatic sac tumor</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>Dominant</td>
<td>10q23 PTEN</td>
<td>Lhermitte–Duclos disease</td>
<td>Trichilemmomas</td>
</tr>
<tr>
<td></td>
<td>1/200,000</td>
<td></td>
<td></td>
<td>Breast, endometrial, and thyroid cancer</td>
</tr>
<tr>
<td>Li–Fraumeni syndrome</td>
<td>Dominant</td>
<td>17p13.1 P53</td>
<td>Astrocytoma, Medulloblastoma, PNET, Neuroblastoma</td>
<td>Breast cancer</td>
</tr>
<tr>
<td></td>
<td>Very rare</td>
<td></td>
<td></td>
<td>Sarcoma</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adrenocortical carcinoma</td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>Variable</td>
<td>APC/ mismatch</td>
<td>Medulloblastoma, Astrocytoma, Ependymoma</td>
<td>Colorectal polyposis (FAP/HNPCC)</td>
</tr>
<tr>
<td></td>
<td>Dominant/ recessive</td>
<td>repair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>Dominant</td>
<td>9q22.3 PTCH1</td>
<td>Medulloblastoma, Dural calcification, Medulloblastoma, Meningioma</td>
<td>Basal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>50% sporadic</td>
<td></td>
<td></td>
<td>Jaw cysts, Rib abnormalities</td>
</tr>
<tr>
<td></td>
<td>1/60,000</td>
<td></td>
<td></td>
<td>Dural calcification</td>
</tr>
</tbody>
</table>

CNVII, cranial nerve 7; FAP/HNPCC, familial adenomatous polyposis/hereditary non-polyposis colon cancer; MPNST, malignant peripheral nerve sheath tumor; NF1, neurofibromatosis type I; NF2, neurofibromatosis type 2; OPG, optic pathway glioma; PNET, primitive neuroectodermal tumor; SEGA, subependymal giant cell astrocytoma.

and enable early detection. Recognizing these syndromes is also important for selecting the appropriate therapy and for prognostication, both of which often differ from sporadic tumors. Finally, the diagnosis of these syndromes is important for providing genetic counseling regarding the risk to family members and the approach
to family planning, including the possibility of preimplantation genetic diagnosis [2, 3].

This chapter discusses the most common inherited tumor predisposition syndromes affecting the nervous system, including neurofibromatosis 1 (NF1) and 2 (NF2), von-Hippel–Lindau (VHL) disease, tuberous sclerosis complex (TSC), Cowden syndrome (CS), Li–Fraumeni syndrome (LFS), Turcot syndrome (TS), and Gorlin syndrome (GS). The focus here is on the neuro-oncological aspects of these syndromes, with an emphasis on the clinical features and management of associated nervous system tumors.

Neurofibromatosis

Overview

Neurofibromatosis (NF1), previously known as von Recklinghausen’s disease or peripheral neurofibromatosis, is a multisystem genetic disorder associated with an increased risk of developing both benign and malignant tumors. It is caused by a constitutional mutation in the \( NF1 \) gene on the long arm of chromosome 17 (17q11.2). Typical clinical manifestations include skin lesions (café-au-lait macules, intertriginous freckling), ocular findings (Lisch nodules), musculoskeletal abnormalities (bony dysplasia, scoliosis, short stature), nervous system tumors (neurofibromas, malignant peripheral nerve sheath tumors (MPNSTs), pilocytic astrocytomas), and non-nervous system tumors (leukemias, gastrointestinal stromal tumors, and pheochromocytomas).

Epidemiology

With an estimated prevalence of about 1 in 3,000 individuals, NF1 is one of the most common inherited disorders affecting the nervous system and the most common known cancer predisposition syndrome [4]. It occurs equally between males and females in all populations without clear differences among ethnic groups.

Clinical Genetics

The disease is inherited in autosomal dominant fashion with complete penetrance; importantly, it has highly variable expressivity within and between families. About half of patients have a discernable family history of NF1; the other half represent de novo cases apparently resulting from new germline mutations. This new mutation rate represents one of the highest described in humans (estimated to be as high as 100 times greater than most other genes) [5].
**Molecular Genetics and Pathogenesis**

**NF1, Neurofibromin**

NF1 is caused by an inactivating mutation in *NF1*, a large gene that contains 60 exons and spans more than 350 kb on chromosome 17q11.2 [6, 7]. *NF1* encodes neurofibromin, a 2,818-amino acid cytoplasmic protein that functions as a negative growth regulator or tumor suppressor. Neurofibromin contains a GTPase-activating protein (GAP) domain which negatively regulates the RAS oncogene by accelerating its conversion from an active (GTP-bound) form to an inactive (GDP-bound) form. Mutations in *NF1* therefore lead to increased RAS activation which inhibits apoptosis and stimulates cell proliferation through the activation of a series of signaling cascades including the RAF–MEK–ERK [8], Rho–ROCK–LIMK2 [9], and phosphoinositide-3-kinase–Akt–mammalian target of rapamycin (PI3K–Akt–mTOR) pathways [10, 11]. The result is increased cell growth and the development of a range of tumors.

**Mutations**

*NF1* is a classic tumor suppressor gene and behaves in accordance with Knudson’s hypothesis: a single mutation is inherited and present in all cells (i.e., a constitutional mutation), while a subsequent mutation within a specific tissue (i.e., a somatic mutation) leads to tumorigenesis [1]. Mutations representing this “second hit” have been confirmed in benign and malignant tumors associated with NF1 [12–19].

A large number of different constitutional mutations have been demonstrated in NF1, and there is no predilection for any single portion of the gene. Mutation types include insertions, deletions, and point mutations that lead to nonsense, missense, frameshift, or splice-site errors. No clear genotype–phenotype correlation exists except in rare patients with an *NF1* microdeletion (which results in a more severe form of the disease with a heavy burden of cutaneous neurofibromas and an apparent elevated risk of MPNST) [20] or in the case of a specific three basepair deletion in exon 17 (which results in a milder form without clinically detectable neurofibromas and with a lower incidence of serious complications) [21]. The lack of overall genotype–phenotype correlation has led to the hypothesis that the manifestations of NF1 may be modified by the microenvironment [22] or other genes [23].

**Genetic Testing**

Despite the large size of the *NF1* gene and the large number of possible mutations, genetic testing can be performed through a series of complimentary techniques that have been able to detect germline mutations in up to 95% of individuals who meet clinical criteria for diagnosis of NF1 [24]. The lack of strict genotype–phenotype correlation means that testing cannot predict an individual patient’s clinical course. Instead, molecular testing is used to assist families who wish to have prenatal or preimplantation genetic diagnosis. Molecular testing is not indicated to confirm a diagnosis in individuals who meet clinical criteria.
**Clinical Features**

**Diagnostic Criteria**

NF1 is marked by characteristic cutaneous, ophthalmologic, musculoskeletal, and neurologic lesions. Several benign manifestations of the disorder can aid in establishing the diagnosis, which identifies patients at risk for the development of a number of malignancies. The diagnosis of NF1 is based on clinical criteria initially established by the National Institutes of Health (NIH) Consensus Development Conference on Neurofibromatosis in 1987 and subsequently revisited in 1990 and 1997 [25, 26]. The diagnostic criteria require that two of the following seven cardinal features of the disorder be present in order to establish a diagnosis of NF1: (1) six or more café-au-lait macules (≥ 5 mm in prepubescent individuals and ≥ 15 mm in post-pubescent ones), (2) intertriginous freckling, (3) two or more Lisch nodules (iris hamartomas), (4) two or more neurofibromas or one plexiform neurofibroma, (5) an optic pathway glioma, (6) distinctive bony abnormalities such as sphenoid wing or long bone dysplasia, or (7) a first-degree relative with NF1.

**Developmental Expression of Phenotype**

The clinical features of NF1 increase with age, the typical order of appearance being café-au-lait macules (99% of children by 1 year), osseous lesions (14% within the first year), symptomatic optic pathway gliomas (4% by age 3), intertriginous freckling (90% by 7 years), Lisch nodules (>70% by 10 years), and neurofibromas (84% by 20 years) [27]. By 1 year of age, 70% of children with NF1 meet diagnostic criteria, and this increases to 97% by age 8 and 100% by age 20. Because of the age-related appearance of symptoms, the current criteria may not confirm the diagnosis in young children [27]. This scenario is common in children with multiple café-au-lait macules but no family history. These children are typically followed in clinic to document the emergence of diagnostic criteria. Several other features have been proposed as additions to the diagnostic criteria for pediatric patients, including macrocephaly, short stature, and T2-hyperintense lesions on magnetic resonance imaging (MRI), but these criteria have not been formally adopted. Other clinical features of NF1 include a high incidence of learning disabilities and attention-deficit hyperactivity disorder (ADHD), cardiovascular abnormalities such as pulmonary artery stenosis and congenital heart disease as well as vasculopathies (particularly renal artery stenosis).

**Associated Tumors**

**Neurofibromas**

Neurofibromas are the most common tumors in NF1 and its hallmark feature. These tumors are benign Schwann cell neoplasms that arise from the nerve sheath surrounding peripheral nerves and are composed of Schwann cells, perineural cells, fibroblasts, and mast cells within a collagenous extracellular matrix. Clinically
and histologically, several distinct neurofibroma subtypes occur in NF1. Dermal or cutaneous neurofibromas are most common; they typically appear around puberty and increase in number thereafter, ranging from a few to thousands. They can occur anywhere on the body (particularly on the trunk), but seldom cause pain or other deficits. Multiple dermal neurofibromas are characteristic of NF1, but these tumors do not undergo malignant transformation. Nodular or subcutaneous neurofibromas arise from deeper peripheral nerves and can be associated with pain, paresthesias, or sensory symptoms. These neurofibromas can involve spinal nerve roots and occasionally grow into the spinal canal resulting in a characteristic “dumbbell” shape on imaging studies and a risk of myelopathy (Fig. 20.1a). Plexiform neurofibromas occur in at least 30% of NF1 patients and are thought to be congenital. They arise from multiple nerve fascicles and grow along the length of nerves, often invading surrounding tissue and resulting in disfiguration, regional neurologic dysfunction, and significant pain. Unlike dermal neurofibromas, subcutaneous andplexiform neurofibromas can undergo malignant transformation to form MPNSTs [26].

Fig. 20.1 Common tumors associated with neurofibromatosis type 1 (NF1). (a) Coronal fast spin echo inverse recovery (FSEIR) image of a patient with NF1. Spinal neurofibromas (arrows) are often bilateral and affect multiple levels; cord compression is uncommon even in patients with a heavy tumor burden. (b) Coronal post-contrast T1-weighted image showing an optic pathway glioma (arrow) affecting the optic chiasm

Malignant Peripheral Nerve Sheath Tumors (MPNSTs)

MPNSTs are the most common malignant tumors in NF1 [28], occurring in approximately 10% of patients during their lifetime [29]. MPNSTs most often occur in the setting of NF1 [30–32] and most arise within pre-existing plexiform neurofibromas and/or in areas of prior radiation exposure. Patients typically present with pain, neurologic deficit, or rapid changes in plexiform neurofibromas. MPNSTs are
highly malignant tumors with metastatic potential and poor overall prognosis that appear to be worse in NF1 than in sporadic cases. The 5-year overall survival for NF1 patients with MPNST is 21% [29].

**Gliomas**

Patients with NF1 are predisposed to the development of glial tumors [33]. These tumors are most common in children with NF1, but even in older patients, the relative risk of brain tumor has been estimated to be 100 times higher than in patients without NF1 [34]. Gliomas in NF1 are typically pilocytic astrocytomas (WHO grade 1) that infrequently progress; however, high-grade gliomas do occur in adults and are associated with poorer prognoses [35]. It is estimated that two-thirds of gliomas in NF1 arise in the optic pathway, making pilocytic astrocytomas of the optic pathway or optic pathway gliomas (OPGs) the most common associated CNS tumors (estimated to occur in 15–20% of NF1 patients) (Fig. 20.1b). The majority of OPGs are seen in NF1 and are so characteristic of the disease that any child found to have an OPG should undergo evaluation for NF1. Most arise in the first 6 years of life [36], though they may occur in older children and adults [34]. OPGs are most frequently prechiasmatic in NF1 and only rarely involve the optic radiations [37] whereas sporadic tumors occur more often at or posterior to the optic chiasm and more frequently extend into the hypothalamus or outside the optic pathway [38, 39].

About one-third of NF1 patients with OPGs are symptomatic [40]. Symptoms depend on tumor location along the optic pathway and include visual field deficits, loss of visual acuity, diplopia, proptosis, and precocious puberty. OPGs arising in the setting of NF1 exhibit a more indolent course than sporadic tumors [35, 41]. They rarely progress, even when symptomatic, and may even regress spontaneously [42–44].

Gliomas also occur with increased frequency in the brainstem, diencephalon, and cerebellum in patients with NF1 [45]. These brain tumors can be of various grades and histologies, and though most are low grade [46], as a group they have a poorer prognosis than tumors arising in the optic pathway [35].

**Management**

The multisystem effects of NF1 require a multidisciplinary approach to patients with the disorder, including the involvement of specialists from neurology, neurosurgery, dermatology, ophthalmology, and orthopedic surgery. Examination and testing should be directed to detect potential medical complications that arise in NF1 including learning disabilities, ADHD, scoliosis, focal neurologic deficits, pain, and hypertension (due to underlying renal artery stenosis or rarely pheochromocytoma) [26]. Because of the predisposition to malignancy, an important component in the management of NF1 is the screening, detection, and treatment of malignant tumors. Despite current screening, diagnosis, and treatment, the life expectancy
of patients with NF1 is 10–15 years shorter than that of unaffected patients, and malignant tumors are one of the major reasons for this increased mortality [47]. Current treatment for NF1-associated benign and malignant tumors remains primarily surgical; however, ongoing research and improved understanding of the underlying molecular mechanisms involved in the pathogenesis of NF1 are now leading to the investigation of targeted molecular therapies.

**Neurofibromas**

Asymptomatic neurofibromas should be followed conservatively. Cutaneous or subcutaneous neurofibromas causing pain or disfigurement can be surgically removed. Similarly, symptomatic plexiform neurofibromas are often treated with surgery, but their size, vascularity, extensive nerve plexus involvement, and diffusely infiltrating nature often precludes complete resection. Because of the risk of malignant transformation, there has been debate about early removal of plexiform neurofibromas, but this decision should be approached cautiously considering the risk of post-operative neurologic deficits. However, in cases where there is concern for malignant transformation to MPNST, prompt investigation and treatment are necessary.

**MPNSTs**

1. Screening

Most MPNSTs arise from pre-existing plexiform neurofibromas. However, transformation to MPNST is difficult to predict and detect. The diagnosis is further complicated by the possibility that as many as one-third of MPNSTs may arise in NF1 patients without a previous history of plexiform neurofibroma [48]. Patients with MPNSTs commonly present with the subacute development of unexplained pain, new neurologic deficits, and changes in plexiform neurofibroma consistency or size. Current clinical practice is to monitor for these clinical signs of MPNST. MRI is able to characterize the site, extent, and growth of plexiform neurofibromas, but has unfortunately, been unable to reliably recognize malignant transformation [49]. Still, some MR characteristics may help to distinguish MPNSTs from benign plexiform neurofibromas [50], and FDG-PET has been identified as a sensitive and specific method for distinguishing MPNSTs from their benign precursors [51–54].

2. Treatment

MPNSTs are treated with attempted wide surgical excision, including consideration of amputation for extensive or recurrent tumor when necessary [49]. Adjuvant radiotherapy provides local control and delays recurrence but does not prolong survival. It is offered for intermediate-grade and high-grade lesions or subtotally resected low-grade lesions. Chemotherapy is controversial and is typically reserved for metastatic disease. Treatment with doxorubicin with or without ifosfamide has been used although no formal studies have been performed in NF1 patients. In spite of aggressive surgical and medical therapies, prognosis of these highly aggressive tumors is quite poor with overall 5-year survival rates as low as 20% [29].
Glioma

1. Screening

Because OPGs only rarely progress and are often asymptomatic [36], the primary concern is for tumors that produce symptoms. Full ophthalmologic exams by an ophthalmologist familiar with NF1 should be performed annually between the ages of 2 and 7. Any unexplained ophthalmologic abnormality should prompt an MRI of the brain and orbits. Similarly, children should be monitored for growth and pubertal development in order to identify signs of precocious puberty which should prompt imaging to look for OPG involving the hypothalamus. Routine screening of asymptomatic children with computed tomography (CT), MRI, electroencephalography (EEG), and visual-evoked potentials is not warranted.

2. Treatment

Because the natural history of OPGs can be unpredictable, deciding whether and when to initiate treatment can be difficult. Symptomatic OPGs should initially be followed clinically and radiographically with treatment reserved for those tumors that produce progressive ocular or endocrinologic signs or have concerning radiographic progression [33].

The optimal treatment for NF1 patients with progressive symptomatic OPGs is an area of ongoing debate, and individualized treatment approaches depend on patient age, tumor size, location, and growth rate. Surgical excision should be reserved for progressive tumors causing proptosis or pain in an eye without usable vision.

Radiation therapy is highly effective for sporadic OPGs, resulting in upward of 80–90% local control [55–57]. In NF1 patients, radiation is typically omitted from upfront therapy due to increased toxicity including cognitive dysfunction, endocrinologic disturbances, moy-a-moya syndrome, and secondary malignancies [33, 58]. There may be a role for fractionated stereotactic radiotherapy in the future [59], but this approach requires further study.

Chemotherapy for NF1-related OPG is associated with up to an 89% 5-year survival [60]. Current first-line treatment consists of carboplatin and vincristine [61]. Temozolomide (alone or in multidrug combinations) may be beneficial [62, 63], though there is concern about the possibility of secondary malignancies following treatment with alkylating agents.

Asymptomatic gliomas outside the optic pathway should be followed serially by MRI without intervention. Rapid tumor growth or clinical deterioration should prompt surgical biopsy to determine tumor grade and consideration of treatment. Treatment of low-grade tumors is similar to sporadic cases, though some clinicians postpone radiation therapy to avoid the complications outlined above. High-grade tumors are treated similarly to sporadic tumors with excision, radiation, and chemotherapy.

Future Directions

Improved understanding of the function of neurofibromin has led to the consideration of targeted therapies to block the signaling pathways responsible for tumor formation in NF1. Because neurofibromin inactivates RAS, the RAS pathway has...
been proposed as a target for drug therapy. Farnesyltransferase inhibitors and 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (statins) inhibit RAS translocation that is necessary for downstream signaling, and these are being studied in NF1 [64]. A phase 1 study of the RAS inhibitor tipifarnib in pediatric patients with refractory solid tumors or NF1 plexiform neurofibromas showed no evidence of tumor activity [65]. Downstream effectors of RAS including the mTOR pathway are also being considered as targets for treatment, and mTOR inhibitors such as rapamycin have shown efficacy in preclinical NF1 models [66–68]. The mTOR inhibitors sirolimus and everolimus (RAD001) are currently being studied for treatment of plexiform neurofibromas and optic pathway gliomas in NF1. The vascular and cellular support of NF1 neurofibromas are being targeted with vascular endothelial growth factor receptor (VEGFR) inhibitors [69], thalidomide [70], and antifibrotic agents [71]. As research improves our understanding of how neurofibromin regulates cell growth, therapies can be developed that target the predisposition to benign and malignant tumor formation in NF1.

Neurofibromatosis

Overview

NF2, previously known as central neurofibromatosis, is characterized by a predisposition for developing multiple nervous system tumors including schwannomas, meningiomas, and spinal cord gliomas. The average age of symptom onset is between 17 and 21 and typically precedes the diagnosis of NF2 by 5–8 years. Features of eighth nerve dysfunction from vestibular schwannomas (deafness, tinnitus, or imbalance) are the most common presenting symptoms in adults, but occur in only a minority of pediatric patients. In younger patients, presenting signs include cranial nerve dysfunction, peripheral nerve dysfunction, myelopathy, seizures, skin tumors, café-au-lait macules, and juvenile cataracts.

Epidemiology

NF2 has a birth incidence of 1 in 25,000 to 1 in 40,000 people [72]. It occurs equally between males and females in all populations without clear differences among ethnic groups.

Clinical Genetics

NF2 is transmitted in autosomal dominant fashion with complete penetrance. Like NF1, about half of all patients have de novo mutations with clinically unaffected parents. Expression is variable in unrelated patients, although the disease course tends to be somewhat similar within families. Approximately 25% of founders with bilateral vestibular schwannomas are mosaic for their mutation.
Molecular Genetics and Pathogenesis

The $\text{NF2}$ gene was initially mapped to chromosome 22 in 1987 [73, 74] and then identified in 1993 [75, 76]. The $\text{NF2}$ gene is composed of 17 exons spanning 110 kb. There are three alternative messenger ribonucleic acid (mRNA) species (7, 4.4, and 2.6 kb) that result from variable length of the 3′-untranslated region. The predominant $\text{NF2}$ gene product is a 595-amino acid protein termed “Merlin” (moesin, ezrin, radixin-like protein) because of its relationship with various cytoskeletal proteins. Merlin links membrane-associated proteins to the actin cytoskeleton, thereby acting as an interface with the extracellular environment [77].

Mutations

The NF2 protein acts as a true tumor suppressor, so that inactivation of both copies of the gene leads to tumor growth. Inactivating mutations of the $\text{NF2}$ gene can be detected in the vast majority of sporadic vestibular schwannomas [78] and in 50–60% of sporadic meningiomas.

Genetic Testing

Comprehensive mutational analysis of the $\text{NF2}$ gene identifies a causative mutation in about 70% of founders and in 90% of individuals with a family history of NF2. The presence of large deletions, mutations in promoter or intronic regions, and somatic mosaicism contributes to the difficulty in identifying a mutation in all patients. As with NF1, genetic testing is not used to confirm a clinical diagnosis of NF2, but can be used for genetic counseling and family planning.

Clinical Features

Diagnostic Criteria

Clinical criteria for the diagnosis of NF2 were first formulated at the National Institutes of Health (NIH) Consensus Conference in 1987 and revised in 1991. Under NIH criteria, a diagnosis of NF2 is based on either (1) the presence of bilateral vestibular schwannomas or (2) a family history of NF2 and either a unilateral vestibular schwannoma or any two other tumors typically associated with NF2 [25, 79]. According to these criteria, only patients with bilateral vestibular schwannomas or a family history can qualify for a diagnosis of NF2. Patients who do not meet these criteria but have multiple features associated with NF2 represent a diagnostic dilemma that led to the proposal of revised criteria in 1992 and in 1997, though the use of these criteria continue to be debated by researchers.
Associated Tumors

Vestibular schwannomas (VSs) invariably develop in patients with NF2 and are the hallmark of the disorder (Fig. 20.2a), though schwannomas involving non-vestibular cranial nerves and spinal nerves are also common. NF2-related schwannomas are histologically benign, but MPNSTs may arise in patients who have received prior radiation therapy. About 50% of patients with NF2 develop intracranial meningiomas (Fig. 20.2b). Though these tumors are usually histologically benign, meningiomas involving the optic sheath occur in 4–8% of NF2 patients and are a disproportionate cause of decreased visual acuity. Spinal ependymomas and astrocytomas occur in up to 53% of NF2 patients, and two-thirds of those with ependymomas have multiple tumors. The cervicomedullary junction or cervical spine are most commonly affected (63–82%) followed by the thoracic spine (36–44%). The brain and lumbar spine, which are common sites for sporadic tumors, are rarely involved. Radiographic evidence of tumor progression occurs in less than 10% of patients and progressive neurologic dysfunction requiring surgical intervention occurs in only 12–20% of patients.

![Post-contrast cranial magnetic resonance imaging (MRI) of a patient with NF2.](image)

**Fig. 20.2** Post-contrast cranial magnetic resonance imaging (MRI) of a patient with NF2. (a) Bilateral vestibular schwannomas (VSs) are the hallmark of NF2 (arrows). VSs arise from the vestibular portion of the eighth cranial nerve and grow into the cerebellopontine angle. (b) Cranial meningiomas (arrows) are a major source of morbidity and mortality for NF2 patients.

Management

Initial Evaluation

Initial evaluation of patients with a new diagnosis of NF2 or those who are at risk for NF2 should include testing to confirm the diagnosis and to identify potential complications. Medical history should include questions about auditory and vestibular function, focal neurologic symptoms, skin tumors, seizures, headache, and vision.
Family history should explore unexplained neurological and audiological symptoms in all first-degree relatives. MR imaging of the brain should be obtained with gadolinium as well as axial and coronal thin cuts (3-mm thickness) through the internal auditory canal (IAC) to look for vestibular schwannomas. MRI of the cervical spine should be performed because of the predilection of ependymomas for this region of the spinal cord. Some clinicians recommend imaging the thoracic and lumbar spine while others reserve these exams for patients with neurologic symptoms referable to these locations. Ophthalmologic examination should be performed to identify characteristic lesions such as lens opacities, retinal hamartomas, or epiretinal membranes. A complete neurological examination serves to establish a baseline for future comparison and may assist in the selection of sites within the nervous system that require imaging. Audiology (including pure tone threshold and word recognition) measures hearing function and documents a baseline for future comparison.

Subsequent Evaluation

After initial diagnosis, patients should be followed closely (every 3–6 months) until the growth rate and biologic behavior of NF2-related tumors are determined. Consultation with an experienced surgeon after initial diagnosis is often helpful for presymptomatic patients to discuss the feasibility of hearing-sparing surgery. Most patients without symptoms can be followed on an annual basis. Evaluation of these follow-up visits should include complete neurological examination, MRI of the brain with thin cuts through the IAC, MRI of symptomatic lesions outside the brain if present, and audiology. Ophthalmologic evaluation should be performed in selected patients with visual impairment or facial weakness. Yearly audiology serves to document changes in pure tone threshold and word recognition. This information can be helpful in planning early surgical intervention for vestibular schwannomas and in counseling patients about possible deafness. The frequency with which routine spinal imaging is obtained varies among clinics, but is clearly indicated in patients with new or progressive symptoms referable to the spinal cord.

The approach to the management of NF2-associated tumors differs from that of sporadic tumors. Surgery is the mainstay for treatment of NF2-related tumors, but the removal of every lesion is not possible or advisable. The primary goal is to preserve function and maximize quality of life. Surgery is clearly indicated for patients with significant brainstem or spinal cord compression or with obstructive hydrocephalus, while patients with little or no neurologic dysfunction from their tumors can be managed conservatively with observation in an attempt to preserve neurologic function for as long as possible [80]. Indications for surgical resection in other cases are less well defined.

In general, non-vestibular cranial nerve schwannomas are slow growing and produce few symptoms. Surgical resection in these patients should be reserved for those with unacceptable neurologic symptoms or rapid tumor growth. Patients with meningiomas typically have more than one tumor and resection of all lesions is often not advisable. The benefit of surgery must be carefully weighed against
potential complications. As a general rule, indications for resection include rapid
tumor growth and worsening neurologic symptoms. Intervention for spinal
cord tumors is necessary only in a minority of patients [81]. Surgery is more often
required in patients with extramedullary tumors (59%) than for intramedullary
tumors (12%) [82].

Radiation is often used as adjuvant therapy for treatment of sporadic brain
tumors. Treatment outcomes for patients with NF2-related vestibular schwannomas
are worse than for patients with sporadic tumors [83]. More recently, fractionated
stereotactic radiotherapy has been advocated to minimize the risk of hearing loss.
The actuarial 5-year local control rate using this technique is 93% and the hearing-
preservation rate is 64% [84]. The role of adjuvant radiation in other tumors such as
meningiomas and ependymomas is not established but the majority of these tumors
are histologically benign and can be controlled surgically. No case series have been
published on treatment of NF2-related meningiomas.

Most clinicians prefer surgical extirpation of tumors when possible and reserve
radiation treatment for tumors that are not surgically accessible. This practice
is based on the experience that radiation therapy makes subsequent resection of
vestibular schwannomas and function of auditory brainstem implants more difficult
[85]. In addition, there are reports of malignant transformation of NF2-associated
schwannomas after radiation treatment and indirect evidence of increased number
of malignancies in NF2 patients who have received radiation [86, 87].

**Future Directions**

Recognizing that increased levels of VEGF and its receptor correlate with schwan-
noma growth rate, a recent study investigated the activity of anti-VEGF monoclonal
antibody treatment for progressive vestibular schwannomas in a small group of
patients with NF2 [88]. Results demonstrated that bevacizumab treatment led
to clinically meaningful improvement in hearing and/or reduction in vestibular
schwannoma tumor volume in some NF2 patients. This study raises the possibility
of an effective medical therapy for vestibular schwannomas in patients with NF2 and
opens the door to further study of targeted treatments for NF2-associated tumors.

**Tuberous Sclerosis Complex**

**Overview**

Tuberous sclerosis complex (TSC) is a neurogenetic syndrome characterized by
hamartomatous and tumorous changes involving the nervous system, skin, and
visceral organs. The nervous system is most commonly affected; lesions include
cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas
(SEGAs) [89, 90].
Epidemiology and Clinical Genetics

TSC is the second most common genetic tumor syndrome after NF1, occurring approximately once every 6,000 live births without predilection for either sex or race [91]. It has autosomal dominant inheritance, high penetrance (80–95%), and variable expressivity. Causative mutations have been demonstrated in either one of two distinct genes, \textit{TSC1} and \textit{TSC2}, and at least half of cases appear to be due to \textit{de novo} mutations.

Molecular Genetics and Pathogenesis

\textit{TSC1} is located on chromosome 9q34 and encodes the protein Hamartin, while \textit{TSC2} resides on chromosome 16p13 and encodes for Tuberin. These two gene products associate to form a heterodimer which regulates cell cycle progression by inhibiting mTOR. The mTOR pathway plays an important role in cell growth and proliferation through the regulation of ribosome biosynthesis and protein translation. A wide variety of mutations in either \textit{TSC1} or \textit{TSC2} can impair the ability of the complex to inactivate mTOR, resulting in unregulated cell growth. In addition, \textit{TSC1} and \textit{TSC2} have been implicated in mTOR-independent pathways that may contribute to tumor formation. Inactivation of either gene leads to aberrant cellular differentiation, proliferation, and neuronal migration that underlie the TSC phenotype. Though no strict correlation exists between specific mutations and clinical outcome [92], nearly 70% of sporadic cases involve a new mutation in \textit{TSC2}, which often leads to more severe manifestations of the disease [93, 94].

Clinical Features

Presentation

Historically, TSC was diagnosed based on Vogt’s triad of seizures, mental retardation, and facial angiofibromas. However, it is now clear that because of variable expressivity, this complete triad is only found in about one-third of patients. Approximately 85% of children and adolescents with TSC have nervous system manifestations, with seizures and cognitive disability being the most common [95, 96]. However, because lesions arise in multiple organs, TSC can present with a wide array of symptoms referable to dermatologic, ophthalmologic, and nervous systems as well as several visceral organs, with symptoms generally becoming evident in early childhood.

Diagnostic Criteria

Despite variability in its presentation, TSC remains principally a clinical diagnosis. Diagnostic criteria were proposed at the NIH Tuberous Sclerosis Complex
A consensus Conference in 1998 [97]. Characteristic features of the disease were designated as major criteria for the diagnosis, and additional minor criteria were selected to establish the diagnosis in patients with only one characteristic lesion. Two major features or a major feature and two minor features are necessary to make the diagnosis of TSC. Major features include several distinctive skin lesions [98] including hypopigmented macules (“ashleaf spots”), acne-like facial angiofibromas, flesh-colored ungual or periungual fibromas, raised fibrous forehead plaques, and roughly-textured shagreen patches. The other major criteria include characteristic nervous system manifestations, namely, cortical tubers, subependymal nodules, and SEGAs, as well as ocular and visceral hamartomas including retinal nodular hamartomas, cardiac rhabdomyomas, pulmonary lymphangioleiomyomatosis, and renal angiomyolipomas. In patients suspected of having TSC, multiorgan screening should be performed to establish the diagnosis and identify clinically significant lesions through dermatologic and neurologic examinations, neurodevelopmental testing, fundoscopy, brain MRI, cardiac echocardiogram, and renal imaging.

**Genetic Testing**

Genetic testing to detect mutations in TSC1 and TSC2 is available, but because of the variability and complexity of the disorder, mutations cannot be detected in 10–20% of cases. Because of such a high false-negative rate, testing is typically only performed if the clinical diagnosis is unclear, for prenatal testing, or to assess risk in asymptomatic family members.

**Screening**

Patients who meet diagnostic criteria for TSC should be screened for multisystem involvement of the disease [99]. MRI of the brain should be obtained at the time of diagnosis and every year thereafter in children and adolescents up to age 21 and every 2–3 years thereafter in order to monitor for progression of cortical tubers, subependymal nodules, and the development of SEGAs. Ultrasound and CT imaging of the kidneys should occur every 1–3 years to monitor for renal angiomyolipoma and its complications. A CT scan of chest should be obtained in women to look for pulmonary lymphangioleiomyomatosis. Beyond these screening recommendations, additional testing should be performed as clinically indicated by patient symptoms.

**Associated Tumors**

Brain lesions are a prominent part of TSC and lead to some of its most debilitating clinical manifestations, including seizures, mental retardation, and behavioral disorders. The vast majority (85%) of patients with TSC develop seizures [100], most beginning in the first 2 years of life, and as many as 20–30% of infants with TSC...
develop infantile spasms. Cognitive dysfunction occurs in half of patients and is strongly correlated with seizure onset and control.

**Cortical Tubers**

Cortical tubers are hamartomas consisting of dysplastic neurons, glial cells, and glioneuronal giant cells [101] that disrupt the normal laminar architecture of the cortex. They are found in 95% of patients with TSC and are characteristically located at the gray–white junction within the frontal lobes but may occupy any lobe. Because of their cortical location, tubers are highly epileptogenic and are widely felt to underlie the high frequency of seizure disorders in TSC [102]. The extent to which tubers involve brain parenchyma correlates with the severity of epilepsy, mental retardation, and behavioral abnormalities. Cortical tubers appear as multiple non-enhancing lesions on brain imaging, with frequent cystic degeneration and calcification. They can be hyperdense on CT scan but are better visualized as T2-hyperintense, T1 hypointense/isointense lesions on MRI. Because of their benign nature, cortical tubers are treated only when symptomatic (most often when they produce refractory seizures). Surgical resection to treat medical refractory seizures may be complicated by the presence of multiple tubers and difficulty in localizing a single responsible epileptogenic focus [103]. Invasive seizure monitoring, positron emission tomography (PET), and magnetoencephalography (MEG) may allow better localization and successful surgical treatment [104]. Corpus callosotomy is an option for patients with debilitating refractory seizures or drop attacks and no clear surgical focus. It remains unclear whether earlier and more aggressive treatment of seizures can improve cognitive outcomes in TSC, though this is an active area of research.

**Subependymal Nodules**

Subependymal nodules are hamartomatous collections of abnormal glial cells and vascular tissue covered by a layer of ependyma. These lesions are found in most patients with TSC. They are located beneath the ependymal lining of the ventricles, often between the head of the caudate and the lateral ventricle, and can protrude into the ventricular cavity. They are non-enhancing heterogeneous lesions on MRI whose calcifications can be best identified on CT scan. They have been described to resemble “candle drippings” along the wall of the lateral ventricle. Subependymal nodules are benign hamartomas that are usually asymptomatic and do not require treatment. They do, however, have the potential to develop into SEGAs, and therefore require close monitoring to detect the increased growth or enhancement that heralds the transition to a SEGA [99, 105].

**SEGAs**

SEGAs are unique to TSC and are thought to develop from subependymal nodules [106]. They are slow-growing, low-grade neoplasms that develop in up to 20%
of patients with TSC [107] and occur at a particularly high rate in familial cases [108]. SEGAs tend to be hyperdense on CT scan (secondary to intratumoral hemorrhage and calcification), though their incomplete calcification can help differentiate them from subependymal nodules. Unlike their precursors, SEGAs almost always enhance. The majority of SEGAs are located within the ventricular system, and they have a predilection for the region near the foramen of Monro (Fig. 20.3). As a result, enlarging SEGAs can cause non-communicating hydrocephalus. SEGAs that produce symptoms such as hydrocephalus, increased intracranial pressure or focal neurologic deficits, or those that demonstrate concerning radiographic progression should be treated with surgical resection in order to prevent devastating and even life-threatening consequences. Gross total resection is curative, but because of the location of these tumors, surgery is often not possible [106]. In cases where surgery is not an option, cerebrospinal fluid (CSF)-diverting procedures should be considered to treat symptomatic hydrocephalus. Asymptomatic SEGAs should be monitored with surveillance imaging annually in order to detect tumor growth or changes in enhancement patterns that may signal the need for surgical removal. Recent reports have shown a marked clinical response of SEGAs to mTOR inhibition [109, 110] and everolimus was recently approved for treatment of inoperable SEGAs.

**Fig. 20.3** Post-contrast coronal T1-weighted image of a patient with TSC demonstrates an enhancing lesion consistent with subependymal giant cell astrocytomas. The tumor obstructs the Foramen of Monro resulting in obstructive hydrocephalus.

**Other Malignancies**

In addition to the several brain lesions associated with TSC, the disease predisposes patients to a number of other benign and malignant tumors [111–113]. TSC predisposes patients to several renal lesions that can lead to local and systemic
complications. These include benign, often bilateral, and multiple renal angiomyolipomas, renal cysts (including polycystic kidney disease if neighboring TSC2 and PKD1 genes are lost), oncocytomas, and renal cell carcinomas. Retinal astrocytomas occur in 50–75% of TSC patients but do not generally impair vision. Cardiac rhabdomyomas occur in up to half of newborns with TSC, but often completely regress during childhood. Pulmonary lymphangiomyomatosis is a rare but clinically important tumor that develops in young women with TSC and is often fatal.

**Prognosis and Future Directions**

The prognosis of TSC is highly variable, ranging from mild forms with little obvious impairment to those with significant disability. Intracranial and renal lesions produce the most serious complications from the disease, including mental retardation, refractory seizures, hydrocephalus, renal failure, and early death [114]. Until recently, the management of TSC has been largely symptomatic, but improved understanding of the function of TSC1/ TSC2 in regulating mTOR signaling has led to the consideration of targeted therapies, including the mTOR inhibitor, sirolimus [115]. Important recent studies of TSC patients treated with sirolimus have demonstrated remarkable regression of SEGAs [109, 110] and renal angiomyolipomas [116]. These results underscore the important therapeutic role of mTOR inhibition in this disease and usher in a new era of targeted treatment for TSC-related neoplasia.

**Von Hippel–Lindau Disease**

**Overview**

Von Hippel–Lindau (VHL) disease, descriptively known as retinocerebellar angiomatosis, is a genetic tumor syndrome characterized by the multi-organ development of cystic and neoplastic lesions, particularly involving the ophthalmologic, endocrinologic and nervous systems [117–119].

**Clinical Overview**

Characteristic lesions in VHL include benign hemangioblastomas of the CNS and retina, renal cell carcinoma, pheochromocytoma, pancreatic tumors, endolymphatic sac tumors, and benign cysts in multiple visceral organs [117–119].

**Epidemiology and Clinical Genetics**

Like most tumor predisposition syndromes, VHL is inherited in an autosomal dominant fashion with high penetrance (>90% by age 60) and variable expressivity [120]. The incidence of VHL is approximately 1 in 40,000 live births [121, 122]. It is caused by a germline mutation in the VHL tumor suppressor gene on chromosome
3p25 [123], so that a second somatic mutation in the remaining allele gives rise to tumors in various organs [124]. Most VHL cases are familial [120], though de novo mutations and mosaicism have been described [125–127].

**Molecular Genetics and Pathogenesis**

**VHL, pVHL**

The *VHL* gene encodes two splice variants of the ubiquitously expressed pVHL protein. Under normal conditions pVHL forms a complex that targets the transcription factor hypoxia-inducible factor (HIF) for degradation [128]. However in the setting of hypoxia, pVHL is inactivated leading to an increase in HIF levels. HIF upregulates transcriptional targets that are important for the cell’s response to hypoxia such as VEGF, erythropoietin, platelet-derived growth factor (PDGF), and transforming growth factor (TGF-α) [129, 130]. pVHL is therefore involved in the cell’s ability to sense hypoxia and trigger angiogenesis, and inactivating mutations in the *VHL* gene result in dysregulation of angiogenic and mitogenic factors [131]. pVHL is apparently also involved in interactions with the extracellular matrix, cytoskeleton, mitotic spindle, and in cell cycle regulation [132, 133].

**Mutations**

Mutations in the *VHL* gene are varied both in their type and position. More than 300 germline mutations have been identified, with missense mutations being the most common, though deletions, insertions, nonsense, and splice-site mutations also occur. There is tremendous variability in the phenotype of individual mutations, such that the severity and spectrum of VHL manifestations cannot be reliably predicted based on a particular *VHL* gene defect. There are, however, some strong genotype–phenotype correlations in VHL, particularly with respect to the risk of developing pheochromocytoma and renal cell carcinoma [134]. A marked variation in the risk of renal cell carcinoma and pheochromocytoma has led to the recognition of different VHL subtypes that result from particular *VHL* mutations. Deletions or truncating mutations confer a low risk of pheochromocytoma (type 1 VHL), while missense mutations lead to a high risk of pheochromocytoma (type 2 VHL) and either low (type 2A), high (type 2B), or no risk of renal cell carcinoma (type 2C), depending on the specific missense mutation [134].

**Clinical Features**

**Diagnostic Criteria**

As with other tumor predisposition syndromes, the recognition of VHL is important to identify patients at risk for several malignancies. In the past, the diagnosis was established by clinical criteria [135], which include either multiple hemangioblastomas or a single hemangioblastoma plus a characteristic visceral
lesion (renal cell carcinoma, pheochromocytoma, or pancreatic cancer). In the setting of a family history, only one hemangioblastoma or a visceral lesion is required to establish the diagnosis. More recently, a suspected diagnosis has been confirmed by molecular confirmation of a mutation in the VHL gene. Any patient discovered to have a single hemangioblastoma should be screened for other features of VHL.

Genetic Testing

Patients suspected of having VHL or known to be at risk for developing the disease can undergo molecular testing to confirm the diagnosis. Current genetic testing can nearly always detect mutations in the VHL gene in patients with a family history of the disease, but de novo (sporadic) cases may produce false-negative results due to the presence of mosaicism.

Screening

After confirmation of the diagnosis, patients should be screened and monitored for the development of systemic lesions found in VHL [136]. Serial imaging of the neuroaxis should be conducted every 2 years after age 10 to monitor for the development of CNS hemangioblastomas. Annual ophthalmologic exams are recommended from infancy to look for retinal hemangioblastomas, whose detection can be aided by fluorescein angiography. Regular otologic examination and high-resolution imaging through the temporal bone are recommended in symptomatic patients for the early detection of endolymphatic sac tumors. Serial abdominal imaging (ultrasound/CT) is recommended to screen for renal cell carcinoma and pancreatic tumors, while plasma or urine catecholamines are measured annually beginning in early childhood as well as in hypertensive patients to screen for pheochromocytoma.

Associated Tumors

CNS Hemangioblastoma

1. Overview

Hemangioblastoma is an uncommon, benign (WHO grade I), highly vascular neoplasm that can arise in the brain (primarily in the cerebellum), brainstem, spinal cord, or retina. At least one quarter of hemangioblastomas in the CNS occur in patients with VHL, and the diagnosis should be considered in all patients with hemangioblastoma [137]. These tumors are the most common finding in VHL, with up to three quarters (60–80%) of patients developing CNS hemangioblastomas [120]. Despite their benign histology, these tumors can cause significant morbidity and mortality. Compared with sporadic cases, patients with VHL present with symptoms at an earlier age, are more likely to develop multiple hemangioblastomas (90%) (Fig. 20.4) and more commonly have hemangioblastomas in the spine (25%).
Both sporadic and VHL-associated hemangioblastomas result from mutations in the \textit{VHL} tumor suppressor gene and have similar histology, behavior, and treatment [138, 139].

2. Symptoms
Symptoms result from tumor location and frequently reflect increased intracranial pressure (headache, vomiting, and visual disturbance) or cerebellar dysfunction (ataxia, dysmetria, and gait disturbance). Spinal tumors may cause pain or sensory-motor deficits [140]. Hemangioblastomas most often manifest in early adulthood and tend to grow sporadically and unpredictably with alternating periods of growth and quiescence [141, 142]. Hemangioblastomas commonly contain peritumoral cysts which can exacerbate symptoms. However, because of their prominent vascularity, hemangioblastomas can also hemorrhage and cause acute mass effect. Such hemorrhages into the posterior fossa can cause rapid neurologic decline with decreased level of consciousness and even death.

3. Imaging
Hemangioblastomas are well-circumscribed, cystic lesions with a broad dural attachment and a characteristic strongly enhancing mural nodule, often abutting the pial surface [143]. Vascular flow-voids are often seen, and because of the marked vascularity of these tumors, conventional angiography is a sensitive method for detecting small hemangioblastomas. Spinal tumors are typically intramedullary, though most contact the pial surface of the cord, and they are often associated with a syrinx.
4. Treatment
   a. Surgery
   The current treatment approach to hemangioblastomas is similar in VHL and sporadic cases and consists primarily of microsurgical resection. The primary goal of surgery is complete resection of the mural nodule while maintaining neurologic function. The cystic portions of the tumor do not require removal. Retained nodules can give rise to recurrent hemangioblastomas, and because of difficulty in achieving total resection of these highly vascular tumors from the posterior fossa, recurrence rates are as high as 17% [139]. VHL predisposes patients to multiple recurrent hemangioblastomas, which makes the surgical cure of these lesions even more difficult and often unsuccessful (more than two-thirds of VHL patients develop new CNS lesions in follow-up) [139]. In general, symptomatic or clearly growing hemangioblastomas in VHL patients should be treated surgically if possible, while asymptomatic tumors can be observed, particularly in the spinal cord and brainstem where operative morbidity is high [144].

b. Radiotherapy
   Stereotactic radiotherapy has been used to treat hemangioblastomas in VHL [145–147], and this approach may slowly reduce tumor volume, but does not entirely eliminate the tumor or its risk of subsequent cystic enlargement. Radiotherapy may in the future offer an alternative to resection in select high surgical risk patients, but further studies with long-term follow-up are necessary.

Other Malignancies

1. Retinal Hemangioblastomas
   Retinal hemangioblastomas can occur sporadically or in the setting of VHL. Approximately half of patients with retinal hemangioblastomas have VHL and these tumors are often the first manifestation of the disorder [120]. VHL patients are at increased risk of visual loss due to multiple bilateral tumors which can cause retinal detachment, hemorrhage, glaucoma, and cataracts. Retinal hemangioblastomas are treated with laser photocoagulation or cryocoagulation therapy, ideally performed while the lesions are small and asymptomatic in order to improve visual outcomes and minimize complications. As in the CNS, the multifocal and recurrent nature of retinal hemangioblastomas in VHL makes them more difficult to treat than their sporadic counterparts [148].

2. Endolymphatic Sac Tumors (ELSTs)
   Endolymphatic sac tumors (ELSTs) occur within the temporal bone in approximately 10–15% of patients with VHL [149]. These tumors arise from the vestibular aqueduct portion of the endolymphatic duct system [150] and are benign but locally invasive tumors that can erode or hemorrhage into audiovestibular structures or cause endolymphatic hydrops [151]. As a result, they frequently lead to irreversible hearing loss, tinnitus, vertigo, disequilibrium, and aural fullness, with symptom onset typically in young adulthood. ELSTs are best detected on high-resolution CT or MRI as heterogeneous tumors that expand, destroy, and incorporate temporal bone. Treatment involves early complete resection in an effort to preserve hearing [152].
3. Visceral Malignancies

VHL predisposes patients to renal cell carcinoma which is predicted to develop in most patients (>70%) if they live long enough [120] and is frequently multicentric and bilateral. Renal cell metastases to brain or to hemangioblastomas themselves (tumor–tumor metastases) should be considered in the differential diagnosis of CNS mass lesions in patients with VHL [153]. Pheochromocytoma occurs in 7–18% of VHL patients and is often multiple and bilateral, though rarely malignant. Pancreatic lesions in VHL are found in 17–56% of patients and are generally benign cysts, though pancreatic neuroendocrine tumors also occur. Finally, benign cystadenomas of the reproductive adnexal organs (epididymis or broad ligament) are a classic finding in VHL.

Prognosis

Patients with VHL experience numerous complications as a result of multi-organ tumorigenesis. Visual impairment and blindness can result from the ophthalmologic complications of retinal hemangioblastomas and their treatment. Endolymphatic sac tumors can lead to early deafness, a significant morbidity in a population already at high risk for blindness. Neurologic deficits from multiple CNS hemangioblastomas are also a major source of morbidity as well as mortality in patients with VHL. Renal cell carcinoma is the leading cause of death in VHL and together with hemangioblastomas is responsible for the significantly reduced life expectancy of patients with the disease, who only live an average of 50 years [154]. Pheochromocytoma and pancreatic cancer are the sources of further morbidity and mortality in this patient population.

Future Directions

Recognition of the mechanisms by which VHL mutations lead to dysregulated hypoxic signaling and angiogenesis has led to intense interest in the use of VEGF inhibitors and tyrosine kinase inhibitors in the treatment of VHL-associated tumors [155–159]. At this time, only case reports and small series of anti-angiogenic therapies for VHL have been published. These targeted approaches may eventually improve the outcome in VHL patients with progressive inoperable tumors.

Cowden Syndrome

Overview

Cowden syndrome (CS) is an autosomal dominant tumor predisposition syndrome with variable expression that is characterized by the development of hamartomas in multiple organs, as well as an increased risk of developing breast, thyroid, and
endometrial cancers [160]. CS is estimated to occur in 1 out of every 200,000 individuals [161], though as a result of its variable expression and subtle cutaneous manifestations, this figure almost certainly underestimates the true prevalence of the disorder. Approximately half of patients with CS do not appear to have a family history, though because of the difficulty establishing the diagnosis, it remains unclear what proportion of cases represent de novo mutations.

**Molecular Genetics and Pathogenesis**

Up to 80% of patients with CS harbor a germline mutation in the PTEN tumor suppressor gene on chromosome 10q23 [162]. The PTEN gene product is a phosphatase with multiple, incompletely understood functions including regulation of the PI3K–Akt–mTOR [163] and RAF–MEK–ERK pathways [164] that are important for controlling cellular proliferation, migration, and apoptosis. PTEN mutations have recently been associated with a group of phenotypically overlapping disorders [165] that include frequent hamartoma formation and can be broadly referred to as “PTEN hamartoma tumor syndrome” [166].

**Clinical Features**

CS leads to the formation of hamartomatous lesions in the skin and mucosa, CNS, eyes, gastrointestinal tract, genitourinary system, and bones. The most common clinical features of CS are benign mucocutaneous lesions including trichilemmomas, acral keratoses, papillomatous papules, and palmoplantar keratoses. The hallmark lesion in the CNS is a dysplastic gangliocytoma of the cerebellum, also known as Lhermitte–Duclos disease (LDD) [167]. Other nervous system manifestations include macrocephaly, heterotopias, seizures, vascular abnormalities, and mental retardation. Finally, CS is associated with a high risk for developing several malignancies including breast (25–50% lifetime risk), thyroid (10% lifetime risk), and endometrial carcinoma (5–10% lifetime risk), underscoring the importance of establishing the diagnosis in order to identify and screen patients who are at risk for these malignancies [160].

**Diagnostic Criteria**

Criteria for the diagnosis of CS were initially proposed in 1983 [168] and subsequently revised by an international consortium that established pathognomonic features as well as major and minor criteria for the disorder. Recent updates to the diagnostic criteria have designated adult LDD as pathognomonic for CS, while pediatric LDD is thought to be an isolated syndrome unrelated to CS. A specific constellation of mucocutaneous lesions is also pathognomonic for the disorder, while breast, thyroid, endometrial cancer, and macrocephaly make up the major diagnostic criteria. Patients meet the National Comprehensive Cancer Network
(NCCN) criteria (www.nccn.org) if they have (1) adult Lhermitte–Duclos disease or a specific number of mucocutaneous features, or (2) macrocephaly plus another major criterion, or (3) one major and three minor criteria (structural thyroid lesions, mental retardation, gastrointestinal hamartomas, fibrocystic disease of the breast, lipomas, fibromas, genitourinary tumors or structural malformations, uterine fibromas), or (4) four minor criteria. In cases of suspected CS, PTEN mutation analysis can be carried out to help in establishing the diagnosis.

Associated Tumors: LDD

LDD is a rare, slow-growing, hamartomatous enlargement of the cerebellar cortex that results from dysplastic replacement of cerebellar Purkinje and granule cells with abnormal ganglionic neurons [169]. LDD is considered to be pathognomonic for CS in adults, though the frequency of this lesion in CS is not known. The dysplastic enlargement of the cerebellum in LDD can lead to cerebellar dysfunction, headaches, nausea, vomiting, and visual problems. Though not a malignant process, LDD can become life-threatening in advanced cases where mass effect leads to secondary obstructive hydrocephalus and increased intracranial pressure.

Although the definitive diagnosis of LDD is made histopathologically, the unique features of this lesion can allow the diagnosis to be made by neuroimaging. MRI reveals well-circumscribed, non-enhancing enlargement of the cerebellar folia that are T2-hyperintense and lead to a striated or “tiger-striped” appearance (Fig. 20.5) [170].

Fig. 20.5  T2-weighted image of a patient with Lhermitte–Duclos syndrome reveals the characteristic tiger-striped appearance
Management

Although LDD is a hamartomatous lesion, it frequently demonstrates progressive growth that can lead to obstructive symptoms and clinical decline. Though the initial management of asymptomatic lesions can involve observation, surgical resection is considered the only effective treatment. Even with resection, recurrences are common, most likely due to difficulty identifying the margin between affected cortex and normal cerebellum. Radiation therapy is generally thought to be ineffective in the treatment of LDD, but the demonstration of increased mTOR activity in LDD samples suggests that mTOR inhibitors such as sirolimus may have an effect [171].

Li–Fraumeni Syndrome

Overview

Li–Fraumeni syndrome (LFS) is a rare autosomal dominant disorder that predisposes affected individuals to numerous primary tumors over the course of their lifetimes, including particularly high rates of sarcomas, breast cancer, brain tumors, and adrenal cortical carcinoma. LFS is inherited with high penetrance but is both clinically and genetically heterogeneous.

Molecular Genetics and Pathogenesis

Missense mutations in the TP53 tumor suppressor gene are the underlying genetic defect in the majority of patients with LFS [172]. Numerous critical functions of the TP53 gene product, p53, have been characterized in detail, including its roles in cell cycle arrest, deoxyribonucleic acid (DNA) repair, and apoptosis. The importance of p53 as a tumor suppressor is underscored by the fact that aberrant p53 expression has been demonstrated in more than 50% of sporadic human cancers [173].

Clinical Features

Presentation

Patients with LFS often present at a young age with any of a variety of cancers, with sarcomas and premenopausal breast cancer being the most common. Brain tumors develop at a mean age of 16 years in approximately 13% of individuals with a TP53 mutation [174]. Astrocytomas are most common, but medulloblastomas, primitive neuroectodermal tumors (PNETs), choroid plexus carcinomas, and ependymomas also occur. Additionally, tumors of the peripheral nervous system including neuroblastoma have been reported in LFS families.
Diagnostic Criteria

The diagnosis of LFS is a clinical one and should be considered in young brain tumor patients who have a history of another malignancy or a family history of malignancy, especially sarcoma. Diagnostic criteria require an index patient (proband) with a sarcoma before the age of 45 and a first-degree relative with any cancer before the age of 45, as well as an additional first-degree or second-degree relative with a sarcoma at any age or any other cancer before the age of 45. Nearly 80% of patients meeting these clinical criteria can be demonstrated to have $TP53$ mutations [172]. Less restrictive criteria have defined a Li–Fraumeni-like (LFL) variant [175, 176] and 30–40% of patients with this diagnosis harbor a $TP53$ mutation [172].

Management

Treatment of brain tumors associated with LFS is similar to that for sporadic tumors, although LFS patients are felt to be at increased risk for developing secondary malignancies following DNA damage from ionizing radiation or chemotherapy [177–179]. This risk should be considered in treatment planning, and patients who receive radiation or chemotherapy should be followed closely for the development of secondary tumors.

Turcot Syndrome

Overview

Turcot’s syndrome (TS) refers to the rare concurrence of primary CNS tumors and colorectal polyposis. The clinical manifestations of TS are highly variable, ranging from a single to thousands of polyps and involving the development of a number of histopathologically diverse brain tumors. In fact, TS can be divided both clinically and molecularly into at least two distinct tumor predisposition syndromes that can be differentiated by their colorectal presentation [180].

Clinical Presentation

Patients who develop hundreds to thousands of polyps in the colon and rectum during adolescence are recognized to have familial adenomatous polyposis (FAP), an autosomal dominantly inherited cancer syndrome. Though these numerous colonic polyps are benign, eventual malignant transformation typically occurs by 35–40 years of age. Patients with FAP have a low but increased risk for developing brain tumors compared with the general population. The most common tumors include medulloblastoma (60%), malignant glioma (14%), and ependymoma (10%). This association between FAP and brain tumors is known as Turcot syndrome type 2 [181].
In contrast, patients with a similar strong family history of colon cancer but fewer adenomatous polyps that tend to be larger and have a greater likelihood of developing into adenocarcinoma may have hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome. Patients with HNPCC have a greatly increased risk of developing extracolonic malignancies, including primary glial tumors such as glioblastoma. This association is known as Turcot syndrome type 1 [180].

Molecular Genetics and Pathogenesis

The molecular basis for Turcot syndrome is similarly associated with two different genetic defects [180]. Tumors that arise in FAP result from mutations in the APC gene on chromosome 5q21. Resulting loss of function of the APC protein leads to overactivity of the Wnt signaling pathway which is also commonly disrupted in sporadic colorectal carcinoma and medulloblastoma.

HNPCC-related tumors result from mutations in a series of DNA-mismatch repair (MMR) genes (hMSH2, hMLH1, hPMS1, hPMS2, and hMSH6) whose loss of function leads to accumulation of DNA mutations and microsatellite instability, predisposing patients to the development of high-grade gliomas [182]. Interestingly, sporadic gliomas have been shown to develop inactivating mutations in hMSH6 during temozolomide treatment that lead to a hypermutation phenotype and treatment resistance [183]. Patients with homozygous recessive mutations in MLH1, MSH2, and MSH6 may have an NF1 phenotype of café-au-lait macules associated with childhood cancers.

Diagnostic Criteria

Turcot syndrome is a clinical diagnosis that is generally made when a patient presents with a primary CNS tumor and evidence of colorectal polyposis. Molecular studies can differentiate mutations in MMR genes from APC mutations, a distinction that is most relevant in affected patients who have milder forms of FAP with fewer adenomatous polyps.

Management

Although Turcot’s syndrome is an extremely rare disorder, patients known to have FAP or HNPCC who present with new neurologic symptoms must be thoroughly investigated for the presence of a CNS neoplasm. Treatment of brain tumors in this population is similar to that for sporadic tumors; however, DNA-damaging agents such as ionizing radiation may increase the risk of secondary malignancies and should be used with caution.
Gorlin Syndrome

Overview

Gorlin syndrome (GS), also known as nevoid basal cell carcinoma syndrome, is a rare inherited cancer predisposition syndrome with multisystem manifestations including the development of multiple basal cell carcinomas, odontogenic keratocysts, palmoplantar pits, dural calcifications, bony abnormalities, and a risk of various neoplasms or hamartomas including medulloblastomas, lymphomesenteric cysts, fetal rhabdomyomas, and ovarian fibromas. GS has an autosomal dominant inheritance pattern with high penetrance and variable expressivity; about 35–50% of patients have no family history and harbor de novo mutations. The prevalence of GS is estimated to be 1 in 60,000. An underlying diagnosis of GS is present in 0.4% of all patients with basal cell carcinoma and in 2% of patients younger than 45 with basal cell carcinoma [184].

Molecular Genetics and Pathogenesis

GS is caused by germline inactivation of the tumor suppressor gene PTCH1 located on chromosome 9q22.3 [185]. Reduced PTCH protein expression is thought to underlie the developmental abnormalities seen in GS, while complete loss of protein expression following a second somatic mutation leads to tumor formation. The protein product of PTCH1 is a large transmembrane receptor that functions as a cell cycle regulator. The secreted ligand sonic hedgehog (SHH) binds two extracellular loops on PTCH protein, allowing signal transduction that controls cell fate, patterning, and growth. PTCH1 mutations lead to increased activity of this pathway, uncontrolled growth, and tumor formation. PTCH1 mutations are not only the cause of tumor formation in GS, but have also been demonstrated in two-thirds of sporadic basal cell carcinomas [186] and in keratocystic odontogenic tumors [187] and medulloblastomas. Mutations in a related but distinct gene, PTCH2, have been demonstrated in a Chinese kindred with GS [188], and mutations in other downstream members of the PTCH pathway have been shown to cause GS [189].

Clinical Features

Presentation

Patients with GS present in infancy with congenital abnormalities (macrocephaly, bifid ribs, cleft lip/palate, cortical bone defects), and subsequently develop multiple tumors. Medulloblastoma is the characteristic CNS tumor associated with GS, although ectopic dural calcifications are present in about 70% of patients and meningioma in 5% [190]. Medulloblastoma may be the presenting manifestation of the disorder, generally appearing within the first 2 or 3 years of life. The lifetime risk
for developing medulloblastomas in GS is approximately 3–5% and is three times higher in males than in females. Of all patients diagnosed with medulloblastoma, only 1–2% will have GS.

**Diagnosis**

The diagnosis of GS is made based on the presence of a collection of compatible clinical findings. Clinical criteria have been proposed which require a combination of major criteria (palmoplantar pits, basal cell carcinomas, jaw keratocysts, meningeal calcification, bifid ribs, a first-degree relative with GS) and minor criteria (macrocephaly, congenital malformations, skeletal abnormalities, radiologic abnormalities, ovarian fibromas, medulloblastoma) [191]. Children with a family history that are known to be at risk for the disorder should have detailed physical and radiographic examination to look for signs of GS, as should any child younger than 5 years who present with a medulloblastoma. Direct mutation analysis of the PTCH1 gene can confirm the diagnosis.

**Management**

Management of patients who have GS-associated medulloblastomas is similar to the treatment of sporadic tumors, with the best outcomes occurring in patients treated with aggressive resection, chemotherapy, and radiation. However, because GS patients are predisposed to radiation-induced secondary malignancy, the use of radiation should be minimized or avoided where possible. Increased understanding of the molecular mechanisms that cause medulloblastoma has led to the development of small molecule inhibitors of the SHH pathway, which have demonstrated remarkable success in treating mouse models of medulloblastoma [192, 193]. These results may represent a targeted approach to the future treatment of both sporadic and GS-associated medulloblastoma [194].

**References**


20 Genetic Syndromes


Chapter 21
Rare Tumors

Erik J. Uhlmann and Andrew D. Norden

Introduction

An array of rare central nervous system tumors have been described. Because these entities occur infrequently, published data are often limited to case reports and small case series. For the purposes of this chapter, they have been organized by the World Health Organization (WHO) classification scheme.

Tumors of Neuroepithelial Tissue

Choroid Plexus Tumors

The choroid plexus is a combination of neuroepithelial tissue and endothelium, located in the ventricular system. The neuroepithelial tissue that makes up choroid plexus is thought to be a specialized ependyma, and thus there is sometimes histological overlap between high-grade choroid and ependymal tumors. The function of the choroid plexus is production of cerebrospinal fluid (CSF), and it is thought to be the site of entry of white blood cells into the CSF. Choroid plexus tumors are rare in adults, but represent the most common brain tumors in the first year of life, when they are usually found above the tentorium. In adults, the tumors most commonly occur in the lateral and fourth ventricles, as well as the cerebellopontine angle, reflecting the quantity of choroid tissue in these locations. Adult patients typically present with headache, a symptom thought to represent increased intracranial pressure resulting from obstruction or impaired CSF reabsorption. Fourth ventricle lesions may have mass effect upon the brainstem resulting in focal deficits such as
hemiparesis. In infants the presentation is non-specific. Rarely, seizures have been described in temporal horn lesions [6]. Occasionally, metastasis of these tumors to the spinal cord, sacral nerve roots, or leptomeninges occurs, with symptoms that correspond to the disease site [1, 2, 7].

**Choroid Plexus Papillomas**

These tumors are considered low or intermediate grade and usually have a benign course with therapy. Typical radiologic features include a high degree of vascularity and contrast enhancement. Histological features of the tumor are those of normal choroid tissue, with cilia, microvilli and without pleomorphism or atypia. Analysis of histological features and recurrence showed correlation only with mitotic index [10], and this was incorporated into the most recent WHO classification [11]. Intermediate or atypical choroid plexus papillomas (WHO grade II) are defined by at least two mitotic figures per ten high-power fields, while tumors with fewer mitotic figures represent benign (WHO grade I) lesions. Ki-67/MIB-1 index is not part of the pathological classification, however, it correlates with the mitotic index and is reported by many pathologists.

Gross total resection of choroid plexus papilloma typically results in cure. Malignant transformation is presumably rare, but has been reported with partially resected tumors [8]. Patients with recurrence after the initial surgery still have an excellent prognosis. Therefore, adjuvant radiation or chemotherapy is not used. Radiation therapy may be considered for recurrent lesions [5]. Atypical choroid plexus papilloma has a higher rate of recurrence and is associated with a less favorable 5-year event-free survival, 83%, as compared to 92% for WHO grade I tumors [12]; 10-year survival was found to be 85% for patients with total resection and 56% for patients with partial resection [3].

**Choroid Plexus Carcinoma**

These are high-grade tumors arising from the choroid plexus. Imaging appearance is similar to choroid plexus papilloma, however, there may be radiologic evidence of extension into the brain parenchyma, with resulting mass effect and vasogenic edema. The tumor may appear heterogeneous owing to focal necrosis. Histopathologic features include disruption of papillary architecture, sheets of epithelial cells with pleomorphic nuclei, increased nuclear-to-cytoplasmic ratio, mitotic figures, focal necrosis, and invasion into the brain parenchyma [14]. In adult patients, the pathologic finding of multifocal lesions within normal-appearing choroid plexus tissue should raise the possibility of metastatic adenocarcinoma [15]. In addition, teratoma in young males and medulloepithelioma in infants should also be considered in the differential diagnosis. Immunostaining for excitatory amino acid transporter-1, CA19-9, and aquaporin 1 has been proposed as identifying tumor cells of choroid origin [16–18].
Optimal treatment is total surgical resection, however, it is rarely possible due to tumor invasiveness. Consequently, the prognosis is poor with surgery alone. Various chemotherapy protocols, including cyclophosphamide, etoposide, vincristine, cisplatin, carboplatin, lomustine, as well as radiation, 1.5- to 2-Gy fractions once per day for a total of 54 Gy locally, have been reported. A meta-analysis of 347 cases of choroid plexus carcinoma found both surgery and irradiation to be beneficial [9], however, the median age of these patients was 3, and these findings may not be applicable to adult patients. In order to design targeted treatment approaches for high-grade choroid plexus tumors, investigators studied the molecular basis of malignant behavior, including overexpression of growth factor receptors, such as platelet-derived growth factor receptor (PDGFR), alterations in DNA repair pathways such as methylguanine methyltransferase (MGMT) promoter methylation, karyotype, and PARP1 expression. No clear therapeutic target has been identified thus far [4, 13].

**Neuronal and Mixed Neuronal–Glial Tumors**

Tumors containing cells of neuronal and glial differentiation based on histological features, gene expression, and FISH analysis of chromosomal changes are discussed below. This is a group of rare tumors, each with unique features that justify their further subclassification. The few cases reported and limited number of tumor specimens available hinder thorough laboratory analysis. Similarly, clinical experience of the natural history and optimal management of these lesions are limited.

**Ganglioglioma and Gangliocytoma**

Gangliogliomas and gangliocytomas are rare tumors with neuronal and glial components. Most gangliogliomas are located in the temporal lobe, but they can arise anywhere along the neuraxis. Seizure is the most common presenting symptom [22]. There are no specific radiologic findings; a T2-hyperintense and homogenously enhancing solid tumor or a cystic lesion with variable enhancement is seen on MRI, with no significant vasogenic edema in the surrounding brain parenchyma [23, 24]. Calcification is often seen on computed tomography (CT), and tumors are usually hypometabolic by $^{18}$F-fluorodeoxyglucose positron emission tomography (FDG-PET) [25]. Histological features include dysplastic neurons of variable sizes and sometimes binucleated as well as neoplastic glial cells. Areas of astrocyte-like or pilocytic cells, Rosenthal fibers, desmoplasia, lymphocytic infiltrate, and calcification may be present. Mitotic figures are not seen, and Ki-67/MIB-1 index is less than 1%, with positive cells mainly of the astrocytic phenotype [20]. Most tumors show positivity for CD34, a marker expressed by hematopoietic progenitors but not normal brain cells. Gangliogliomas can exhibit clusters of tumor cells infiltrating adjacent brain parenchyma, however, these tumors do not behave aggressively. The cell of origin or the mechanism of tumor development is not known. It is believed that neurodevelopmental abnormalities, rather than cell proliferation or
DNA repair pathways, are involved [21]. Anaplastic transformation can occur rarely. This is thought to involve the glial component and results in tumor behavior that is equivalent to secondary high-grade glioma [29].

Optimal treatment has not been established. The initial treatment is often surgical resection. Radiotherapy does not further improve outcomes if total resection can be achieved, but appears beneficial for patients with partial resection. Chemotherapy has been used with unestablished efficacy. Long-term survival is approximately 90% [19, 26–28]. In the absence of clinical evidence, anaplastic gangliogliomas may be treated with surgery, radiation, and chemotherapy following treatment guidelines for high-grade gliomas.

Desmoplastic Infantile Astrocytoma and Desmoplastic Infantile Ganglioglioma

Desmoplastic infantile astrocytoma and desmoplastic infantile ganglioglioma are low-grade tumors of children and young adults. Common presenting symptoms are seizure in adults and enlarging head circumference in infants. These tumors arise from the superficial cerebral cortex and may be large at presentation. Imaging findings are non-specific, however, the lesion often has a small solid core attached to the dura and a large cystic component. The solid core is T1-isointense and T2-isointense in comparison to brain tissue, with homogenous gadolinium enhancement. CT of the head may show calcifications [31, 32]. The tumor may be multifocal at presentation. Histological analysis reveals glial fibrillary acidic protein-positive spindle-shaped cells in a collagen-rich reticulin-positive desmoplastic stroma. Necrosis or mitotic figures are not seen, and Ki-67/MIB-1 index is less than 5%.

The treatment is surgical resection. Complete removal is associated with an excellent prognosis, and adjuvant therapy is not recommended. Subtotal resection is thought to result in recurrence, and successful use of vincristine and carboplatin has been reported in cases or small series [30]. Radiation therapy can be considered, however, clinical data supporting its efficacy are lacking.

Dysplastic Gangliogliocytoma of the Cerebellum (Lhermitte–Duclos disease)

Dysplastic gangliocytoma of the cerebellum is a rare condition, with a slowly growing mass lesion arising from the cerebellar cortex, typically seen in adults [35]. The left side of the cerebellum is more frequently involved. Presenting symptoms include headaches, cerebellar ataxia, and the neurological consequences of non-communicating hydrocephalus. MRI reveals a T1-hypointense and T2 isointense mass in one of the cerebellar hemispheres, with possible mass effect on the brainstem and fourth ventricle. The lesion may show restricted diffusion by MRI and may appear hypodense on unenhanced head CT, and thus could be mistaken for an infarction. Unenhanced head CT may also show calcifications. Histologically,
there is widening of the molecular layer, due to the presence of dysplastic ganglion cells, showing variable expression of synaptophysin, S-100, neuron-specific enolase, and CD34. In addition, the Purkinje cell layer is absent, there is hypertrophy of the granule cell layer, and variable amounts of gliosis can occur with glial fibrillary acidic protein immunoreactivity. Germline mutations of phosphatase and tensin homolog deleted on chromosome 10 (PTEN), an important inhibitor of phosphatidylinositol-3 kinase (PI3K), have been found in most cases [34]. Cowden syndrome, a tumor predisposition syndrome with high risk of multiple malignancies, has the same underlying genetic abnormality [33], and patients with this syndrome sometimes develop dysplastic gangliocytoma of the cerebellum. Most, if not all patients presenting with dysplastic gangliocytoma of the cerebellum subsequently develop manifestations of Cowden syndrome [Robinson], and thus dysplastic gangliogliocytoma of the cerebellum (Lhermitte-Duclos disease) disease may be a milder form of Cowden syndrome.

The treatment of choice is total resection, as this reduces, but does not eliminate the risk of recurrence. Owing to the close association, if not identity to Cowden syndrome, careful cancer survey at presentation and close monitoring thereafter are obligatory [36–38]. Radiation therapy has no established role in this disease.

Cerebellar Liponeurocytoma

Cerebellar liponeurocytomas are extremely rare tumors, described in adults [39, 40]. Tumors contain small, round neoplastic cells with neuronal differentiation and mature adipocytes. Precise characterization is difficult due to the few specimens available for analysis, but this tumor is considered to be distinct entity based on chromosome analysis and expression profiling [41]. Imaging characteristics include a circumscribed lesion that is hypodense or isodense on CT and shows T1-hypointensity and heterogeneous T2-hyperintensity on MRI. Heterogeneous enhancement can be observed on both CT and MRI.

The natural history, optimal treatment, and the overall prognosis are not known. These tumors appear to be slow growing [42, 43]. Complete resection has been recommended as initial management, and second surgery and radiation therapy if the disease recurs [44].

Central Neurocytoma and Extraventricular Neurocytoma

Central neurocytoma is a low-grade intraventricular tumor. Although these lesions are rare, they constitute approximately 50% of intraventricular lesions. A less common variety with similar histopathologic characteristics occurs in the cerebral hemispheres, particularly in the frontal and parietal lobes, thalamus, cerebellum, pons, amygdala, pineal gland, and spinal cord. This entity, called extraventricular neurocytoma, is more aggressive and often results in local recurrence and leptomeningeal dissemination, unlike central neurocytomas [45–47, 50]. Typical clinical manifestations of central neurocytoma are increased intracranial pressure
from hydrocephalus, visual problems, and cognitive deficits; extraventricular neurocytoma often presents with seizures and focal neurological deficits. Imaging reveals an often large, partially cystic mass, heterogeneously hyperdense on CT and T1-hyperintense on MRI with a variable degree of heterogeneous contrast enhancement. These characteristics depend on cellularity and degree of calcification and are not specific; the radiographic differential diagnosis often includes high-grade glioma, primitive neuroectodermal tumor, oligodendroglioma, gangliocytoma, ganglioglioma, ependymoma, and meningioma. Histological findings include pleomorphic round tumor cells with ganglion cell differentiation, diffuse, strong immunolabeling for synaptophysin, and focal glial fibrillary acidic protein reactivity without astrocytic features. Atypical features may be present, particularly in extraventricular neurocytoma, and include mitotic figures, vascular proliferation, and necrosis. Because oligodendroglioma can possess neurocytic differentiation and synaptophysin immunoreactivity, there may be a pathogenetic link between these more common tumors and extraventricular neurocytoma [51]. Interestingly, about 20% of extraventricular neurocytomas show chromosome 1p and 19q co-deletion.

The optimal treatment is complete surgical resection, although prolonged survival may be achieved with subtotal resection, owing to slow tumor growth. Low Ki-67/MIB-1 index and typical histological findings are favorable prognostic factors [47, 48]. For patients with unfavorable prognosis due to subtotal resection, atypical histology, or extraventricular location, adjuvant radiotherapy may be useful for local control, although its effect on survival is not known [48, 49, 52]. At least one report suggests that recurrent central neurocytomas may be responsive to systemic chemotherapy [45].

**Papillary Glioneuronal Tumor**

The fourth edition of the WHO classification of Tumors of the Nervous System, published in 2007, reclassified this tumor as a distinct entity, rather than as a ganglioglioma variant [Louis]. Papillary glioneuronal tumors are rare, well-circumscribed lesions in the temporal lobes or cerebral hemispheres, affecting mostly young adults [11, 53]. Affected patients usually present with seizures, and imaging findings are similar to other glioneuronal tumors. Imaging usually shows an enhancing solid core with calcifications and a cystic component. The tumor cells exhibit a distinctive pseudopapillary architectural pattern. Expression of nestin, CD133, glial fibrillary acidic protein, and synaptophysin by the tumor cells indicates combined astrocytic and neuronal differentiation, possibly from a common progenitor [54]. Most cases lack atypical features, such as necrosis, vascular proliferation, or high mitotic index, but rare cases have been reported to the contrary.

Total surgical resection of papillary glioneuronal tumors results in long-term remission in most cases. The prognostic value of atypical histological features is not known, however, for patients with these, along with those with recurrent disease, fractionated radiation and chemotherapy should be considered, on the basis of the limited data available [55, 56].
Rosette-Forming Glioneuronal Tumor of the Fourth Ventricle

This entity was added to the fourth edition of the WHO classification of Tumors of the Nervous System, published in 2007. Rosette-forming glioneuronal tumor of the fourth ventricle is a rare neoplasm arising primarily from the cerebellar vermis. Most cases reported thus far have occurred in young adult females [58]. Contrary to the index case, most subsequent reports found no involvement of the fourth ventricle, and revision of the name was proposed [57]. Most patients present with several months’ history of headaches or ataxia. Hydrocephalus can occur in patients with fourth ventricle involvement. Imaging shows a heterogeneous cystic mass, with areas of enhancement and little or no surrounding edema. The presurgical diagnosis often includes pilocytic astrocytoma, ependymoma, cerebellar dysembryoplastic neuroepithelial tumor, and oligodendroglioma. The defining pathological characteristics are the presence of pilocytic astrocytes mixed with neurocyte-forming pseudrosettes. The clinical outcome was excellent in most reported cases after complete resection.

Dysembryoplastic Neuroepithelial Tumor

Dysembryoplastic neuroepithelial tumors are neoplasms of children and young adults that were first described in 1988 [60]. Commonly, there is a long-standing history of treatment-resistant localization-related epilepsy. No other neurological deficits or other associated symptoms are identified, although there are reports of families with several affected probands, raising the possibility of an unidentified genetic predisposition syndrome. The lesions are supratentorial and cortical. Imaging often demonstrates a hypodense lesion on CT, T1-hypointensity and T2-hyperintensity on brain MRI, and little or no contrast enhancement. Due to the slow growth of the lesion, there is usually no mass effect or surrounding edema. Skull molding adjacent to the lesion is sometimes seen, as further indication of slow growth [59, 63, 64]. These lesions may have a microcystic nodular appearance at low power. The nodules are composed of neuron-like, astrocyte-like, and oligodendroglia-like cells in a mucinous background. The sparse astrocytic component is arranged along the blood vessels and may exhibit Rosenthal fibers. Isolated neurons with normal appearance may be seen in a mucoid background with the appearance of “floating.” Nuclear pleomorphism, mitosis, or endothelial proliferation is rarely seen. Focal cortical dysplasia, with the replacement of the normal architecture by aggregates of neurons, is sometimes present adjacent to the tumor and may be the seizure focus [62, 65].

The main indication for surgery is refractory seizures, although there is a risk of cortical injury and continued seizures [61]. Rarely, tumor recurrence or even malignant transformation may occur [66].

Intracranial and Intraspinal Paraganglioma

Intracranial paraganglioma is a rare, slow-growing vascular tumor, however, it is locally invasive and can involve the sigmoid sinus and inferior petrosal sinuses, vas-
cular lumens, skull base foramina, cerebellopontine angle, and Eustachian tube [71]. The most common presenting symptoms are pulsatile tinnitus, headache, hearing loss, dysphagia, hoarseness, aspiration, tongue paralysis, shoulder drop, imbalance, cerebellar signs, and facial palsy [74]. The tumor cells are derived from paraganglia, a collection of small neuroendocrine organs, which in turn are formed from neural crest cells. Paraganglia of the head and neck region are part of the parasympathetic nervous system, acting as pO₂, pCO₂, and pH sensors. Intracranial paraganglia arise from the glomus bodies which are normally located in the region of the jugular foramen of the temporal bone. Primary intraspinal paragangliomas are more common than intracranial paragangliomas, with cauda equina being the preferred location [73]. Paraganglioma is sometimes familial, inherited in an autosomal dominant fashion, and linked to mutations of the genes SDH-D, SDH-B, and SDH-C, encoding the subunits of succinate dehydrogenase [199]. Occasionally, paragangliomas are associated with genetic syndromes, including von Hippel–Lindau disease, multiple endocrine neoplasia type 2, and neurofibromatosis type 1.

CT of the head is useful to provide information about the bony structures of the middle ear and jugular foramen. MRI is useful to image the lesion and its relationship with vascular structures. Post-contrast T1 images typically show patchy enhancement, while T2-weighted images reveal bright areas alternating with dark flow-voids, called the “salt and pepper” pattern. CT angiography, MR angiography or even catheter angiography is used to further characterize the relationship of the lesion with vascular structures. The differential diagnosis of jugular foramen lesions includes vagal neuroma, jugular fossa meningioma, adenoid cystic carcinoma, metastatic carcinoma, squamous cell carcinoma, chondrosarcoma, chordoma, rhabdomyosarcoma, histiocytosis, and primary cholesteatoma [198]. Histological features include cells arranged in compact nests separated by delicate fibrovascular stroma. Distinct cell populations show synaptophysin and S-100 immunoreactivity.

Optimal treatment is complete surgical resection. However, most patients present with advanced lesions, and total resection is not possible without any cranial nerve injury in the majority of the patients [67, 68]. External beam radiotherapy is considered excellent in achieving local control, although complication rates are high and include sensorineural hearing loss, radiation injury to the brain, delayed osteoradionecrosis, and radiation-induced malignancy. Stereotactic radiation therapy has been proposed, but its efficacy and safety are undetermined [69, 72]. Genetic testing is available for SDH mutations in case familial paraganglioma is suspected.

**Embryonal Tumors**

Embryonal tumors consist of central nervous system (CNS) primitive neuroectodermal tumors, atypical teratoid/rhabdoid tumor, pinealoblastoma, and medulloblastoma. Medulloblastoma is discussed elsewhere.
CNS Primitive Neuroectodermal Tumors

CNS primitive neuroectodermal tumors are defined by the WHO as “a heterogeneous group of tumors occurring predominantly in children and adolescents that may arise in the cerebral hemispheres, brain stem, or spinal cord, and are composed of undifferentiated or poorly differentiated neuroepithelial cells which may display divergent differentiation along neuronal, astrocytic and ependymal lines” [75]. Primitive neuroectodermal tumors are further classified as supratentorial primitive neuroectodermal tumor, CNS neuroblastoma, ganglioneuroblastoma, medulloblastoma, ependymoblastoma, and embryonal tumor with abundant neuropil and true rosettes. Histologically, these are highly cellular and composed mostly of small cells with high nucleus to cytoplasm ratio and infiltrative margins, although there is a variant with large, anaplastic cells. Homer-Wright or neuroblastic rosettes may be present. Frequent, but not universal molecular pathologic features that may also be adverse prognostic factors are amplification of the myc gene and polysomy of chromosomes 2 and 8 [76]. Of note, these tumors do not carry the EWSR1 rearrangement seen in Ewing’s sarcoma. There is nuclear expression of the SMARCB1/INI1 gene product, and this immunophenotype analysis is recommended for all primitive-appearing pediatric CNS tumors to exclude CNS atypical teratoid/rhabdoid tumors, which lack SMARCB1/INI1 expression.

Supratentorial Primitive Neuroectodermal Tumor

Supratentorial primitive neuroectodermal tumors are rare, poorly differentiated, rapidly growing, high-grade tumors. Older children with supratentorial primitive neuroectodermal tumors may present with signs of increased intracranial pressure, while infants present with lethargy, irritability, anorexia, and enlarging head circumference. Seizures or focal neurological deficits are less common. Leptomeningeal dissemination, if present, can result in cranial neuropathies, encephalopathy, or spinal cord symptoms. Imaging usually reveals a well-defined, heterogeneous hemispheric mass, with cystic areas. Calcifications and hemorrhages may be present. There is heterogeneous contrast enhancement. Peritumoral edema is seen, but considered relatively mild in light of the size of the lesion [85].

The optimal management is not known. Despite histological similarity to infratentorial primitive neuroectodermal tumors, i.e., medulloblastoma, response to treatment and clinical outcomes are significantly worse. Surgical resection followed immediately by radiation to the entire neuraxis has been used with apparent benefit [129]. Adjuvant chemotherapy regimens similar to those used for medulloblastoma have been added [82], however, despite aggressive treatment, recurrence is common, and 3-year survival is reported as 57–73% [83, 84, 86]. High-dose chemotherapy with autologous hematopoietic progenitor cell rescue seems promising, especially for those patients with no prior radiotherapy [80, 81, 88], and this approach may become the standard up-front treatment.
Ependymoblastoma

This term has been used to describe various entities, at times with some ambiguity. Currently, this is a unique subcategory of CNS primitive neuroectodermal tumors featuring ependymoblastic rosettes and abundant neuropil-like regions and prominent neurocytic differentiation [89, 91]. Ependymoblastoma is a highly malignant, rapidly expanding mass that typically affects children less than 5 years old. The lesion is often supratentorial but has been reported at other locations along the neuraxis. The clinical presentation of a supratentorial lesion is typically vomiting and enlarged head circumference. Imaging reveals a T1-hypointense and T2-hyperintense hemispheric mass, with variable, patchy enhancement, and without significant surrounding edema. Histologic studies revealed ependyma cells in various stages of differentiation, perivascular rosettes, and anaplastic features such as glomeruloid vascular proliferation, focal necrosis, and pleomorphism. Tumor cells exhibit immunoreactivity for vimentin, glial fibrillary acidic protein, and epithelial membrane antigen, while usually negative for cytokeratin, synaptophysin, and desmin. The Ki-67/MIB-1 index is very high among the rosette-forming cells. Despite aggressive treatment with surgery, craniospinal irradiation, and chemotherapy, the prognosis is poor and death usually occurs within a year [90].

Medulloepithelioma

Central nervous system medulloepitheliomas are rare high-grade (WHO grade IV) tumors of childhood.

These tumors may be found anywhere in the brain or in the orbit. Histological features include papillary, tubular, and trabecular arrangements of neoplastic neuroepithelium mimicking the embryonic neural tube. They may show focal immunoreactivity with epithelial membrane antigen, glial fibrillary acidic protein, and synaptophysin [92]. These tumors are noted to have a dismal prognosis, with progression, recurrence, and dissemination despite therapy and a median survival of 5 months [93, 95]. High-dose chemotherapy with hematopoietic progenitor cell rescue has been proposed, but its efficacy is yet to be determined [94].

CNS Ganglioneuroblastoma

Central nervous system neuroblastoma and ganglioneuroblastoma are embryonal tumors with neuronal differentiation. They are occasionally found in young adults but are most common in children below the age of 5. Patients may present with seizures or focal deficits. Imaging shows a well-demarcated, round tumor, often with calcification. Histologically, there are small, round, neuroblastic cells mixed with scattered large ganglion-like cells with abundant cytoplasm and large pale nuclei, in the background of a variable amount of fibrillated neuropil. The tumor cells may show immunoreactivity for synaptophysin, neurofilaments, and chromogranin. Lack of atypia and low Ki-67/MIB-1 index suggest low-grade tumor. There is insufficient clinical data to establish prognosis and optimal treatment, however, some
observations suggest that contrary to their embryonal appearance, these tumors have a favorable prognosis. Total resection followed by fractionated radiotherapy with or without concurrent daily temozolomide has been used with complete remission at 18 and 14 months, respectively [96, 97].

**CNS Atypical Teratoid/Rhabdoid Tumors**

These are highly malignant tumors mostly affecting children less than 3 years old that typically involve the cerebellopontine angle. Clinical presentation may include emesis, lethargy, hemiparesis, and cranial neuropathies [77]. Imaging usually reveals a cystic or hemorrhagic lesion, hyperintense on T1 and isointense or hypointense on T2-weighted MRI. There is heterogeneous enhancement often with nodular leptomeningeal involvement anywhere along the neuraxis. Histologically, there is a rhabdoid cell component, however, differentiation from CNS primitive neuroectodermal tumors based on morphological features is not reliable. In contrast to CNS primitive neuroectodermal tumors, CNS atypical teratoid/rhabdoid tumors lack nuclear expression of \( \text{SMARCB1/INI1} \), which can be used to reliably identify these tumors [76]. High-grade features are typically present, including mitotic figures and focal necrosis. The prognosis is poor despite aggressive treatment with chemotherapy and radiation therapy [78, 79, 87].

**Other Neuroepithelial Tumors**

This group was previously termed “tumors of uncertain origin” [11] and includes the rare entities, namely, astroblastoma, chordoid glioma of the third ventricle, and angiogetic glioma.

**Astroblastoma**

This rare tumor has been mostly described in children and is almost exclusively supratentorial [98]. Patients present with nausea, vomiting, hemiparesis, hemianopia, and cranial neuropathies. Imaging shows a cystic lobulated lesion with solid components that is typically T1-isointense, T2-hyperintense, and with variable contrast enhancement and calcification. The numerous cysts within the tumor may give it a “bubbly” appearance. Histological findings are perivascular pseudorosettes with focal perivascular hyalinization. The tumor cells may exhibit glial fibrillary acidic protein, epithelial membrane antigen, cytokeratin, and synaptophysin immunoreactivity. The Ki-67/MIB-1 index may be elevated and necrosis may be present, both of which predict an unfavorable prognosis. Gross total resection of a lesion without atypical features frequently results in a long disease-free interval. High-grade lesions are treated with surgery, radiation therapy, and chemotherapy with temozolomide, although the optimal treatment is not known [116].
Chordoid Glioma of the Third Ventricle

First described in 1998, chordoid glioma is a rare, low-grade tumor of the third ventricle that occurs in adults with a female to male ratio of 2:1. Patients typically present with hydrocephalus. Imaging reveals a well-demarcated lesion, sometimes invading the hypothalamus. The lesions are T1-isointense on MRI with intense, homogenous enhancement. Histologically, cords and clusters of epithelioid cells are seen that stain for glial antigens. High-grade features were absent in published cases, and these tumors are classified as WHO grade II. They show immunoreactivity for glial fibrillary acidic protein, epithelial membrane antigen, vimentin, CD31, CD34, epidermal growth factor receptor, and S-100 but are negative for pankeratin and E-cadherin. The Ki-67/MIB-1 index is low. Recently, comparative genomic hybridization followed by fluorescence in situ hybridization revealed recurrent genetic alterations at 9p21 and 11q13 [101]. Total resection is considered to be curative. Fractionated radiotherapy or stereotactic radiosurgery was proposed for cases with incomplete resection [100].

Angiocentric Glioma

Angiocentric glioma is a rare subcortical tumor of the cerebral hemispheres that was only recently classified as a distinct entity by the WHO. There is no apparent age or gender predilection. Patients present with treatment-refractory seizures. Imaging by MRI reveals discrete, T2-hyperintense, non-enhancing lesions. Histologically, there is a moderately hypercellular glial neoplasm with prominent angiocentric growth. The tumor cells are bipolar with oval nuclei and copious eosinophilic cytoplasm. Neither mitotic figures nor necrosis is found. Tumor cells show immunoreactivity for glial fibrillary acidic protein, epithelial membrane antigen, vimentin, and S-100 [102, 103]. Surgery is frequently curative.

Tumors of the Meninges

Mesenchymal Tumors

Tumors of Adipose Tissue

Brain tumors containing a component of adipose cells include lipomas, angiolipomas, hibernomas, and intracranial liposarcomas.

Intracranial Lipoma

Intracranial lipoma is a rare, benign, slow-growing, congenital hamartomatous lesion, first reported by Rokitansky [106]. Of all intracranial tumors, this category makes up from 0.46 to 1% [107]. Intracranial lipomas are thought to arise from the persisting and abnormally differentiating mesenchymal cells from the neural
crest, and they are associated with brain malformations in more than 50% of cases [108, 110]. These tumors are most frequently found near the midline, such as in the pericallosal interhemispheric region (45%), the quadrigeminal cistern (25%), and the suprasellar or interpeduncular cistern (14%) [108]. In addition, CNS lipomas can be found along the entire neuraxis. Many patients with intracranial lipomas are asymptomatic. Seizures, headache, behavioral changes, and cranial nerve palsies are reported as presenting symptoms. The mechanism of seizure development in patients with intracranial lipomas is not known. Focal cortical irritation, disruption of inhibitory white matter tracts, and associated brain malformations have been implicated [109]. A lipoma of the corpus callosum may be seen on CT images or plain skull films as an X-ray-lucent zone surrounded by curvilinear calcifications. The lesion produces a homogenous T1-hyperintense signal on MRI that is suppressed upon fat saturation. It is isointense or hypointense on T2-weighted sequences and does not show contrast enhancement or surrounding edema [104, 105]. Owing to its imaging characteristics, intracranial lipomas may be mistaken for aneurysms or pneumocephalus when incidentally found in patients with unrelated medical problems [111, 112].

Lipomas are slow-growing and the prognosis is excellent without treatment. Surgical resection is sometimes considered in patients with refractory seizures, although the risk and efficacy of this intervention is not established [107].

Central Nervous System Angiolipoma

Angiolipomas are mesenchymal hamartomas composed of abnormal blood vessels and mature adipocytes [113]. Intracranial angiolipoma is extremely rare. In a review of the published literature, 8 intracranial and 86 spinal cord tumors were identified, most of which were epidural [114, 115]. Women are more often affected than men, and age at presentation is approximately 50. The clinical presentation often includes back pain, headache, and symptoms of spinal cord compression. Intracranial angiolipomas associated with aneurysms and subarachnoid hemorrhage have been described [117, 118]. The imaging characteristics of angiolipomas are similar to those of lipoma, however, angiography may help in the diagnosis by identifying tumor vascularity [119]. On histological review, these are composed of dilated capillaries, sometimes with thrombi, and cavernous vessels. There is collagenous stroma with mature adipocytes and a variable lymphocytic inflammatory infiltrate.

Surgical resection is not recommended due to hemorrhagic risk, however, stereotactic radiation has been used with success [113, 119].

Central Nervous System Hibernoma

Hibernoma is a rare tumor composed of cells that resemble brown adipose tissue. In the CNS, extramedullary intradural spinal cord and intracranial lesions have been reported [120, 121]. The imaging findings are similar to those of lipomas or
angiosarcomas. The tumors are well demarcated and surgical resection results in long-term remission [120, 121].

Liposarcoma

Primary intracranial liposarcoma is an extremely rare tumor with a wide range of differentiation [124, 125]. Pleomorphic liposarcoma has a poor prognosis. Metastatic intracranial liposarcoma may be more common than primary disease [122, 123, 126]. Patients present with focal neurological signs and imaging reveal a T1-hypointense, T2-hyperintense-enhancing mass with surrounding edema. The tumor cells may have a “soap-bubble” histological appearance with clear cytoplasmic droplets that distort the nucleus. Mitotic figures and atypia are seen in pleomorphic varieties. The tumor cells are immunoreactive for vimentin but not for glial fibrillary acidic protein, S-100 protein, and epithelial membrane antigen.

Primary CNS liposarcoma is a malignant tumor, and treatment should include surgery and radiation therapy. Chemotherapy should also be used for disease with pleomorphic features [124, 125].

Fibrous Tumors

Intracranial fibrous tumors arise from mesenchyma of the dura, pia, and also from fibroblasts of deep perforating vessel adventita. Tumors of this category include solitary fibrous tumor, fibrosarcoma, and malignant fibrous histiocytoma.

Solitary Fibrous Tumor

Solitary fibrous tumors are mostly pleura-based, however, a few cases have been reported in the CNS. Since 2000, the WHO classifies this entity as a mesenchymal, non-meningothelial tumor. Most of the reported CNS cases are intracranial rather than spinal and originate from the dura. Patients present with focal neurological signs or with consequences of increased intracranial pressure [131]. They appear as large, but well-defined, nodular, extra-axial masses with T1-hypointensity, heterogeneous T2-hyperintensity, and dense contrast enhancement. On histological review, irregular, elongated tumor cells arranged in interconnecting platforms are seen within dense collagenous connective tissue. Solitary fibrous tumors exhibit a unique and diagnostic phenotype, with immunoreactivity for CD34, CD99, vimentin, and Bcl-2, but not with epithelial membrane antigen, S-100, cytokeratin, CD117, factor VIII, estrogen receptor, progesterone receptor, synaptophysin, glial fibrillary acidic protein, calretinin, desmin, smooth muscle actin, and CD31. The prognosis is good for cases without anaplasia if complete resection is performed [127]. Local recurrence is reported after subtotal resection [132]. Recurrent tumors may be treated with repeat surgery, radiotherapy, or stereotactic radiosurgery [128, 131].
Primary fibrosarcoma of the CNS is an exceedingly rare, malignant spindle cell tumor arising from the dura or leptomeninges. These tumors tend to affect young and middle-aged adults and involve the cerebrum. The clinical presentation may include symptoms of increased intracranial pressure, hemiparesis, seizure, and cranial neuropathies. Imaging shows a contrast-enhancing mass with areas of hemorrhage. Bone destruction may be seen on CT \[134\]. Histological review shows atypical fibroblasts and collagen \[133\].

The prognosis is poor, despite aggressive treatment. Nonetheless, patients are treated with surgery, radiation, and chemotherapy. There is a high rate of local recurrence \[130, 135, 136\].

Primary fibrous histiocytoma of the CNS is a rare condition, described mostly in children, and can be either benign or malignant. The tumor may be intraparenchymal or dural-based. Patients may present with headache, seizures, hemiparesis, or cranial neuropathy. Imaging reveals a large heterogeneous extra-axial mass with T2-hypointensity and some areas of hemorrhage or necrotic cysts within the lesion. There is irregular contrast enhancement \[Ogino\]. Histological review shows atypical fibroblasts and histiocytes \[137\].

While benign fibrous histiocytomas can be managed with surgery alone, even aggressive treatment of malignant fibrous histiocytomas in the past has been disappointing \[200\].

Chordoma and chondrosarcoma are pathologically distinct cartilaginous tumors, here grouped together based on similar anatomic location, clinical manifestations, and imaging characteristics; however, their biological behavior may be different. The clivus is involved in most cases, with or without involvement of the cavernous sinus, craniospinal junction, and the petrous bone. Skull base chordomas develop from the primitive notochord at the sphenop-occipital synchondrosis, whereas chondrosarcomas originate from primitive mesenchymal cells of the cranium \[140, 141\]. The clinical presentation often includes cranial neuropathies, most frequently sixth nerve palsy, but headache, facial pain, nasal obstruction, hemiparesis, visual disturbance, and galactorrhea have been reported. Imaging reveals a large lesion with T1-isointensity or hypointensity, and T2-hyperintensity. Enhancements present in approximately 75% of chordomas and an even higher portion of chondrosarcomas. Bone erosion and arc-like calcifications may be seen. Histologic review of chordoma reveals uniform cells with small, oval, eccentric nuclei and many cytoplasmic vacuoles. Chondrosarcoma is characterized by pleomorphic chondrocytes within cartilage. Chordoma shows immunoreactivity with cytokeratin and epithelial membrane antigen, while chondrosarcoma does not, but both
tumors are positive for S-100 and vimentin [138, 142]. Enchondromatosis is a rare, non-hereditary condition with multiple cartilaginous tumors. It has two variants, Ollier’s disease, featuring isolated enchondromatosis, and Maffucci’s syndrome, with enchondromatosis associated with cutaneous hemangioma [144].

Skull base chondrosarcoma carries a markedly more favorable prognosis than chordoma, with rare recurrence and excellent long-term control with maximal resection followed by radiotherapy. To reduce complications from radiation therapy, proton beam may be used, or treatment may be deferred for patients with complete resection. The optimal treatment for chordomas includes radical surgical resection followed by high-dose radiotherapy [143]. Chordomas have a high rate of disease recurrence despite aggressive surgery and outcomes are poor [139–141].

**Primary Meningeal Hemangiopericytoma**

Primary meningeal hemangiopericytoma is a rare, aggressive tumor, mostly dural based, that can arise anywhere in the intracranial compartment [145, 146]. It is considered to be a derivative of pericytes. The disease mainly affects adults and has a slight predilection for men [147]. Although this tumor shares anatomic location, imaging appearance, and presenting signs with meningioma, they are pathologically distinct. Hemangiopericytomas are more aggressive than meningiomas with higher rates of recurrence and capacity for distant metastasis. The distribution of intracranial hemangiopericytoma is similar to that of meningiomas (70% supratentorial, 15% posterior fossa-based, 15% spinal, and rarely intraventricular) [148, 153]. Patients present with headache, focal neurological deficit, and seizures. Imaging reveals a heterogeneous hyperattenuating lesion with bone erosion by CT, and T1-isointensity and T2-isointensity, flow-voids, and heterogeneous contrast enhancement by MRI. Of note, a dural tail sign more often seen in meningioma may be present. On histological review, hemangiopericytomas are highly cellular lesions with spindle cells, large nuclei, and scant cytoplasm arranged in short fascicles. Areas with few cells and hyalinization may be seen. Mitotic figures are seen but not necrosis. Dilated thin vasculature can be seen, sometimes in a “corkscrew” or “staghorn” pattern. The tumor stroma is reticulin-positive, while the tumor cells are immunoreactive for bcl-2, CD34, vimentin, and S-100 and negative for epithelial membrane antigen, CD31, and glial fibrillary protein. The Ki-67/MIB-1 index may be focally elevated.

Hemangiopericytoma is a very aggressive tumor. Local or distant recurrence is common, even after complete resection. The efficacy of radiation therapy is not known, however, local control, disease-free survival, and overall survival rates appear to be greater in patients treated with radiation. In one retrospective series of 29 cases, 5-year disease-free survival was 80% versus 38% with complete and partial resection, respectively. At 15 years, 21% of the patients remained in remission [149]. Post-operative external beam radiation therapy and stereotactic radiosurgery have been proposed [150]. In recurrent disease, chemotherapy has been tried, including anti-angiogenic drugs [151, 152].
Ewing’s Sarcoma – Primitive Neuroectodermal Tumor

Ewing’s sarcoma – primitive neuroectodermal tumor is a rare condition, involving the CNS by extension from dura, bone, or paraspinal soft tissue. The peak incidence is in adolescence. On MRI, these tumors are well-circumscribed, lobular, homogeneously enhancing masses with broad dural attachments that may be indistinguishable from meningioma [156]. Ewing’s sarcoma may be mistaken for CNS primitive neuroectodermal tumor on histologic review. However, molecular testing for the EWSR1 translocation is diagnostic. The prognosis and optimal therapy are not known; surgery, radiation, and chemotherapy have been tried with some success, but long-term remission is rare. Local recurrence, leptomeningeal spread, and systemic metastases are common [154, 155].

Primary Melanocytic Lesions

Abnormal proliferation of melanocytes in the CNS can result in diffuse or localized and benign or malignant conditions [157, 158]. Melanocytes are derived from the neural crest and normally reside in the pia mater at the ventral medulla and the upper cervical cord. Tumors derived from these melanocytes are typically leptomeningeal and may be low-grade lesions (e.g., melanocytomas) or highly malignant melanomas. Melanoma metastatic to the CNS is discussed elsewhere.

Primary Malignant Melanoma of the Central Nervous System

Primary melanoma of the central nervous system is rare, comprising about 1% of all melanoma cases. It is often meningeal-based, rather than at the gray–white matter junction as in metastatic disease, and tends to be more diffuse, poorly circumscribed, and invasive. However, it progresses more slowly than metastatic melanoma lesions [160, 163]. Patients usually present with symptoms of increased intracranial pressure, but seizures, focal sensory or motor deficits, and cranial neuropathies can be seen. Imaging reveals a T1-hyperintense and T2-hypointense lesion, an unusual pattern that likely relates to blood products or paramagnetic free radicals associated with intracellular melanin. The tumor exhibits contrast enhancement. Susceptibility sequences may reveal previous hemorrhage. Tumor cells can invade the subarachnoid space, and CSF cytology studies may be diagnostic [161, 162]. Histological review reveals a highly cellular tumor with a fascicular or nested pattern, possibly with focal necrosis or hemorrhage. Nuclear atypia and prominent nucleoli are present. There is diffuse immunoreactivity with S-100, vimentin, Melan A, MART-1, and HMB-45, but not with epithelial membrane antigen. One-third of these tumors do not contain visible melanin, however, HMB-45 immunoreactivity and electron microscopy demonstrating melanosomes are more sensitive and highly specific tests for the diagnosis. Mitotic figures are seen, and the Ki-67/MIB-1 index is elevated. The pathogenesis of primary CNS melanoma is not known. Like cutaneous melanoma, these tumors often have BRAF and GNAQ mutations, but NRAS
and HRAS mutations are absent. These findings suggest a distinct but overlapping pathogenesis for cutaneous and primary CNS melanomas [159].

Primary melanoma of the CNS is an aggressive tumor. Total surgical resection is recommended. The tumor is relatively radioresistant, and the roles of radiation and chemotherapy are controversial. Interferon-alpha 2a has been tried on an individual basis [163]. Overall, the prognosis is poor, with most patients not surviving more than a year [164–167].

Melanocytoma

Leptomeningeal melanocytoma is a rare, well-differentiated tumor arising from melanocytes of the leptomeninges. Melanocytomas typically present in the fifth decade of life. These are slow-growing, encapsulated, non-infiltrative lesions, however, malignant transformation, leptomeningeal spread, and distant metastasis have been reported [171–174]. The lesion is frequently located in the posterior fossa or spinal cord [167, 170]. Patients present with cerebellar symptoms, myelopathy, radiculopathy, or seizures [167, 168]. Imaging shows a hyperattenuating lesion without calcifications on CT. On MRI, melanocytomas are T1-hyperintense and T2-hypointense, with contrast enhancement and without surrounding edema [178].

The optimal therapy is not known, but surgical resection alone or followed by radiotherapy has been advocated, especially for cases of subtotal resection. The 5-year survival was reported to be 42% without and 90% with radiotherapy. Local recurrences are common [169, 175–177].

Melanocytosis and Melanomatosis

Primary leptomeningeal melanomatosis is a rare and highly aggressive neoplasm. It is characterized by disseminated leptomeningeal involvement and has a very poor prognosis. Patients may present with signs of hydrocephalus, seizures, cognitive deficits, and cranial neuropathies. Imaging shows pachymeningeal enhancement. No effective therapy has been reported [179, 180].

Cystic Lesions

A variety of non-neoplastic lesions can simulate a brain tumor and give rise to neurologic symptoms. These include epidermoid, dermoid, arachnoid, and colloid cysts.
**Epidermoid Cyst**

Epidermoid cysts, also known as primary cholesteatomas, are thought to arise from mislocalized epithelial cells that persist after the closure of the neural tube. These cells form cysts with an inward-facing squamous epithelium lining that produces keratin. The accumulation of cholesterol and keratin results in enlargement of the cysts, which can encase nearby nerves and arteries. Epidermoid cysts usually occur within the basilar cisterns but are occasionally reported in the cerebral parenchyma, ventricles, or brainstem [181]. Patients present with loss of hearing, tinnitus, headache, hemifacial spasm, or trigeminal neuralgia, compression of the internal carotid artery or aseptic meningitis due to leakage of cyst contents [182]. Imaging reveals an extra-axial lesion, with CSF-like radiologic properties, without contrast enhancement, however, calcifications may be seen [183].

Treatment is surgical, but complete resection is rarely possible [184]. Malignant transformation of an epidermoid cyst to squamous cell carcinoma can occur, either from a previously unsuspected cyst or from a remnant of a previously resected lesion [185].

**Dermoid Cyst**

Dermoid cysts are similar to epidermoid cysts in cellular origin and pathogenesis, with the additional elements of hair follicles, sweat glands, and sebaceous glands. Intracranial dermoid cysts are found in the posterior fossa, fourth ventricle, and suprasellar cistern. Cerebellar dermoid cysts are associated with occipital dermal sinuses and bacterial meningitis. Patients usually present with headache and seizures. Rare spontaneous cyst rupture can be fatal [186–188]. Imaging reveals a hypodense lesion on CT and a T1-hyperintense, T2-variable lesion on MRI [188]. Symptomatic dermoid cysts are treated with resection. Recurrence is common. Malignant transformation of dermoid cysts may occur and is associated with a poor prognosis [185].

**Colloid Cyst**

A colloid cyst is a rare developmental malformation composed of an outer fibrous layer and an inner ciliated or mucinous epithelium [184, 189]. It commonly occurs between the fornical columns in the roof of the third ventricle. Patients may present with drop attacks, intermittent headaches, nausea, vomiting, gait problems, papilledema, and occasionally sudden death from obstruction of the ventricular system [189, 191]. Imaging reveals an isodense or hyperdense lesion on CT and a T2-hyperintense non-enhancing lesion on MRI. Complete excision is curative but
not always feasible. Patients with hydrocephalus are treated with a ventriculoperi-
toneal shunt. Stereotactic aspiration of the cyst is limited by a high recurrence 
rate [190]. Patients with small asymptomatic colloid cysts without evidence of 
hydrocephalus may be closely followed by serial examinations and neuroimaging 
studies.

**Arachnoid Cyst**

These are commonly seen arachnoid membrane-lined closed structures. The mecha-
nism of the enlargement of arachnoid cysts over time is not known. One hypothetical 
explanation is that CSF is actively transported or passively diffuses into the lumen 
and becomes trapped due to a valve effect [192, 193]. Arachnoid cysts account 
for about 1% of intracranial masses. The incidence of asymptomatic arachnoid 
cysts is increasing as more patients undergo neuroimaging procedures for unre-
related conditions. Of the symptomatic arachnoid cysts, 75% occur in children. 
Arachnoid cysts contain clear CSF with a normal cell count and protein concen-
tration. Xanthochromia indicates hemorrhage into the cyst, and elevated protein or 
pleocytosis suggests a cystic neoplasm rather than an arachnoid cyst. Approximately 
50% of arachnoid cysts arise in the Sylvian fissure; other common sites include the 
cerebral convexity, interhemispheric fissure, suprasellar cistern, quadrigeminal cis-
tern, cerebellopontine angle, midline of the posterior fossa, craniospinal junction, 
and the spine [194]. Patients present with headache, seizure, focal neurological 
deficits, or subdural hematoma. Suprasellar cysts may cause obstructive hydro-
cephalus and visual or endocrine dysfunction. Quadrigeminal and posterior fossa 
cysts may cause brainstem symptoms as well as hydrocephalus [195]. Plain films 
of the skull may reveal thinning of adjacent bone, especially with long-standing 
lesions. CT of the head and MRI of the brain show a homogenous mass with CSF 
signal characteristics. There may be mild mass effect without contrast enhance-
ment. Diffusion-weighted imaging shows no restriction of diffusion, in contrast to 
epidermoid cysts [196, 197].

Treatment is not indicated for asymptomatic lesions. Surgical options include 
craniotomy for partial or complete cystectomy, fenestration into the subarachnoid 
space, or cyst–peritoneal shunting. Needle aspiration usually is of temporary benefit 
[184].

**References**


Incidence and Prevalence of Primary Neoplasms of the Spine

Nearly 1.5 million new cases of cancer are diagnosed annually. Among novel cases, more than 2,000 are bone and joint cancers and about 10,000 are soft tissue cancers. Of the latter, about 5% are primary malignant spine tumors and 1% are primary benign spine tumors. Spine tumors can be categorized based upon their location as extradural, intradural–extramedullary, and intramedullary [1]. Primary extradural spinal neoplasms that involve the osseous spine account for less than 10% of all spinal osseous neoplasms [2] and have a prevalence ranging from 2.5 to 8.5 cases per 100,000 persons [3]. Their incidence is about 7,500 cases annually in the United States [4]. The grade and distribution of primary spinal extradural tumors vary with age. In adults the most common benign primary vertebral tumors of the spine are hemangiomas, accounting for 30% of all primary spine tumors. Among primary vertebral malignant tumors, the most common in adults are plasmacytomas (30%). In children the most common benign primary vertebral tumors are osteoid osteoma/osteoblastomas (12%), aneurysmal bone cysts (10%), and eosinophilic granulomas (12–25%). Among malignant primary vertebral tumors in children, the most common are Ewing’s sarcoma (4–10%) [4]. Furthermore, the age at presentation also correlates with the potential aggressiveness of the lesion, evidenced by the fact that the mean age at diagnosis for benign tumors is approximately 21 years and 49 years for malignant tumors. The incidence of chondrosarcomas, chordomas, plasmacytomas, osteochondromas, osteoblastomas, and osteoid osteomas is twice as high in men as in women. However, giant cell tumors and aneurysmal bone cysts...
have a marginally higher incidence in women. Osteosarcomas and hemangiomas have no predilection for one sex. Thus far, there is no evidence of ethnic or racial differences in incidence of primary vertebral tumors [4].

Among primary intraspinal lesions, 66% are intradural–extramedullary spinal cord tumors (IESCTs). Schwannomas and meningiomas are the most common, followed by myxopapillary ependymomas [5]. Stawicki et al. conducted a study in which 67 patients underwent surgical intervention for primary IESCTs between 1974 and 2001. They found that schwannomas were more common in men, meningiomas in women, and ependymomas were distributed equally among both sexes. The distribution of age at presentation was bimodal with a major peak around 40 years and a minor peak around 70 years.

Intramedullary neoplasms account for approximately 10% of primary central nervous system neoplasms and 20% of all spinal cord tumors [7]. The incidence of primary intramedullary spinal tumors is 2.5/100,000 annually in the United States, and women are at slightly higher risk than men [6]. Primary intramedullary spinal tumors occur most frequently among women in their 60s and men in their 50s. Unlike the pattern observed for extradural tumors, primary intramedullary spinal tumors are more common than metastatic intramedullary spinal tumors (1.3 vs 0.7/100,000 per year) [6].

**Anatomical Distribution**

**Epidural Tumors**

Vertebral tumors differ in location along the spine axis and within individual vertebrae. For example, 50% of chordomas occur in the coccyx or sacrum, 35% in the skull base, and 15% in the mobile spine. Chondrosarcomas and plasmacytomas present most frequently in the thoracic spine. Giant cell tumors are most prevalent in the thoracolumbar spine and sacrum. Osteoid osteoma/osteoblastomas and aneurysmal bone cysts are most often present in the lumbar spine. Chondromas usually develop in the cervical spine, most often the second cervical vertebra.

With respect to localization on individual vertebrae, giant cell tumors, plasmacytomas, and chordomas usually occur in the vertebral body and involve the posterior elements to a varying degree. Aneurysmal bone cysts often occur on the posterior arch or the vertebral body. Chondromas and osteoid osteoma/osteoblastomas most often involve the posterior elements [4].

**Intradural–Extramedullary Spinal Cord Tumors**

In a longitudinal study of 360 IESCT patients, most tumors were found in the dorsolateral division, followed, respectively, by the ventrolateral, dorsal, and ventral
divisions. Along the longitudinal axis, most IESCTs present in the thoracic spine, followed by the cervical and lumbar spines, respectively [7].

**Intramedullary Spinal Cord Tumors**

The three most common types of malignant intramedullary spinal cord tumors are high-grade astrocytomas, low-grade astrocytomas, and ependymomas. Most intramedullary tumors are of glial origin, but non-glial tumors are also common. Intramedullary tumors do not exhibit a preference for a particular spinal level. ISCTs can be focal, only involving a few centimeters of cord or cauda equina, or they can spread diffusely along the longitudinal axis of the cord. In the case of holocord spinal astrocytomas, which most commonly occur in pediatric patients, the tumor may extend from the conus to the medulla [8].

**Diagnostic Utilities**

**Imaging Studies**

A thorough history and neurological examination are crucial to a proper diagnosis. Plain radiographs are frequently ordered next due to their simplicity and low cost. They can be helpful for screening lytic lesions, pathologic fractures, abnormal masses, and spinal deformities. However, plain radiographs are sometimes insufficiently sensitive to detect lesions, particularly in the case of lytic lesions, due to the fact that 50% vertebral body involvement is required for detection.

Nuclear scintigraphy, also called a bone scan, is used to detect metabolically active bone lesions. This technique is far more sensitive than plain radiographs. However, areas of inflammation or infection may be mistaken for tumors. Positive bone scans should be accompanied by magnetic resonance imaging (MRI) or computed tomography (CT) imaging in order to exclude benign lesions and are also required if surgical intervention is planned. Other complete body surveillance imaging modalities are fluorodeoxyglucose positron emission tomography (FDG-PET) and single-photon emission computerized tomography (SPECT). PET directly measures the metabolic activity of bone, which permits early lesion detection and detection of cystic and necrotic tumors. PET, however, has a limited spatial resolution and must be accompanied by an MRI or CT study. SPECT is similar to nuclear scintigraphy but permits three-dimensional imaging; this may improve its ability to distinguish between malignant and benign tumors.

Multidetector CT imaging has numerous advantages. These scans provide a detailed representation of osseous anatomy. When performed simultaneously with myelography, CT scans also permit visualization of neural structures which may be compressed or involved by tumor. With use of intravenous contrast agents, CT scans
can image the arterial supply and venous drainage of a tumor. Finally, CT scans are essential for planning surgical intervention.

MRI is the gold standard for diagnosing both primary and metastatic spine diseases due to its exceptionally high sensitivity. This is the only imaging modality that has sufficiently high spatial resolution and contrast to visualize bone–soft tissue interfaces and soft tissue structures such as ligaments, paraspinal musculature, spinal cord, nerve roots, and intervertebral disks. MRI also allows for distinguishing between benign and malignant compression fractures through the use of diffusion-weighted sequences.

Digital subtraction angiography is the optimal technique for vascular imaging and also allows embolization during the procedure. Angiographic embolization is an effective treatment for some benign, highly vascular, tumors, and it may be used preoperatively to minimize hemorrhage during surgery [1].

Biopsy

For tumors that are limited to the posterior elements such as osteoblastomas and aneurysmal bone cysts, excisional biopsies can be both diagnostic and therapeutic. Excisional biopsies are also useful for establishing the diagnosis of round cell tumors, such as lymphomas or Ewing’s sarcoma, where the primary therapeutic intervention is chemotherapy. Needle biopsies are appropriate in the case of primary malignant tumors that are treated with neoadjuvant chemotherapy, such as osteosarcoma. Needle biopsies are also frequently used to document recurrence prior to the start of radiation therapy. Needle biopsies may be non-diagnostic 10–25% of the time. If an open incisional biopsy is needed, several components of the procedure should be critically considered and well executed. Meticulous surgical technique and homeostasis are essential. Aggravation of pathologic fractures should be avoided via carefully planned small bone windows and adequate packing with bone wax and gelfoam. Care must be taken to minimize postoperative hematomas, as they have the potential to disseminate tumor cells along fascial planes [9].

Laboratory Studies

Blood and serum studies do not contribute significantly to the diagnosis of primary spinal tumors. An elevated erythrocyte sedimentation rate may be found in patients with round cell tumors, but this finding is non-specific. Multiple myeloma can be detected using urinary protein and serum electrophoresis with immunofixation. Bone marrow infiltrative processes should be suspected when blood counts are abnormal [1].
Presentation, Diagnosis, and Management

Main Types of Epidural Spinal Cord Tumors

Chordomas

Presentation: Chordomas are considered to be slow growing, locally invasive neoplasms with a low tendency to metastasize (Fig. 22.1). Due to the fact that these tumors are slow growing, patients develop symptoms gradually, often over 4–24 months. Chordomas constitute about 1–4% of bone tumors and occur with nearly equal frequency in the sacrum, bony spine, or skull. Chordomas may also invade paraspinal soft tissues. As many as 30% of sacroccocygeal chordomas eventually metastasize [3, 10].

Sacral lesions usually present with non-specific low back or sciatic region pain. In addition, nearly 40% of patients experience hemorrhoidal bleeding, tenesmus, obstipation or constipation, and rectal dysfunction. On rectal examination, a tumor can be palpated in nearly all patients [9].

Patients with chordomas that involve the true spine (32.8%) frequently present with radicular back or neck pain of relatively short duration. More than 33% of these patients have weakness or other neurologic deficits at presentation [9]. Chordomas of the cervical spine may also present concomitantly with an oropharyngeal mass, airway obstruction, or dysphagia due to an extensive soft tissue component of the tumor [10].

Diagnosis: CT scans delineate bony and soft tissue components of chordomas. On CT, these lesions often have lytic bone components and a large soft tissue mass. Additionally, invasion of intervertebral disks and growth-associated calcification (in 30% of patients) can also be visualized on CT imaging [10]. Gadolinium-enhanced MRI shows the full extent of the tumor with excellent anatomical detail. MRI can also demonstrate foci of low-signal attenuation, signifying areas of calcification. On T1-weighted MRI, chordomas are hypointense or isointense to muscle, and they enhance avidly. On T2-weighted sequences, chordomas are hyperintense to muscle [10]. For this reason, T2-weighted MRI is optimal for elucidating soft tissue tumor extensions, the absence or presence of a tissue plane between the chordoma and rectum, and perineural invasion [9].

Despite characteristic imaging findings, histopathological diagnosis is required prior to initiating therapy [10]. Chordomas are known to seed along biopsy tracts; thus, when chordoma is suspected, a needle biopsy must not enter any other body cavities. Furthermore, the tract should be clearly marked so that it can be confidently identified and included in tissue targeted for resection during surgery [10].

Prognosis and Management: Poor prognostic factors of chordomas include large tumor size, non-delineated margins, incomplete resection, tumor necrosis, and a Ki-67/MIB-1 index that is greater than 5% [9, 10]. Management requires en bloc resection, due to a strong correlation between extent of surgical resection and
Fig. 22.1 Images of a patient with a chordoma of L4 as viewed via T2-weighted images in the sagittal (a) and axial (b) views.

duration of disease-free survival [10]. A wide margin of normal tissue should be included in resection to minimize the risk of local recurrence. Adjuvant radiation and chemotherapy may be required for tumors that are incompletely resectable or recur following surgical resection.
Sacral chordomas necessitating aggressive resections require highly demanding procedures due to the complex anatomy of the sacral region. These operations are multidisciplinary and require the cooperation of multiple surgical specialties such as plastic surgery, vascular surgery, orthopedic surgery, surgical oncology, and neurosurgery. Preoperative planning is essential in order to develop a clear surgical objective and requires extensive anatomic knowledge of the sacral region. Unfortunately, wide sacral resections frequently require sacrifice of one or more sacral roots. This can lead to sexual dysfunction and loss of bladder and bowel control [10]. Potential complications from aggressive sacral tumor resections include the following: blood loss, infection due to proximal contamination from the anus or piercing of the bowel, and spinopelvic instability due to high sacral amputation. Spinopelvic instability can be managed with novel instrumentation techniques that allow for the reconstruction of the pelvic ring and spinal column [10].

Chordomas that involve the mobile spine are ideally resected via spondylectomy, a procedure in which a complete vertebral segment is removed. It is best suited for neoplasms that have neither metastasized nor extended intradurally, but involve all vertebral elements circumferentially. Surgery for chordomas in the cervical spine is multidisciplinary, often requiring the participation of plastic and otolaryngologic surgeons in order to aid in approach and closure. Transglossal or transmandibular approaches are recommended for achieving successful complete resection due to the ample working room and visualization they provide. For lumbar or thoracic chordomas, standard unidirectional approaches (i.e., lateral, perineal, posterior, or anterior) can be used individually or sequentially to achieve adequate exposure and complete resection [10].

Complications from en bloc resection may arise from manipulation of vital structures like the great vessels following previous radiation or surgery, inadequate management of hemodynamic instability, injury from extensive approaches, such as a double combined approach, and inadequate posterior fixation [11]. Complications arising from en bloc resection of tumors located on the cervical spine include hypoglossal nerve injury, Horner’s syndrome, hoarseness, and dysphagia [10]. In instances when en bloc resection is not possible, intralesional extracapsular excision is an alternative. Intralesional extracapsular excision is frequently employed in managing cervical spine chordomas, which often have an intralesional margin and are challenging to resect en bloc [10, 12].

Chondrosarcomas

Presentation: Chondrosarcomas are rare malignant cartilage-forming tumors. They account for 7–12% of all primary spine tumors and more commonly affect men. Most chondrosarcomas localize to the bony spine. Symptoms develop gradually due to their slow growth rate. The most common symptoms are focal pain, radiculopathy, myelopathy, and cauda equina syndrome. The pain is usually described as a dull, aching back pain that is worse at night. Nearly 50% of patients present with some degree of neurological deficit [2, 13].
Diagnosis: In the case of chondrosarcomas, CT may reveal lytic and destructive lesions, bony focal expansion, thickening of the vertebral cortex, and exophytic extension into soft tissue. Mesenchymal and undifferentiated chondrosarcomas typically demonstrate bone destruction. Clear cell chondrosarcomas show rounded and lytic lesions with calcifications and encompassing sclerosis. MRI is better than CT for revealing soft tissue invasion. T2-weighted sequences are optimal because neoplastic cartilage appears hyperintense [2, 13] (Fig. 22.2). On MRI, chondrosarcomas

Fig. 22.2 Images of a patient with a chondrosarcoma of C3 as viewed via T2-weighted images in the sagittal (a), coronal (b), and axial (c) views
often show enhancement at the scalloped margins of the tumor in a “ring-and-arc” pattern. The enhancing areas correspond to fibrovascular bundles surrounding hyaline cartilage lobules. The “ring-and-arc” pattern reflects the lobulated growth pattern of cartilaginous tumors and helps to distinguish them from other bone tumors.

**Prognosis and Management:** Prognosis is mainly dependent upon the location, size, and World Health Organization (WHO) histological grade of the lesion. Ideal management of chondrosarcomas is complete excision of the lesion via en bloc resection with wide surgical margins. Breaching of the tumor arising from complications of en bloc resection, or intralesional extracapsular excision, results in higher rates of local recurrence and decreased survival. Local recurrence often results in a grim prognosis, with a majority of patients succumbing to their illness within 2 years. Aggressive surgical resection of recurrences has not yet been established as an ideal intervention. However, studies on analogous recurrent pelvic chondrosarcomas have shown that as much as a 50% long-term survival can be achieved. Chondrosarcomas are resistant to radiation and chemotherapy. However, proton beam therapy, high-dose radiotherapy, and hypofractionated stereotactic radiosurgery are modestly effective [2, 13].

**Osteosarcomas**

**Presentation:** Osteosarcomas are the most frequent malignant condition of the bone and 5% of them occur in the axial skeleton. They are most frequent during the adolescent growth spurt and ionizing radiation exposure increases the risk of developing osteosarcomas. Furthermore, patients with hereditary retinoblastomas have an increased risk of developing secondary cancers, 50% of which are osteosarcomas. Most patients present with neurologic deficits and an insidious onset of back pain that is most severe at night [2, 9].

**Diagnosis:** Radiographic findings vary, and typically include combinations of sclerotic and osteolytic lesions. Pathologic fractures may also be seen. MRI visualization of osteosarcomas depends significantly on the degree of tumor mineralization. Non-mineralized tumors display high-signal intensity on T2-weighted sequences, and relatively low-signal intensity on T1-weighted sequences. Mineralized tumors display low intensity signal on both T1-weighted and T2-weighted sequences. PET scans yield the best diagnostic information due to their inherent quality of measuring bone turnover. Serial PET scans can be employed to measure the response of tumor to therapy [2, 9].

**Prognosis and Management:** Osteosarcomas overall have a poor prognosis, with median survival less than 2 years. The ideal management is wide margin-en bloc excision. Careful planning and execution must be exercised in order to avoid entry into tumors. The breaching of a tumor results in higher rates of local recurrence, often earlier than expected, in addition to significantly lower survival rates. Standard adjuvant and neoadjuvant chemotherapies should be coupled to surgical intervention with the purpose of minimizing the probability of local recurrence. Conventional radiotherapy as a primary form of management should be avoided as osteosarcomas
are highly resistant to ionizing radiation. However, conventional radiotherapy may effectively treat residual microscopic tumor after surgery [2, 9].

Ewing’s Sarcoma and Peripheral Neuroectodermal Tumor

Presentation: Ewing’s sarcoma is the second most common cancer of the bone in children and adolescents, with an annual incidence of 2.1 per 1 million children in the United States. Ewing’s sarcoma is a small round cell neoplasm that also includes other small, round cell malignancies such as Askin’s tumor, neuroectodermal tumor of the bone, and other round cell tumors of childhood. Ewing’s sarcoma occurs most frequently during adolescent years and is rare among individuals of Asian or African-American descent. There is no compelling evidence to suggest that Ewing’s sarcoma is caused by exposure to irradiation. Most common presenting symptoms are swelling and pain, concomitant with other systemic symptoms such as fever. Due to the latter, this condition is commonly misdiagnosed as infection. Furthermore, spinal lesions also commonly present with neurologic symptoms due to cord compression. Lesions that metastasize, or occur primarily in the pelvis, may also present as a neurogenic bladder [9].

Diagnosis: Ewing’s sarcoma has a mottled, moth-eaten appearance on plain X-rays. When located in the sacrum, there may be a “cracked ice” or ground glass appearance. Whole-body imaging with CT or nuclear scintigraphy should be performed to exclude the possibility of metastases. In the event that suspicious lesions are located elsewhere, a biopsy should be performed in order to histologically verify the presence of metastatic disease [9].

Prognosis and Management: The most important prognostic factor is the presence of metastatic disease at the time of diagnosis. Overall, systemic chemotherapy is the initial treatment of choice for Ewing’s sarcoma. The standard therapy is a four-drug regimen that is composed of doxorubicin, cyclophosphamide, vincristine, and dactinomycin [14]. However, recent studies have demonstrated that the addition of ifosfamide and etoposide to the standard four-drug regimen may yield 3-year survival rates as high as 80%, whereas patients who received the standard four-drug regimen had a 56% 3-year survival rate [14, 9]. Conventional radiation therapy may be administered jointly with chemotherapy. Dose recommendations include 40–65 Gy to the involved bone or whole bone. A boost dose employing a smaller and more targeted field, delivering 50–60 Gy to the tumor, is recommended [9].

The role of surgical intervention has not yet been established as standard treatment. However, studies have demonstrated a failure of local control as high as 20% via chemotherapeutic intervention, thereby suggesting that en bloc surgical resection with wide margins should be performed in centers with the required expertise to execute such an operation [9].

The treatment of Ewing’s sarcoma patients who present with already established metastatic disease is very challenging. Nearly 75% of these patients incur relapse in 5 years. Novel therapies such as myeloblative therapy and stem cell transplantation
have demonstrated only limited success. A significant amount of work remains to be done in order to better manage these patients [9].

Multiple Myeloma and Plasmacytomas

**Presentation:** Plasmacytomas are the most common primary malignant neoplasm of the spinal column, representing nearly 30% of primary spinal tumors. Plasmacytomas may evolve into more aggressive and numerous neoplasms, collectively known as multiple myeloma. Multiple myeloma is characterized by malignant plasma cells in the bone marrow, in addition to monoclonal immunoglobulins present in the serum or urine (Bence-Jones proteins) or both in 99% of patients. Patients present clinically with diffuse osteoporosis, with or without fractures, and osteolytic bone destruction. Among patients in whom the bony spine is affected, neurologic deficits may also be present. Neurologic deficits include myelopathy, radiculopathy, and are typically the result of epidural soft tissue growth or vertebral body fractures. Other systemic complications associated with multiple myeloma that may also be evident at the time of presentation include renal failure, infections, hypercalcemia, and anemia [2, 9, 15].

**Diagnosis:** Plain radiograph bone surveys including long bone of the extremities, pelvis, skull, ribs, and spine should be performed. Such conventional radiographs demonstrate lytic bone destruction in as many as 80% of patients. CT scans may also be useful. Whole-spine MRI scans are critical to evaluate the possibility of epidural spinal cord compression [15, 9].

In cases where a pathologic vertebral compression fracture is found in a patient without known cancer, lab tests including serum and urine protein electrophoresis and immunofixation should be obtained. Laboratory studies may also find hypercalcemia, hyperuricemia, elevated erythrocyte sedimentation rate, and elevated levels of alkaline phosphatase [15, 9].

In order to establish the diagnosis of multiple myeloma (vs a solitary plasmacytoma), a collection of abnormal plasma cells must be found in multiple locations. A bone marrow aspirate from a location such as the iliac crest can aid in establishing the diagnosis of multiple myeloma and differentiate it from a solitary plasmacytoma. Diagnostic bone marrow aspirates are present when more than 15% of plasma cells are found in the aspirate. Complete bone surveys, as discussed earlier, are also capable of establishing the diagnosis of multiple myeloma via the finding of potential additional lesions [15].

**Prognosis and Management:** Plasmacytomas alone tend to have a benign course and afflicted patients have a median survival time exceeding 10 years. However, plasmacytomas can evolve into multiple myeloma, in which case the median survival is 28 months. Medical management of multiple myeloma with plasmacytomas includes bisphosphonates, corticosteroids, and chemotherapy, often with thalidomide or a thalidomide analog. Bisphosphonates such as pamidronate and zoledronic acid should be administered intravenously, as oral bisphosphonates are not effective in the treatment of multiple myeloma [2, 9, 15].
Plasmacytomas and multiple myeloma are particularly sensitive to chemotherapy and radiotherapy, and thus do not typically necessitate surgical intervention. Radiation results in the apoptosis of multiple myeloma cells and is thus capable of resolving spinal cord compression, as long as cord compression is not being caused by retropulsion of bony fragments. Low-dose radiation (20 Gy in 10 fractions) is often sufficient to effectively treat non-bony cord compression and pain. Surgical intervention is reserved for cases that present with gross spinal instability and myelopathy due to compression from retropulsed bone fragments. Furthermore, if not extremely severe, symptoms of segmental instability or compression fractures can be treated via percutaneous or open kyphoplasty and vertebroplasty. Novel therapies such as proteasome inhibitors (bortezomib) and RANK ligand inhibitors (denosumab) are expanding the arsenal available to treat this disease [2, 9, 15].

**Other Spinal Epidural Tumors**

**Giant Cell Tumors (GCTs)** are benign but locally aggressive tumors that usually affect the articulations of extremities or sacrum when involving the spinal skeleton. They present mostly during the third and fourth decades of life and are derived from multinucleated, osteoclastic giant cells of macrophage origin. GCTs comprise 5% of all primary bone tumors. Lesions that involve the spinal cord have a slight female predominance and most frequently occur in the thoracolumbar spine. The typical clinical presentation is an insidious onset of back pain that is most severe in the evening. In addition, pathological fractures occur in nearly 30% of patients. Recommended treatment is complete en bloc surgical resection. Prognosis is variable. GCTs are locally aggressive and may have up to a 50% recurrence rate. Intralesional excisions or curettage should be avoided due to their correlation with higher recurrence rates [2, 16].

**Aneurysmal Bone Cysts** are benign lesions of the bone of unclear pathophysiology that affect people most often during the second and third decades of life. When found in the bony spine, they most commonly affect the neural arch with nearly 90% of the lesion extending into the vertebral body. The most common presenting symptom is insidious nocturnal back pain. Surgical intervention may be curative. Embolization during preoperative planning should be considered due to the extreme vascularity of tumors. In some cases, embolization alone may be curative. Prognosis is variable, with recurrence rates as high as 20–30% [2, 17].

**Vertebral Hemangiomas** are relatively common vascular tumors or dysplasias that affect 10–12% of the population, mainly during the fourth to sixth decades of life. They are usually discovered incidentally, as most lesions are asymptomatic. In some cases, the tumors undergo osseous or epidural expansion and can cause pathological fractures. Prognosis is excellent and asymptomatic tumors rarely require treatment. Aggressive lesions can be treated with surgical excision, low-dose radiation, vertebroplasty, or intralesional ethanol injection [2, 18].

**Osteoid Osteomas and Osteoblastomas** are benign lesions that represent 12% of all skeletal neoplasms, 10% of which occur in the spine. They are typically found in
the neural arch of lumbar vertebral bodies. They present most often during the second decade of life, and their most common clinical presentation is that of nocturnal pain. The majority (70%) of patients develop scoliosis caused by muscular spasms. Well-managed cases have an excellent prognosis. Treatment most often involves surgical resection and has the potential to be curative. In order to be curative and avoid recurrence, the entire tumor nidus must be removed [2, 19].

**Intraspinal Extramedullary Spinal Cord Tumors**

**Presentation**

Clinical symptoms are usually non-specific and include radicular symptoms, back pain, and a slow onset of neurological deficits such as gait problems, weakness, paresthesia, impotence, bowel dysfunction, and bladder dysfunction. Physical examination may reveal Brown–Sequard syndrome (ipsilateral hemiplegia with contralateral pain), along with signs of long-tract involvement such as a Babinski sign, hyperreflexia, and clonus. A less common presenting symptom is acute headache due to subarachnoid hemorrhage. Among children afflicted with these types of tumors, findings such as kyphoscoliosis or scalloping of the vertebral bodies are also common [20].

**Diagnosis**

MRI is the imaging study of choice and should be performed in order to investigate the presence of spinal vascular malformations or neoplasms. Plain radiography, CT, and CT with myelography cannot sufficiently characterize or delineate an intradural tumor. However, if MRI is contraindicated for a particular patient, CT with myelography is the suboptimal imaging alternative. In addition, a three-dimensional CT reconstruction of the spine can be helpful in presurgical planning. Conventional angiography may be helpful in detecting vascular malformations, analyzing supply and draining vascular structures surrounding the tumor, and presurgical planning interventions such as embolization [20, 21].

**Types of Tumors**

Schwannomas are benign tumors that are most commonly intradural extramedullary spinal lesions (70%); however, they may also be extradural (30%). They are seen most commonly in adults, and typically in association with neurofibromatosis type II (NF-II). Tumors most commonly arise from the dorsal sensory root of the lumbar or cervical spine and much less commonly from the thoracic region. Schwannomas are best visualized on MRI, where they appear as solid masses that displace dorsal sensory roots. As they grow and expand, they impinge on the spinal cord, filum terminale, or conus medullaris and displace it to the contralateral side. When visualized on T1-weighted images, schwannomas are isointense and enhance avidly; however,
when visualized on T2-weighted images, they display hyperintense signal. Larger schwannomas are capable of invading the prevertebral space and neural foramina in a “dumbbell” fashion. If the latter occurs for a prolonged period of time, scalloping or erosion of the posterior aspect of the vertebral body may occur. In addition, long-term presence can also result in widening of the spinal canal [20, 21].

Meningiomas are the second most common intraspinal tumors. They most often afflict the older population; however, when they do affect younger individuals, they have a tendency to be more aggressive. In addition, females are significantly more affected. They are most often located intraspinally on the postlateral aspect of the thoracic region. Most often they are solitary tumors but can also present as multiple meningiomas in about 2% of patients. Patients with NF-II often develop multiple meningiomas. Histologically, they are solid, well-circumscribed lesions with extensive attachment to the dura. The optimal imaging study to evaluate meningiomas is MRI. On T1-weighted images they are hypointense to isointense and enhance homogeneously. On T2-weighted images, they are mildly hyperintense. Furthermore, they may cause displacement and compression of the spinal cord. On rare occasion, signal changes caused by compression can be observed [20, 21]. A “dural tail” and cerebrospinal fluid cleft are frequently seen on MRI.

Neurofibromas are benign tumors of the peripheral nerves. These types of tumors are characterized by their ability to encase nerve roots, distinguishing them from schwannomas whose asymmetric growth often results in displacement of the nerve root. These tumors are rare, except among patients with NF-II, in whom an increased incidence is observed. On MRI, neurofibromas are fusiform or rounded tumors. They are isointense on T1-weighted images and significantly hyperintense on T2-weighted images. In addition, intense and homogeneous enhancement can be observed following injection of gadolinium. Patients with neurofibromatosis type I (NF-I) often display multiple and plexiform neurofibromas. Slow growing, long-standing tumors can be distinguished by scalloping of the posterior vertebral bodies [20, 21].

Paragangliomas are rare intradural tumors that are commonly benign but sometimes assume a more aggressive phenotype with systemic metastasis. They are typically found in the filum terminale, cauda equina, or conus medullaris. They are endocrinologically inactive, as are other extraadrenal chemodectomas. On MRI, they appear isointense on T1-weighted images, hyperintense on T2-weighted images, and enhance avidly. Intratumoral blood vessels and hemorrhage may be seen [20, 21].

Prognosis and Management

The optimal treatment for IESCTs is complete microsurgical excision [5]. Surgical access to extramedullary tumors should be planned based on the following factors: location of the tumor, spread, and region to which the tumor is localized. Dorsolateral access is ideal for managing cases of ventrolateral meningiomas. In instances of ventrolateral and ventral tumors of the cervical spine a far lateral approach is preferable. Management of neurofibromas is dependent upon their size
Endometriosis of small size, dumbbell shaped, and limited spread, which only occupies the neural foramen, can be surgically managed via a dorso-lateral access. Neurofibromas demonstrating extensive ventral growth through the neural foramen require a ventrolateral approach regardless of the spinal level [7].

Tumors located ventral to the spinal cord may not be completely resectable. Residual benign tumors are often managed with spinal radiosurgery. Radiosurgical approaches can also be considered when benign tumors recur after surgery and in newly diagnosed patients with contraindications to surgery, multiple lesions, and the absence of high-grade compressive myelopathy. Potential benefits of radiosurgery include its ability to avoid operative complications and provide symptomatic relief [7, 22].

Favorable prognostic factors include the following: prompt and early diagnosis prior to the appearance of severe neurological symptoms, young age, complete tumor excision, minor cord compression, absence of intraoperative spinal cord retraction via adequate surgical access, and employment of proper microsurgical techniques [7].

**Intramedullary Spinal Cord Tumors (ISCTs)**

**Presentation**

Intramedullary spinal cord tumors do not have one typical presentation. Signs and symptoms may develop over time or a lesion may be detected incidentally. Among patients in whom symptoms develop gradually, the time frame during which this occurs can range from 14 days to 9 years. Presenting symptoms may include extremity weakness, radicular pain, localized pain, paresthesias, dysesthesias, torticollis, spasticity, Brown–Sequard syndrome, and bowel or bladder dysfunction [8].

**Diagnosis**

ISCTs must be distinguished from extramedullary lesions, metastatic spinal cord tumors, inflammatory lesions, demyelinating processes, and vascular insults [8]. MRI is the imaging modality of choice. The MRI appearance of ISCTs varies among different tumor types [8].

**Main Types of Tumors**

*Ependymomas* are the most common spinal cord tumors in adults, peaking in incidence near the fourth and fifth decades of life, and account for nearly 60% of all intramedullary tumors. Cellular ependymomas are located mainly in the cervical spine. They arise from the ependyma-lined central canal and may grow in a concentric pattern. They are well-circumscribed lesions that are hyperintense on T2-weighted sequences and isointense to hypointense on T1-weighted imaging. Enhancement with gadolinium is typical and cysts and calcifications
may be seen. A syrinx is also characteristic of cervical cellular ependymomas. Myxopapillary ependymomas are most often benign and present in the filum terminale and conus medullaris. They vary vastly in size and can be associated with scoliosis, enlargement of the neural foramina, and scalloping of the vertebral body. Like cellular ependymomas, they are hyperintense on T2-weighted sequences and isointense to hypointense on T1-weighted sequences (Fig. 22.3). Enhancement is usually observed. In some circumstances, they may be hyperintense on T1-weighted

![Fig. 22.3](image-url) Images of a patient with a giant sacral myxopapillary ependymoma as viewed via T1-weighted images in the sagittal plane before (a) and after (b) administration of gadolinium contrast. Sagittally reconstructed CT scan shows the lytic nature of the lesion at the sacrum (c)
sequences due to high mucin content or hemorrhage. Cysts are also common features of myxopapillary ependymomas [20].

Astrocytomas are the second most commonly occurring intramedullary tumor in adults and the most common among children. They are most common in the cervical and upper thoracic regions. On MRI, they are focal, fusiform expansions of the spinal cord with irregular borders. They are typically hyperintense on T2-weighted sequences, hypointense on T1-weighted sequences, and enhancement is unusual, except in high-grade lesions. Syringes and edema are also common findings [20].

**Prognosis and Management**

The main prognostic factor in patients with ISCTs is tumor histology. Tumor histology is correlated with the ability to achieve complete surgical resection. When appropriate, surgical resection is an effective treatment for many intramedullary spinal cord tumors. Patients with infiltrative high-grade astrocytomas have a poor prognosis that is nearly as poor as that of cerebral high-grade astrocytomas. In contrast, patients with low-grade astrocytomas and ependymomas, which are usually well circumscribed, are potentially curable by surgery. Interestingly, the duration of symptoms prior to presentation correlates with prognosis. This may be because patients with less aggressive tumors can tolerate mild symptoms for a longer period of time before seeking medical attention [8].

Most patients that present with ISCTs exhibit some form of neurological dysfunction. Following surgery, patients may incur further neurological deficit due to the risk of excising tissue from the spinal cord. Hence, advances such as continuous intraoperative neurophysiology monitoring of somatosensory-evoked potentials and motor-evoked potentials (MEPs) have been developed. These modalities reduce postoperative neurologic morbidity.

In certain cases complete resection of an ISCT is not possible. Because ependymoma prognosis correlates strongly with extent of resection, a second operation is sometimes recommended. Complications of tumor resection may include CSF leak, nerve or spinal cord injury, infection, and bleeding [8].

Adjuvant radiation therapy often accompanies surgical intervention or is used in cases in which complete resection is not possible. However, there is no definitive evidence to demonstrate that adjuvant radiation therapy improves outcomes. Adjuvant radiation therapy is recommended in the case of low-grade astrocytomas and ependymomas that are not completely resected. The 10-year survival rate is 40–91% and 62–91% after surgery and radiation therapy for low-grade astrocytomas and ependymomas, respectively. In the case of high-grade astrocytomas, adjuvant radiation therapy is almost always recommended. Standard radiation treatment is 50–60 Gy in 1.8–2 Gy fractions over a period of 6 weeks. Potential complications include the late development of a second malignant neoplasm, subluxation, spinal kyphosis, delayed radiation necrosis, and radiation myelopathy. Potential side effects include radionecrosis, spinal cord edema, and impaired wound healing.
Various chemotherapy regimens may also be effective in treating recurrent intramedullary spinal cord tumors. Treatments previously reported to have activity against intramedullary spinal cord neoplasms are carboplatin with vincristine; lomustine, vincristine, and procarbazine.

Finally, stereotactic radiosurgery is a potential treatment avenue that is rapidly advancing. It shows promise due to the fact that it delivers a high dose of radiation to the tumor volume, while simultaneously limiting the dose of radiation that is collaterally endured by healthy structures. Radiation dosage typical ranges from 1,600 to 2,500 cGy, given in 1–5 fractions, mostly in an outpatient setting. Currently, the majority of spine tumor cases that are managed with stereotactic radiosurgery are extramedullary spinal cord tumors. However, novel reports of stereotactic radiosurgery used to treat ISCTs are rising. Nonetheless skepticism remains due to the lack of consistent evidence demonstrating the safety and effectiveness of stereotactic radiosurgery [8].

References

Index

A
Acoustic neuroma, 407
Acromegaly, 392
ACTH-secreting pituitary adenoma, 384
Acute lymphoblastic leukemia (ALL), 362
Acute myeloid leukemia (AML), 106
Adenosine triphosphate (ATP), 212
Adherence gene αE-catenin, 255
Adipose tissue tumors
  CNS angiolipomas, 511
  CNS hibernoma, 511–512
  intracranial lipoma, 510–511
  intracranial liposarcoma, 512
Adult medulloblastoma, 425–426, 428
Aggressive therapy, 143
Alkaline phosphatase, 311
Alopecia, and cranial RT, 119
Alphaamino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, 220
Alpha fetoprotein (AFP), 311
Alpha-tocopherol (vitamin E), 149, 152
5-Aminolevulinic acid (ALA), 201
Anaplasia, 174
Anaplastic astrocytomas, 195, 197, 202
  grade III, 30–31
  See also High-grade astrocytomas (HGAs)
Anaplastic ependymoma, 250, 256
  grade 3 tumors, 249
  radiation treatment, 256
Anaplastic oligoastrocytoma (AOA), 233
  clinical presentation, 234
  genetics, 236–237
  incidence, 234
  localization, 234
  lumped together with AOD, 234
Anaplastic oligodendrogial tumor (AOT), 234
  chemotherapy, 240–241
  at recurrence, 241–243
  genotype, 239
histology, 234–236
newly diagnosed
  adjuvant chemotherapy, 243–244
  upfront chemotherapy, 244–245
radiotherapy, 240
with and without 1p/19q co-deletion, 235
Anaplastic oligodendroglioma (AOD), 31, 233
  assessment of EGFR amplification, 238
  chemotherapy, 240–241
  at recurrence, 241–243
  clinical presentation, 234
  genetics, 236–237
  incidence, 234
  localization, 234
  loss of chromosome 10 or 10q, 238
  treatment, 239–240
  chemotherapy, 240–241
  radiotherapy, 240
  surgery, 240
Aneurysmal bone cysts, 540
  embolization, 540
  presenting symptom, 540
Angiocentric glioma, 510
Angiogenesis, 35, 215
Anterior lesions, and effects, 144
Anti-angiogenic therapy, 215–219
Anticonvulsant therapy, adverse effects, 57
Antidepressants, 157, 159
Anti-epileptic therapy issues, 116
Antimetabolite therapy, 8
Anxiety, 155, 157–158, 160
Apoptosis-associated TRAIL pathway genes, 255
Apparent diffusion coefficient (ADC), 207
Arachnoid cyst, 518
Aryl hydrocarbon receptor-interacting protein (AIP) gene, 379
Astroblastoma, 509

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549
Astrocytic tumors, 174–175
Astrocytomas, 175
  gemistocytic, 175
  intramedullary spine tumors, 545
    common in cervical and upper thoracic regions, 545
low-grade, 28, 175
  IDH1 and IDH2 mutations role, 29
  prognostic and predictive factors, 30
  role of p53 in, 28–29
  role of PDGF, 29
See also Gliomas
molecular alterations in, 198

Attention
  -deficit hyperactivity disorder, 148
donepezil effect on, 152
  impairment and tumors, 144–147
  methylphenidate effect on, 150
  modafinil effect on, 151
  vitamin E and, 152
Atypical teratoid rhabdoid tumor (ATRT), 303
Autocrinergic glutamate activation, 220
Autologous stem cell transplantation (ASCT), 345

B
Basic helix-loop-helix (bHLH) transcription factors, 176
BCL-6 expression, 339
BCNU (carmustine)
  side effects of, 111
  systemic toxicity, myelosuppression, 110
BCNU wafers, 116–117
Behavioral therapy, 156, 159
See also Neurocognitive function
Bevacizumab, 195, 215, 218, 242, 409
  therapy
    complications, 115–116
    dose adjustment and discontinuation parameters, 107–109
    intratumoral hemorrhage risk, 116
    leukoencephalopathy syndrome, 116
    side effects, 115
  Biochemotherapy, 366–367
  Biological endpoints, 90
Biomarkers, prognostic and predictive
  CpG methylator phenotype (CIMP), 38
  MGMT promoter methylation, 38
Bleomycin, 314
Blood–brain barrier, 285
Blood–brain barrier disruption (BBBD), 344
BRAF gene, 272
Brainstem glioma (BSG), 263
  classification, 266
diffuse and focal, characterized by, 263
diffuse-infiltrating, 265
epidemiology, 263
MRI for diagnosis, 265
pathology, 266
  prognostic factors, 267
  surgery role in focal, 269
  symptoms and signs, 265–266
  treatment of, 267
  diffuse tumors, 267–269
  focal tumors, 269–270
See also Gliomas
Brain tumors, 463, 470, 483–484
  age factor role, 5
  anti-epileptic drugs (AEDs) used for, 66–67
  and anxiety, 74
  and cerebral edema, see Cerebral edema
corticosteroids complications, 58–59
  cognitive deficits, 73–74
  gastrointestinal, 59–60
  immunosuppressive effects, 61–63
  intracranial hemorrhage, 72
  musculoskeletal, 60–61
  psychiatric, 61
  thromboembolic, 68–69
depression and, 74
effects of PDGF overexpression, 29
epidemiology, 4–5
genetic alterations
  familial aggregation, 10–11
  polymorphisms, in cancer relevant genes, 11
  genetic differences role, 4
  genetic susceptibility for, 196
geriatric location impact, 4
gliomas, see Gliomas
  immunologic factors, 12–13
  incidence, white/black population, 4
  infections, 12–13
  meningiomas, see Meningiomas
  molecular pathogenesis, see Gliomas
  neurocognitive symptoms
    fatigue, 72–73
    patients, symptoms and quality of life in care and management of patient, 147
    fatigue, and management, 154–157
    impact on patient and family, 160
    mood disturbance, interventions, 157–159
    overview, 153–154
    pathophysiology, 155–156
sleep–wake cycle disturbance, 160
symptom clusters, 160
prognosis
factors associated, 6–7
genes or chromosomal abnormalities, 17
genetic markers role, 6
human telomerase (hTERT) expression, 7
molecular markers role, 6
serum biomarkers role, 6
risk factors, 3, 7
behavioral, 9–10
environmental, 9–10
heritable syndromes, 7
hormone replacement therapy, 8
ionizing radiation exposure, 8
oral contraceptive use, 7–8
role of p53, 28
seizures risk, see Seizures
signs and symptoms, 55
steroid side effects in, 63
survival time in, 5
bevacizumab, 6
temozolomide chemotherapy, 6
and thromboembolic disease association, 68
trials challenges
drug selection, and interactions impact, 94–95
endpoints, 96
historical controls, 98–99
Macdonald criteria, 96–97
radiologic evaluation of response, 97
RANO group criteria, 98
response assessment, 96
T2/FLAIR signal, 98
See also Clinical trials design, cancer trial overview
types, 4
Brain tumors, rare
atypical teratoid/rhabdoid tumors, 509
embryonal tumors
CNS ganglioneuroblastoma, 508–509
CNS neuroblastoma, 508–509
CNS primitive neuroectodermal tumors, 506–507
ependymoblastoma, 508
medulloblastoma, 508
supratentorial primitive neuroectodermal tumors, 507
neuroepithelial tissue tumors
angiocentric glioma, 510
astroblastoma, 509
chordoid glioma, 510
CPC and CPP, 500–501
choroid plexus tumors, 499–500
neuronal, and neuronal-glial tumors
cerebellar liponeurocytomas, 503–504
desmoplastic infantile astrocytoma, 502
desmoplastic infantile ganglioglioma, 502
dysembryoplastic neuroepithelial tumors, 505
dysplastic gangliogliocytoma, cerebellum of, 502–503
extraventricular neurocytoma, 503–504
gangliocytomas, 501–502
gangliogliomas, 501–502
intracranial paraganglioma, 505–506
intraspinal paraganglioma, 505–506
papillary glioneuronal tumor, 504
rosette-forming glioneuronal tumor, IV ventricle, 505
Breast cancer resistance protein (BCRP), 212

C
Calcification, 271
Calcium channel antagonists, 366
Cancer stem cell model, 45–47
properties, 48
See also Gliomas, cell of origin
Candidiasis, steroids immunosuppression and, 63
Carbamazepine, 116, 147
Carboplatin, 211, 273
Caregiver burden, 147
See also Brain tumors
Carmustine wafers, 201–202
Cartilaginous tissue tumors
chondrosarcoma, 513–514
chordoma, 513–514
Ewing’s sarcoma, primitive neuroectodermal tumor, 515
Cataract formation, and corticosteroids effects, 63
CCNU (lomustine), 110
CD133 (aka Prominin-1), 48
CDK inhibitors, 379
CDKN2A gene, 237
Cediranib, 219
Cellular telephones, usage and brain tumors risk, 8–9
Central nervous system (CNS)
lymphoma, 336
malignancy, 286
Central nervous system (CNS) (cont.)
- tumors, 286
  See also Brain tumors, rare
- Central neurocytoma, 503
- Cerebellar astrocytomas, 291
- Cerebellar liponeurocytoma, 503
- Cerebellar mutism syndrome, 315
- Cerebellar PNET, see Medulloblastoma
- Cerebellar syndromes, 316
- Cerebellar tumors, 291
- Cerebellopontine angle (CPA) lesions, 402
- Cerebral angiography, 357
- Cerebral edema
  - characterization, 57
  - corticosteroids complications, 59
    - cognitive deficits, 73–74
    - fatigue, 72–73
    - gastrointestinal, 59–60
    - immunosuppressive effects, 61–63
    - infectious, 61–63
    - intracranial hemorrhage, 72
    - musculoskeletal, 60–61
    - psychiatric, 61
    - thromboembolic, 68–69
  - defined, 55
  - dexamethasone therapy, 57–59
    - therapeutic effects, 59
  - mass effect, 56–57
  - VEGF inhibitors role, 64
  See also Brain tumors
- Cervico-thoracic spinal irradiation, 315
- Chemotherapy complications
  - bevacizumab therapy
    - complications, 115–116
    - dose adjustment and discontinuation parameters for, 107–109
  - etoposide (VP-16), 112
  - irinotecan (CPT-11), 111–112
  - methotrexate, 113–114
  - myelodysplastic syndrome (MDS), 105–106
  - nitrosothioureas, 110–111
  - platinum compounds
    - carboplatin, 112–113
    - cisplatin, side effects, 112–113
    - procarbazine, 111
  - temozolomide therapy, 104–105
    - dose adjustment parameters for, 106
    - TMZ-related side effects, medications used to prevent and treat, 105
    - vincristine, 114–115
- Chemotherapy-related myelodysplastic syndrome (MDS), 105–106
- Chicken wire, 176
- Childhood Lhermitte–Duclos disease, 288
- Choline:N-acetylaspartate (Cho:NAA) ratio, 179
- Chondrosarcomas, 535–537
  - CT scan and MRI, for diagnosis, 536
  - high-dose radiotherapy, effective in, 537
  - hypofractionated stereotatic radiosurgery for, 537
  - location and prognosis, 537
  - malignant cartilage-forming tumors, 535
  - occurrence, in thoracic spine, 530
  - proton beam therapy, effective in, 537
  - resistant to radiation and chemotherapy, 537
  - slow growth rate and symptoms, 535
- Chordomas, 533–535
  - CT scans for diagnosis, 533
  - en bloc resection, complications from, 535
  - gadolinium-enhanced MRI, 533
  - management requirements, 533–534
  - in mobile spine, spondylectomy, 535
  - occurrence
    - in coccyx or sacrum, 530
    - in skull base and mobile spine, 530
  - presentation, 533
  - prognostic factors, 533
  - sarcomal, aggressive resections need complications, 535
  - slow growing, 533
- Choriocarcinomas, 439
- Choroid plexus carcinoma (CPC), 287, 308–310, 500–501
- Choroid plexus papillomas (CPP), 308–309, 500
- Choroid plexus tumors, 308–310, 499–500
  - children diagnosed with, 310
  - diagnostic criteria, 309
  - diagnostic neuroimaging studies, 310
  - gross total resection, 310
  - MRI, 309
  - MR spectroscopy, 309
  - characteristics, 310
  - symptoms, 309
- Cilengitide monotherapy, 219
- Clinical trials design, cancer trial overview, 99
  - components, 86
  - Phase 0 trials, 86
  - objective, 87
  - types, 87–88
  - Phase III trials
    - experimental vs. standard therapy, 94
    - randomization goal in, 94
Phase II trials
  efficacy assessment, MacDonald criteria, 92
  endpoints, for targeted agents, 92–93
  limitations, 93–94
  multi-stage design, 91
  objectives, using cytotoxic agent, 91–92
  progression status, assessments, 92
  quality of life assessment, 93
  surrogate endpoint, 92
  tumor response, 92
Phase I trials
  dose escalation designs, 89
  drug dose determination, recommended, 88
  Fibonacci escalation sequence, 89
  limitations, 91
  pharmacokinetic studies, new agents, 89–90
  principle, dose escalation, 88
  reporting, monitoring, and documenting toxicities, 90
  starting dose deduction, guidelines, 88–89
  principles, 86
  requirements, 85
  typical conditions for, different types, 86
Clonal evolution model, 45–46
  See also Gliomas, cell of origin
11C-methionine, 122
1p/19q co-deletions, 177, 234–239, 242, 244
Cognitive behavioral therapy, 156, 159
  See also Health-related quality of life (HRQOL)
Cognitive function
  alpha-tocopherol effect, 152
  classification by HSCS, 150
  donepezil effect, 151
  modafinil effect, 151
  See also Neurocognitive function
Cognitive impairments, relation to lesion location, 144
Collaborative Ependymoma Research Network (CERN), 257–258
Colloid cyst, 517
Combined modality therapy, 340–343
Comparative genomic hybridization (CGH), 253, 301
Complications, therapy, see Specific therapies
Congenital glioblastoma, 295
Corticosteroids, 339
  therapy complications, in brain tumors, 58–59
cognitive deficits, 73–74
gastrointestinal, 59–60
immunosuppressive effects, 61–63
intracranial hemorrhage, 72
musculoskeletal, 60–61
psychiatric, 61
thromboembolic, 68–69
Cortisol, 384, 392
Cowden syndrome (CS), 288, 480, 503
  associated tumors, 482
  LDD, management of, 482–483
  clinical features, 481
  diagnosis, 481–482
  molecular genetics, 481
  pathogenesis, 481
Cranial irradiation, see Radiation therapy (RT)
cranial, and complications
Craniopharyngiomas, 313–314
  adamantinomatous, 313
  benign non-glial tumors, 313
  chemotherapy, 314
  histology, 313
  MRI features, 313
  progression, 314
  subtotal resection, and field high-dose radiotherapy, 314
  symptoms, 313
CREB-binding protein (CBP), 289
CSF protein, 338
Cushing’s disease, 384, 393
Cystic lesions, 516
  arachnoid cyst, 518
  colloid cyst, 517–518
  dermoid cysts, 517
  epidermoid cysts, 517
Cystic tumors, 405
Cytokeratin, 308
D
DCC gene, 199
Deep vein thrombosis (DVT), 68
diagnosis, 69
Depression, 154–155, 157–160
Dermoid cysts, 517
Desmoplastic infantile astrocytoma, 502
Desmoplastic infantile gangliogliomas (DIGs), 292–293, 296, 298, 502
Dexamethasone therapy, 57
Diencephalic gliomas, 291
Diencephalic syndrome, 291, 293
Diffuse astrocytomas, 174
Diffuse brainstem gliomas, 295
Diffuse intrinsic pontine gliomas, 292, 295
Dienogest (DNG), 291
Dielomatous gangliogliomas, 293
Dilation–distraction–resection, 289
Dilation–distraction–resection–implantation (DDRI), 289
Dilation–distraction–resection–implantation (DDRI), 289
Dilation–distraction–resection–implantation (DDRI), 289
Dilation–distraction–resection–implantation (DDRI), 289
Diffuse large B-cell (DLBCL), 333
Diffuse tumors, 267–269
Donepezil, 149
  limitations, 151–152
  profile of mood states (POMS) changes in, 152
Dynamic contrast-enhanced perfusion MRI (DCE-MRI), 179
Dysembryoplastic neuroepithelial tumors (DNET), 275
Dysembryoplastic neuroectodermal tumors (DNET), 293, 296, 298, 505

E
EGFR, see Epidermal growth factor receptor
EGFR amplification, 197, 199, 237
EGF receptor (EGFR), 368
EGFR inhibitors, 368
Embryonal carcinomas, 439
Embryonal tumors, 286, 303
  CNS ganglioneuroblastoma, 508–509
  CNS neuroblastoma, 508–509
  CNS primitive neuroectodermal tumors, 506–507
ependymoblastoma, 508
medulloblastoma, 303
  adjuvant chemotherapy, 306
  CT scan, 305
  modified Chang classification, 306
  risk stratification, 305
  treatment, 306, 307
  WHO classification, 304
medullopethelioma, 508
pineoblastoma, 307–308
supratentorial primitive neuroectodermal tumors, 507
supratentorial PNET, 307
Endocrine alterations, 315
Enzyme-inducing anti-epileptic drugs (EIAEDs), 116
Ependymoblastoma, 508
Ependymoma(s)
  adjuvant therapy, 302
  chemotherapy, 256, 302
  chromosomal abnormalities
    11q LOH, 253
    22q loss of heterozygosity (LOH), with NF2 mutations, 253
  classification, grades, 249, 251, 301
  ependymoma stem cells, 255
  epidemiology, 252–253
  epigenetic studies
    gene promoter region methylation, 253–254
features, 301
frequency in men, 252
frontal, 250
gene array-based profiles, 253
glioblastomas, 300–303
grade 2 tumors, 249
incidence, 252–253
location and symptoms, 301
located mainly in cervical spine, 543
molecular pathway abnormalities
  ErbB2 and ErbB4 receptors overexpression, 253
integrin αvβ3 increased expression, 253
molecular profiles, 253
MRI appearance, 301
myxopapillary, 249, 251, 257, 303
  associated with scoliosis, 544
cysts, 545
pathologic diagnosis, 251
prognosis, implications for, 255
prognostic factors, 251–252, 302
radiation treatment, 256
spinal cord, 257–258
stem cells, 255
surveillance scanning, 303
syrrinx, characteristic of, 544
treatment, 301–302
  implications for, 255
spinal cord ependymomas, 257–258
treatment, intracranial tumors
  chemotherapy regimens, 256–257
  platinum-based regimens, 256
  radiation treatment, 256
  surgical resection, 255
WHO classification, 249–251, 301
Epidermal growth factor receptor (EGFR), 32, 34, 36–38, 252
Epidermal growth factor receptor (EGFR) gene, 197
Epidermoid cysts, 517
Epidural lipomatosis, chronic steroid treatment, 63
Epidural spinal tumors, 530–531
types
  aneurysmal bone cysts, 540
  chondrosarcomas, 535–537
  chordomas, 533–535
  Ewing’s sarcoma, 538
  giant cell tumors (GCTs), 540
  multiple myeloma, 539–540
  osteoblastomas, 540–541
  osteoid osteomas, 540–541
osteosarcomas, 537
peripheral neuroectodermal tumor, 538
plasmacytomas, 539–540
vertebral hemangiomas, 540
Epipodophyllin, 316
Epstein–Barr virus (EBV), 333–334
Erlotinib, 368
Etoposide (VP-16), 211
complications, neuropathy and encepalopathy, 112
side effects, 112
Ewing's sarcoma, 515, 538
biopsy, 538
common in adolescent years, 538
four-drug regimen, 538
mottled and moth-eaten appearance on X rays, 538
myeloablative therapy for, 538
presenting symptoms, 538
radiation therapy with chemotherapy, 538
stem cell transplantation, 538
systemic chemotherapy for, 538
whole body imaging with CT, 538
Executive function impaired, and tumors, 144–146
F
Familial isolated pituitary adenomas (FIPAs), 379
Fatigue
and brain tumors, 154–156
management, 156–157
α-Fetoprotein (αFP), 439
18F-fluorodeoxyglucose (FDG), 122
18F-fluorodeoxyglucose (FDG)-PET, 208
Fibrillary astrocytoma, 292, 294, 298
Fibrosarcoma, 513
Fibrous histiocytoma, CNS, 513
Fibrous tumors
intracrinal, 512
solitary, 512
5-Fluorouracil, 316
Focal tumors, 269–270
Fondaparinux, 72
Fractionated stereotactic radiotherapy (FSRT), 407
functional MRI (fMRI), 183
Functional pituitary tumors, 383–384
G
Gabapentin, 147
Gamma Knife radiosurgery (GKS), 407
Gliangiocytomas, 501–502
Gliangiogliomas, 291–293, 296, 298, 501–502
Gemcitabine, 211
Gemistocytic astrocytomas, 175
Genetic syndromes, 470–471
Cowden syndrome (CS), 288, 480
Gorlin's syndrome, 288
hereditary retinoblastoma, 289
Li-Fraumeni syndrome (LFS), 287, 483
neurofibromatosis 1 (NF1), 286–287
neurofibromatosis 2 (NF2), 287
Rubinstein–Taybi syndrome, 289
tuberous sclerosis (TS), 287
Turcot's syndrome, 288
von Hippel-Lindau (VHL) disease, 288, 475
Germ cell tumors (GCTs), 310–313, 437
clinical groups, 311
clinical presentation, 311
CSF and serum analysis, 440
CSF markers for pineal, 440
CT and MRI scan, 311
genetics, 439
imaging, 438
immunohistochemistry, 438–439
incidence, 437
location, and presentation, 311
occur in early adolescence, 310
pathology, 438–439
pineal region tumors, 310
prognosis, 440, 443
pure germinomas and non-germinomatous, 311–312
suprasellar regions tumors, 311
treatment, 445
germinomas, 445–446
non-germinomatous germ cell tumors, 447–448
See also Pineal region tumors
Germinomas, 311, 438–439
prognostic factors, 312
See also Germ cell tumors (GCTs)
Giant cell tumors (GCTs), 540
clinical presentation, 540
prevalent in thoracolumbar spine and sacrum, 530
prognosis, 540
Glaucoma, and corticosteroids effects, 63
Gliadel, see BCNU wafers
Gliarial fibrillary acidic protein (GFAP), 175, 297
Gliomas, see Gliomas
Glioblastoma (GB)
classification and subtypes, 35–37
gene expression, 36
high VEGF expression in, 56
Glioblastoma (GB) (cont.)
  molecular alterations, associated with
  grades or subtypes, 37
  primary, 32
  secondary, 31–32
Glioblastoma multiforme (GBM), 198–199
Gliomas, 290–291
  acquired point mutations, 177
  basal ganglia, 287
  cell of origin, 47
    astrocyte(s) progenitors as, 49
    cancer stem cell model, 45–47
    CD133 marker protein, 48
    clonal evolution model, 45–47
    differentiated cells, 38–39
    multipotent neural progenitors as, 50–51
    neurosphere formation, 48
    restricted neural progenitors as, 50
  stem cell caveats, 48
  diffuse brainstem, 295
  diffuse intrinsic pontine, 292, 295
  epidemiology, 196
  female hormones role, 4
    in females, 4
    genes role, 30
  grade, relation with treatment, 292
  growth factor receptor signaling
    receptor tyrosine kinases, 34
  high-grade, 294, 298
  high-grade astrocytomas
    IDH1 and IDH2 mutations in, 29
    role of p53 alterations, 28
  hypothalamic, 291
  incidence, and age, 5
  intermediate-grade, 28
  location and presentation, 291
  low-grade, 292, 299
  See also Low-grade gliomas (LGGs)
  low-grade astrocytomas
    1p/19q loss, 29–30
    anaplastic astrocytomas, 30–31
    DNA and epigenetic level, alterations in, 30
    IDH1 and IDH2 mutations in, 29
    Li–Fraumeni syndrome, 28
    platelet-derived growth factor (PDGF) overexpression, 29
    predictive factors in, 30
    prognostic factors in, 30
    role of p53 mutations, 28
    in males, 4
  malignant, cellular origins, 45–47
  cancer stem cells, 47–48
  mouse models, 38–39
  nestin positive, 298
  optic pathway, 287, 291, 296, 299
  pathogenesis, pathways in, 32
    angiogenesis pathways, 34–35
    p53 pathway, 33
    PI3K/PTEN/AKT/mTOR pathway, 34
    Ras/Raf/MAPK pathway, 34
    Rb pathway, 33
  of pineal region, 445
  predictive markers, 38
  prognostic markers, 38
  subtypes
    astrocytomas, 28
    oligodendrogliomas, 28
  tectal, 292
  thalamic, 291
  tumor stem cell hypothesis, 39–40
  uncommon
    BSG, see Brainstem glioma (BSG)
    clinical and pathologic features, 264
    PA, see Pilocytic astrocytoma (PA)
    PXA, see Pleomorphic xanthoastrocytoma (PXA)
    in white population, 4
    WHO grade I and grade II, 292
Glioma stem cells, 47–48, 51
Gliomatosis cerebri, 295
Glucocorticoid-induced osteoporosis, 60
Gorlin’s syndrome (GS), 288, 316, 486
  clinical presentation, 486–487
  diagnosis, 487
  management of patients, 487
  molecular genetics, 486
  pathogenesis, 486
G-protein coupled receptors, 368
Grade III glioma, 244
Growing teratoma syndrome, 312
Growth factor pathways, receptors, 212
Growth hormone (GH), 316, 383–384
Growth retardation in children, 316
H
Health-related quality of life (HRQOL)
  defined, 153
  factors impact on symptoms occurrence, 154
  relationship among symptoms and, 154
  symptoms and
    in clusters, 160
    fatigue, interventions for, 154–157
    mood disturbance, interventions for, 157–159
sleep–wake cycle disturbance, 160
See also Quality of life (QOL)

Hemangioblastoma

CNS of, 477–479
neurologic deficits due to, 480
retinal
visual impairment and blindness due to, 480

Hemangiomas, spine tumors, see Vertebral hemangiomas

Heparin-induced thrombocytopenia (HIT), 71

Hereditary retinoblastoma, 289

Hiccups, and corticosteroids effects, 63
Hierarchical model, see Cancer stem cell model

High-dose methotrexate, 315, 335
High-grade astrocytomas (HGAs), 195
in children, 294
histology, 297–298
imaging, 295–297
treatment, 298–300
current treatments for, 195
in elderly, 206–207
epidemiology, 196
IDH1 and IDH2 mutations in, 29
management, newly diagnosed, 201–202
biopsy or surgical resection, 201
carmustine wafers, 201–202
chemotherapy, 203
radiation therapy, 202–203
temozolomide (TMZ) therapy, 203–206
molecular alterations in, 198
pathologic findings, 197
Phase II and III trials of molecularly targeted agents, 213
Phase II trials of anti-angiogenic agents, 217
radiographic findings, 202
recurrence
diagnosis, 207–208
locoregional therapy, re-irradiation, 209–210
management, 207
radioimmunotherapy use, 210
radiotoxin use, 210
repeat resection, 208
salvage chemotherapy, 210–211
stereotactic radiotherapy (SRT), 209
role of p53 alterations, 28
signal transduction pathways in, 200
surgical management, 201
targeted therapeutics, 200
treatment approaches, novel, 210

anti-angiogenic therapy, 215–219
molecularly targeted therapy, 211–215
molecular targets, 219–220
High-grade gliomas, 294, 315
Highly active antiretroviral therapy (HAART), 348
Histone deacetylase (HDAC) inhibitors, 220
Hormonal therapy, 365–366
Hormone replacement therapy, 15
House–Brackmann facial nerve grading scale, 406
β-Human chorionic gonadotropin (β-HCG), 311, 313, 437
Hyperglycemia, and corticosteroids effects, 63
Hypermethylation, 177, 255
Hypothalamic gliomas, 291
Hypothalamus, 316

I
Idarubicin, 256

IDH1, see Isocitrate dehydrogenase 1

IDH1 and IDH2 mutations, 178, 180

IDH2, see Isocitrate dehydrogenase 2

Imatinib, 367

Immunocytochemical markers, 176

Immunosuppression, 286

Integrins, 219

Intensity-modulated radiation therapy (IMRT), 306

Internal acoustic canal (IAC), 401

Internal auditory canal (IAC), 402

Intracranial meningiomas
clinical syndromes of, 358
location, by computerized tomography, 358

Intracranial paragangioma, 505–506

Intracranial tumors, 255

Intradural-extramacular spinal cord tumors (IESCTs), 530–531

Babinski sign, 541
Brown–Sequard syndrome, 541
clinical signs, 541

CT with myelography, 541
diagnosis, MRI, 541
embolization, 541
management and prevention, 542–543
mostly found in dorsolateral division, 530
types
meningiomas, 542
neurofibromas, 542
paragangliomas, 542
schwannomas, 541–542
Intramedullary spinal cord tumors (ISCTs), 531, 543–546
adjuvant radiation therapy and complications, 545
chemotherapy regimens, 546
diagnosis, 543
high and low grade astrocytomas, 531
mostly of glial origin, 531
prognosis and management, 545
signs and symptoms, 543
stereotactic radiosurgery for, 546
types
astrocytomas, 545
ependymomas, 543–544
Intraspinal extramedullary spinal cord tumors, 541–543
Ionizing radiation, and CNS tumors, 3, 8, 14
Irinotecan (CPT-11), 111–112, 211, 256
neutropenia and severe diarrhea, 111
Isocitrate dehydrogenase 1 (IDH1), 29–32, 36, 38, 198
gene, 236
mutations, 178, 237, 239
Isocitrate dehydrogenase 2 (IDH2), 29–30, 32
Isocitrate dehydrogenases 1 and 2 (IDH1 and IDH2), 177
Isotretinoin, 256
K
Karnofsky Performance Status (KPS) score, 180
Knudson’s “two-hit” hypothesis, 457
L
Lamotrigine, 147
Late effects
chemotherapy, 316
of radiotherapy, 315
of therapy, 314
Leukemia, 315
Leukoencephalopathy, 315
Levetiracetam, 147
LGG pathogenesis, 177
Lhermitte–Duclos disease, 502–503
Lhermitte’s sign (LS), 123
Lhermitte’s syndrome, 315
Li–Fraumeni syndrome (LFS), 287, 483
clinical presentation, 483
diagnostic criteria, 484
management, 484
molecular genetics, 483
pathogenesis, 483
LINAC-based SRS, 407
Liposarcoma, intracranial, 512
Low (regional) therapies
BCNU wafers, 116–117
intrathecal, Methotrexate
myelopathy and encephalopathy, 117
Lomustine, 187, 233
Loss of heterozygosity (LOH), 177, 253
Low-grade astrocytomas, 292–294
1p/19q loss, 29–30
anaplastic astrocytomas, 30–31
DNA and epigenetic level, alterations in, 30
IDH1 and IDH2 mutations in, 29
Li–Fraumeni syndrome, 28
platelet-derived growth factor (PDGF) overexpression, 29
population epidemiology, 4
predictive factors in, 30
prognostic factors in, 30
role of p53 mutations, 28
See also Gliomas
Low-grade gliomas (LGGs), 173–174, 292, 299
astrocytic tumors, 174–176
chemotherapy
addition to radiation, 188
PCV, 187–188
temozolomide, 187–188
clinical presentations, signs and symptoms, 178
epidemiology, 173–174
histopathological features, 175
imaging
CT scan and MRI, 178
dynamic contrast-enhanced perfusion MRI (DCE-MRI), 179
mixed oligoastrocytomas, 176
molecular genetics of, 176–178
oligodendroglial tumors, 175
oligodendrogliomas, 176
prognostic factors, 180–181
radiation therapy, 185–187
and adverse cognitive effects, 186
and radiosurgery (SRS), 187
and stereotactic brachytherapy (SBT), 187
surgical management, 181–183
innovations in, 183–185
Low molecular weight heparin (LMWH), 69
Lynch syndrome, 288, 485
M
MacDonald criteria, and limitations to, 92, 96–98
Maffucci’s syndrome, 514
Magnetic source imaging (MSI), 183
Malignant dedifferentiation, 401
Malignant peripheral nerve sheath tumors (MPNSTs), 462
Matrix metalloproteinases (MMPs), 252
Maximum tolerated dose (MTD), 88
McCune–Albright Syndrome, 379
Medulloblastoma, 415
in adults, treatment outcome, 425
biology, 417–419
Chang classification, 306, 420
characterization, 304
chemotherapy, 424–428
high-risk medulloblastoma, 427
and late sequelae, 429
standard-risk medulloblastoma, 424–427
common in whites, 304
diagnosis, 419
disease of, young and early school-aged children, 304
follow-up, 430
-genetic syndromes associated with, 304
incidence, 415
rates, 415
long-term sequelae, 429
management, recommendations for, 428–429
medulomyoblastoma, 304
with metastatic spread, 416
MRI image, midline posterior fossa tumor, 305
neurosurgery, 422
origin from medulloblasts, 303
pathology, 417–419
prognosis, 419–421
radiotherapy
with chemotherapy, 423, 427
cognitive deficits and, 429
quality impact, 423–424
and somnolence syndrome, 429
rare tumors, 415
risk factors, 417
risk stratification, 305
staging, 419
subtypes
anaplastic, 304
classic, 304
large cell, 304
nodular/desmoplastic, 304
surgical resection, 422
and high recurrence rate, 423
postoperative radiotherapy with, 429
survival data, 416–417
symptoms, 305
treatment, 422
adjuvant chemotherapy, 306
craniospinal irradiation, 306
neurosurgery, 422
radiation therapy, 422–423
See also Embryonal tumors
Medulloepitheliomas, CNS, 508
Melanocytic lesions
melanocytosis, 516
melanomatosis, 516
primary melanoma of CNS, 515–516
Melanocytoma, leptomeningeal, 516
Memory
alpha-tocopherol impact on, 152
anticonvulsants effects on, 147
CNS disease, and diminished, 145
-d-MPH, for impaired, 150–151
frontal network system dysfunction and effect on, 146
impairment and tumors, 144
left hemisphere lesions effects on, 144
methylphenidate impact on, 150
prostheses, compensatory interventions, 148
radiation treatment, and diminished, 146
steroids effects on, 147
MEN1 gene mutation, 253
Meningiomas, 4, 13, 355, 542
adipose tissue tumors
CNS angioliomatous, 511
CNS hibernoma, 511–512
intracranial lipoma, 510–511
intracranial liposarcoma, 512
biological behavior, 362
in black population, 4
brain imaging
with CT and MRI, 356
MR spectroscopy (MRS), 358
octreotide imaging, 359
positron emission tomography (PET), 358
breast cancer, association with, 16
cerebral angiography for, 357
chemotherapy for, 366–367
classification, 13, 360
clinical presentation, 356
common intraspinal tumors, 542
affect older population, 542
MRI for diagnosis, 542
computerized tomography (CT)
findings, 359
Meningiomas (cont.)
epidemiology, 355–356
familial syndromes, 362
in females, 4, 13
head trauma and risk of, 16
high VEGF expression in, 56
history, 355
hydroxyurea for recurrent, 366
immunohistological markers, 360
incidence rates
and age, 5, 13
in black non-Hispanics, 13
intracranial
clinical syndromes of, 358
history and physical findings, 357
location, 358
ionizing radiation exposure, 14
meningothelial cell origin tumors, WHO classification, 360
mesenchymal tumors
fibrosarcoma of CNS, 513
fibrous histiocytoma, of CNS, 513
intracranial fibrous tumors, 512
solitary fibrous tumors, 512
MIB-1-labeling indices for, 362
natural history, 362–363
neuroradiology, 356–359
pathologic subtypes, 359
primary chromosomal aberration in, 359
receptors identified in, 361
recurrent
hydroxyurea for, 366
with loss of chromosome 14q, 361
multidrug chemotherapy trials for, 367
treatment algorithm, 370
risk
and family history, 16–17
 genetic variants, 17
 hormone replacement therapy, 15
 and hormones role, 14
 oral contraceptives use, 15
 pregnancy and menstruation, 15–16
 Simpson grading system, 364
surgery for, 363, 365
radiation with, 370
TP53, polymorphisms in, 17
treatment, 363
algorithm, 364
biochemotherapy, 366–367
hormonal therapy, 365–366
radiotherapy, 365
stereotactic radiotherapy, 365
surgery, 363–365
targeted therapy, 367–369
Mesenchymal tumors
fibrosarcoma of CNS, 513
fibrous histiocytoma, of CNS, 513
intracranial fibrous tumors, 512
solitary fibrous tumors, 512
Metalloproteinases (MMPs), 252
Methotrexate (MTX), 315, 340
and CNS toxicity, 113–114
hepatic toxicity and, 114
and myelosuppression, 114
renal dysfunction, 114
treatment-induced leukoencephalopathy, 114
Methylphenidate, 149
adverse effects, 148, 150
Lower study, 150–151
Mar Fan study, 150–151
MGMT gene, 255
MGMT methylation, 205
Microarray technology, 254
Mini-gemistocytes, 176
Mitogen-activated protein kinase (MAPK), 199
Modafinil, 149
wake-promoting agent, 151
Molecularly targeted therapy, 211–215
Mood disturbance, 157–159
Moyamoya-like syndrome, 315
Moyamoya syndrome, 299
MTX monotherapy, 344
Multiple myeloma, 539–540
characterized by, 539
diagnosis of, 539
lab studies, 539
proteasome inhibitors for, 540
RANK ligand inhibitors for, 540
sensitive to chemotherapy and radiotherapy, 540
Multitargeted kinase inhibitors (MTKIs), 214
Myelogenous leukemia, 316
Myelopathy, 316
Myxopapillary ependymomas, 249, 251, 257, 301
N
N-acetylaspartate (NAA), 207–208
National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0, 89
Necrosis, 174
Nelson’s syndrome, 384
Nervous system tumors, 457
Neurocognitive assessment, 315
Neurocognitive dysfunction, and brain tumors, 144–146, 153
Neurocognitive function
  adjuvant medications effects
    impact of steroids, 147
    neurobehavioral function deterioration, 146–147
  medical complications effects
    anticonvulsants, side effects, 147
    seizures effects, 147
  sensitive endpoint, 143–144
  treatment effects
    adverse effects of radiation, 146
    cerebellar syndrome, 145
    neurobehavioral effects, 145
    neurological complications, 145
    radiation encephalopathy, 146
    radiation-induced cognitive dysfunction, 146
    radiation necrosis, 146
  tumor impact on, 144
  tumor progression and adverse effects on, 144
Neurocognitive interventions
  and pharmacotherapy
    alpha-tocopherol (Vitamin E), 152
    behavioral intervention, 156
    clinical trials, cognitive deficits in cancer patients, 149
    depression, 158–159
    donepezil, 151–152
    methylphenidate, 148–151
    modafinil, 151
    mood disturbance, 157–158
    non-pharmacologic intervention, 156
    personality changes, 158
    pharmacologic intervention, 156–157
  strategies, goals, 148
Neurocognitive symptoms, 72
See also Brain tumors
Neuroepithelial tissue tumors
  angiocentric glioma, 510
  astroblastoma, 509
  chordoid glioma, third ventricle, 510
  choroid plexus carcinoma, 500–501
  choroid plexus papillomas, 500
  choroid plexus tumors, 499–500
Neurofibromas, 542–543
Neurofibromatosis (NF), 198
Neurofibromatosis type 1 (NF1), 286–287, 459
  associated tumors, 461
  asymptomatic neurofibromas, 464
  gliomas, 463
  MPNSTs, 462–463
  neurofibromas, hallmark feature, 461–462
  clinical features, and age factor, 461
  diagnostic criteria, 461
  epidemiology, 459
  genetics, 459
  management, 463–464
    asymptomatic neurofibromas, 464
    glioma, screening and RT with chemotherapy, 465
    MPNSTs, screening and surgical excision, 464
  molecular genetics, 460
    genetic testing, 460
    inactivating mutation in NF1, 460
    mutations, 460
    neurofibromin, 460
    mutations, 460
    NF1 gene, 460
    NF1 (neurofibromin) gene mutation, 459
    and genetic testing, 460
    NF1 tumors, 300
    overview, 459
    pathogenesis, 460
    phenotypes, expression of, 461
Neurofibromatosis type 2 (NF2), 287, 402, 466
  diagnostic criteria, 467
  epidemiology, 466
  genetics, 466
  genetic testing, 467
  management
    initial evaluation, 468–469
    radiation, 470
    molecular genetics, 467
    mutations, 467
    overview, 466
    pathogenesis, 467
    vestibular schwannomas (VSs) with, 468
Neuronal, and neuronal-glial tumors
  cerebellar liponeurocytomas, 503–504
  desmoplastic infantile astrocytoma, 502
  desmoplastic infantile ganglioglioma, 502
  dysembryoplastic neuroepithelial tumors, 505
  dysplastic gangliogliocytoma, cerebellum of, 502–503
  extracranial parangangioma, 505–506
  intracranial parangangioma, 505–506
Neuronal, and neuronal-glial tumors (cont.)
  papillary glioneuronal tumor, 504
  rosette-forming glioneuronal tumor, IV
  ventricle, 505
Neuronal satellitosis, 174
Neuron-specific enolase (NSE), 308
Neuro-oncology clinical trials, challenges, 86, 94–95
Neurological evaluations, 144, 147
studies, 144, 146
tests, 144, 150
Neurospheres, 48–49
NF2-associated gene SCHIP-1, 254
Nitrosourea-related myelosuppression, 110
Nitrosoureas, 110–111, 211
Non-EIAEDs, levetiracetam, 116
Non-germinomatous germ cell tumors (NGGCTs), 311–312
  adjuvant therapy, 312
  chemotherapy, 312
  incidence, 312
  pre-operative evaluation, 312
Non-HIV-associated PCNSL, 333
Non-Hodgkin lymphoma, 313
Non-steroidal anti-inflammatory drugs (NSAIDs), 196
Norwegian Cancer Registry, 174
Nuclear pleomorphism, 308
O
O6-benzylguanine (O6-BG), 205
Obesity, 291, 316
Objective radiographic response rate (ORR), 96
Olanzapine, 61
Oligoastrocytomas, 174
genetically heterogeneous, 177
Oligodendroglial tumors, 175, 177–178
  diagnostic criteria, 175
  histology, 239
Oligodendrogliomas, 28, 176–177, 294, 296, 298
diagnosis, 237–239
GFAP immunoreactivity, 176
low and intermediate-grade
1p/19q loss, 31
low-grade, 176
See also Gliomas
Ollier’s disease, 514
Optic pathway gliomas, 291, 296, 299
Osteoblastomas
  benign lesions, 540
  occur in lumbar spine, 530
  scoliosis development, 541
  treatment, 541
Osteoid osteomas
  benign lesions, 540
  occur in lumbar spine, 530
  scoliosis development, 541
  treatment, 541
Osteosarcomas, 537–538
  chemotherapies, 537
  occur in axial skeleton, 537
  PET scans for diagnosis, 537
  presentation, 537
  resistant to ionizing radiation, 538
  serial PET scans, 537
  wide margin-en bloc excision, 537
Otitotoxicity, 318
Ovarian function, 316
Oxcarbazepine, 116, 147
P
p53
  pathway, 33
  protein, 176
  role in molecular oncogenesis, 28–29
Panhypopituitarism, 393
Papillary glioneuronal tumors, 504
Papillary tumor of pineal region, 444
Papillary tumors, 313
Papilledema, 178
Paragangliomas, 542
PDGF receptor α (PDGFRα) gene promoter region, 254
Pediatric brain tumors, 286–289
  adjuvant treatment, 299
  brainstem astrocytomas, 292
  chemotherapy regimens, 299
  choroid plexus papillomas, 308
  choroid plexus tumors, 308–310
  craniopharyngiomas, 313–314
  diffuse brainstem gliomas, 295
  embryonal tumors
    atypical teratoid rhabdoid tumor (ATRT), 303
    medulloblastoma, 303–307
    pineoblastoma, 307–308
    supratentorial PNET, 307
    ependymomas, 300–303
  and genetic syndromes, 286–289
  germ cell tumors (GCTs), 310–313
  glial tumors, 290–291
  HGAs, prognosis and treatment
Index

diffuse brainstem gliomas, 295
gliomatosis cerebri, 295
histological examination, 297–298
imaging, characteristics, 295–297
LGAs, prognosis and treatment
desmoplastic infantile gangliogliomas (DIGs), 293
dysembryoplastic neuroepithelial tumors (DNET), 293
fibrillary astrocytomas, 294
gangliogliomas, 293
oligodendrogliomas, 294
pilocytic astrocytomas, 292
pilomyxoid astrocytomas, 293
pleomorphic xanthoastrocytomas (PXAs), 294
management, 300
midbrain astrocytomas, 292
oligodendrogliomas, 294
optic pathway gliomas, 291
primary CNS tumors, 289
direct compression of brain tissue, 289–290
obstructive hydrocephalus, 290
supratentorial high-grade astrocytomas, 294
surgery, 298
thalamic tumors, 291
Pediatric CNS tumors, 286
Pediatric myxopapillary ependymoma, 303
Pediatric oncology programs, 316
Perineuronal satellitosis, 176
Peripheral neurofibromatosis, see Neurofibromatosis type 1 (NF1)
Peripheral neuropathy, 316
Personality change, frontal tumors impact, 144, 158
Pharmaceutical therapies, 103–104
Phenobarbital, 116
Phenytoin, 116, 147
Phosphatase and tensin homolog (PTEN), 197
PI3K activation, 199
PI3K–Akt–mTOR pathway, 177
PI3K/PTEN/akt/mTOR pathway, 34
Pilocytic astrocytomas (PA), 173, 266, 270, 292–293, 296, 298
classification, 271–272
clinical presentation, 270–271
diagnosis, 270–271
epidemiology, 270
grade I tumors, 292
histology, 297
low-grade gliomas, 290
MRI appearance, 295
optic pathway gliomas, 291
pathology, 271–272
prognostic factors, 272
slow-growing, 292
surgery, 298
See also Gliomas
Pineal germ cell tumors, CSF markers, 440
Pineal gland, 435
anatomy, 435–436
history, 435
metastases to, 444
physiology, 435–436
tumors, presentation, 437
See also Pineal region tumors
Pineal meningiomas, 443
Pineal parenchymal tumors (PPTs), 440
diagnosis, 440
imaging, 441
pathology, 441–442
pineoblastomas, 442
pineocytomas, 441–442
treatment
pineoblastomas, 448–449
pineocytomas, 447–448
Pineal parenchymal tumors of intermediate differentiation (PPTID), 440–443, 449–450
ependymomas, 451
genetics, 443
meningiomas, 450
pineal gliomas, 450
prognosis, 443
Pineal region tumors, 435, 451
glioblastomas, 443
gliomas, 443
melatonin level and, 436–437
meningiomas, 444
metastases, 444
overview, 436
papillary tumor, 444
presentation, 437
treatment
hydrocephalus, 445
Pineoblastoma (PBs), 307–308, 436, 441–442, 448–449
See also Embryonal tumors
Pineocytomas (PCs), 441–442, 447–448
Pituitary adenomas, 377
ACTH secretion resulting
Cushing’s disease, 384
Nelson’s syndrome, 384
Pituitary adenomas (cont.)
characteristics, and MR imaging, 386
classification, 379–382
Hardy classification, 379
radiologic classification scale, 380
clinical presentation, and signs, 382–383
epidemiology, 377–378
external beam radiation and risks, 392
familial disorder and, 379
familial isolated pituitary adenomas
(FIPAs), 379
functional pituitary tumors, 383
histopathological classes of, 381
hormonally functional, 380
immunohistochemical staining, 380
medical therapy, 387
pituitary hormone replacement, 387–390
radiation therapy, 392–393
radiosurgery, 392–393
surgical treatment, 390–392
pathogenesis, 378–379
prognosis, and impact on quality of life, 393–394
subclass by WHO, 382
and surgery treatment, 390–391
TSH-secreting adenomas, 384
P. jirovecii pneumonia (PJP)
prophylaxis of, 62
See also Brain tumors
steroids immunosuppression and, 62
Placenta growth factor (PlGF), 215
Plasmacytomas
evolve into multiple myeloma, see Multiple myeloma
malignant spine tumors
common in adults, 529
occur in thoracic spine, 530
proteasome inhibitors for, 540
RANK ligand inhibitors for, 540
sensitive to chemotherapy and radiotherapy, 539–540
Platelet-derived growth factor (PDGF), 29, 367
receptor, 177
signaling pathways, 243
Platinum-based drugs, 316
Platinum compounds
carboplatin, 112–113
cisplatin, side effects, 112–113
Pleomorphic xanthoastrocytoma (PXA), 173,
273, 294, 298
classification, 275
clinical manifestations, 274–275
diagnosis of, 274–275
epidemiology, 273–274
pathology, 275
prognostic factors, 275–276
treatment, 276
See also Gliomas
Polifeprosan 20, 201
Polymorphism, 255
Poly(ADP-ribose) polymerase (PARP), 206
Posterior fossa, see Medulloblastoma
Posterior fossa syndrome, 306
Primary brain tumors, 173
Primary CNS lymphoma (PCNSL), 313, 333
clinical features, 333–334
diagnostic evaluation, 335
IPCG guidelines, 335–336
immunocompetent patients treatment with, 339
neuroimaging, 337–338
neurotoxicity, due to chemoradiation, 346–347
pathobiology, 333–334
prognostic markers, 338–339
treatment, 339
chemotherapy, 344
combination regimens, MTX and WBRT, 340
corticosteroids, 339
high-dose chemotherapy with ASCT, studies of, 345–346
HIV-related, 347–348
intrathecal chemotherapy, 345
radiation, 339–340
salvage therapy, 345–346
selected studies, 341–343
whole brain radiation therapy (WBRT), 339–340
Primary CNS tumors, 286
presentation, 289
direct compression of brain tissue, 289–290
obstructive hydrocephalus, 290
Primidone, 116
Primitive neuroectodermal tumors (PNET), 287, 303, 415
Procarbazine, 187, 233
Procarbazine, and peripheral neuropathy, 111
Procarbazine, lomustine, and vincristine (PCV)
chemotherapy, 233, 239–244, 346
Index

Processing speed
  anticonvulsants side effects, 147
domain, 147
  impaired, 146
  information, 145
Progression-free survival (PFS), 368
Prolactinomas, 383
Protoplasmic astrocytomas, 175
Pseudomonas exotoxin, 209
Pseudoprogression
  defined, 120
  distinction between true progression and, 122
PTEN mutation, 288
Pulmonary emboli (PE), 68

Q
Quality of life (QOL)
  aggressive therapy and, 159
  in brain tumor patients, 153–154
Donepezil effect, 151
impact of seizures, 147
Modafinil effect, 157
neurocognitive deficits impact on, 147
See also Brain tumors; Neurocognitive function
Quetiapine, 61

R
Radiation somnolence syndrome (RSS), 315
Radiation therapy (RT) cranial, and complications, 117, 315
acute toxicities
  alopecia, 119
  fatigue, whole brain radiotherapy (WBRT), 118
  local symptoms, 118–119
craniocerebral axis radiation dermatitis, 120
hematologic toxicity, 119–120
endocrinopathy
deficiencies in thyroid-stimulating hormone (TSH), 129
GH deficiency, 129
late toxicity, neurologic, 123–124
brain necrosis, 124
cranial nerves injury, 126–127
fibrosis, 123
hearing loss risk, 126
multiple sclerosis-related toxicity, 128
optic neuropathy, 125
spinal myelopathy, delayed, 124–125
stroke-like migraine attacks after radiation therapy (SMART), 127–128
tissue necrosis, 123
vasculopathy, 123
for meningioma, 365
non-neurologic late toxicity
  loss of vertebral body height, 128
  lung disease, 128
secondary benign or malignant tumors after RT, 129–130
subacute toxicity
  Lhermitte’s sign (LS), 123
  pseudoprogression, imaging evidence, 120–122
Somnolence syndrome, 123
vasculopathy
  aneurysm, 129
  cerebral artery stenosis, 129
  ischemia, 129
  moyamoya syndrome, 129
  occlusion, 129
See also Chemotherapy complications
Radiation Therapy Oncology Group (RTOG), 186
Radiation toxicity, 146
See also Neurocognitive function
Radioimmunotherapy, 210
Radiosurgery (SRS), 187
Radiotoxin, 210
Rapamycin pathways, 177
Rare tumors of brain, see Brain tumors, rare
RAS-mitogen-activated protein kinase (MAPK) pathway, 199
Ras/Raf/MAPK pathway, 34
Rb Pathway, 33
Receptor tyrosine kinases, 34
Recombinant α-interferon, 366
Rehabilitation, brain tumor patient’s, 147–148, 153
Relative cerebral blood volume (rCBV), 179
The Response Assessment in Neuro-Oncology (RANO) Working Group, 98
Response assessment, in trials, see Clinical trials design, cancer trial overview
The Response Evaluation Criteria in Solid Tumors (RECIST) criteria, 96
Response shift, 153
Retinoblastoma, 289, 308
Retinoblastoma (RB1) gene, 199
Risperidone, 61
Rituximab, 346
Rosette-forming glioneuronal tumor, fourth ventricle, 505
Rubinstein–Taybi syndrome, 289

S
S-100 protein, 175
Schwannomas
  association with neurofibromatosis type II (NF-II), 541
  commonly in adults, 541
  MRI for visualization, 541
  result in spinal canal widening, 542
Secondary glioblastomas, 178
Secondary malignancies, 315–316
Seizures, 178, 314
  anticonvulsant therapy, adverse effects, 64
  anti-epileptic drugs (AED), 64
  epidemiology, 63–64
  pathophysiology, 63–64
  prophylactic treatment, 64–65
  surgical management of, 68
  See also Brain tumors
Serous otitis, and WBRT, 119
Signal transduction pathway, 32–35
Single-nucleotide polymorphisms, 196
Sleep–wake cycle disturbance, 160
Somatostatin receptors, 368
Somatostatin scintigraphy, 368
Somatotropin release-inhibiting factors (SRIFs), 368
Somatic cell genetics, 129
Somnolence syndrome, 123
Speech discrimination testing (SDT), 403
Spinal cord ependymomas, 257
Spinal tumors
  benign, common in children
    aneurysmal bone cysts, 529
    eosinophilic granulomas, 529
    osteoid, 529
    osteoma/osteoblastomas, 529
  diagnostic methods
    biopsies, needle, 532
    digital subtraction angiography, 532
    excisional biopsies, 532
    FDG-PET, 531
    lab studies, 532
    MRI and CT imaging, 531–532
    multidetector CT imaging, 531
    nuclear scintigraphy (bone scan), 531
    PET, 531
    plain radiographs, 531
    SPECT, 531
    epidural, 530–531
    aneurysmal bone cysts, 540
    chondrosarcomas, 535–537
    chordomas, 533–535
    Ewing’s sarcoma, 538
    giant cell tumors (GCTs), 540
    multiple myeloma, 539–540
    osteoblastomas, 540–541
    osteoid osteomas, 540–541
    osteosarcomas, 537
    peripheral neuroectodermal tumor, 538
    plasmacytomas, 539–540
    vertebral hemangiomas, 540
    incidence and prevalence, 529–530
    intradural–extramedullary, 530–531
    clinical signs, 541
    diagnosis and techniques, 541
    management and prevention, 542–543
    meningiomas, 542
    paragangliomas, 542
    schwannomas, 541–542
    intramedullary, 531
    astrocytomas, 545
    diagnosis, 543
    ependymomas, 543–544
    prognosis and management, 545
    signs and symptoms, 543
    malignant, common in children
      Ewing’s sarcoma, 529
      relation with age and sex, 529–530
Spine tumors, see Spinal tumors
Standard RT–TMZ/TMZ regimen, 205
Stereotactic brachytherapy (SBT), 187
Stereotactic radiosurgery (SRS), 393, 402, 407–408
Stereotactic radiotherapy (SRT), 209
Steroid myopathy, 60
Steroid pseudorheumatism, and corticosteroids effects, 63
Stochastic model, see Clonal evolution model
Stroke-like migraine attacks after radiation therapy (SMART), 127–128
Subependymal giant cell astrocytoma (SEGA), 173, 287
Supportive care, 55
  See also Brain tumors
Supratentorial ependymoma, 302
Supratentorial tumors, 291
Symptom clusters concept, 154, 160
Symptom measurement, 153

T
Tamoxifen, 256
Targeted molecular therapy, 115
Targeted therapies
Von Hippel-Lindau (VHL) disease, 288, 475
  associated tumors and malignancies, 477
  CNS hemangioblastoma, 477–479
  endolymphatic sac tumors (ELSTs), 479
  retinal hemangioblastomas, 479–480
  visceral malignancies, 480
clinical genetics, 475–476
diagnosis, 476–477
epidemiology, 475
 genetic testing, 477
molecular genetics, 476
  pVHL complex, 476
  VHL gene, 476
mutations, in VHL gene, 476
pathogenesis, 476
prognosis, 480
screening, 477
von Recklinghausen’s disease, see
  Neurofibromatosis Type 1 (NF1)
W
  Whole brain radiation therapy (WBRT), 339
Y
  Yolk sac tumor, 439