Managing Skin Cancer
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Skin cancer represents the most common cancer in humans, and we are currently facing increasing rates of newly diagnosed cutaneous neoplasm each year. The high incidence of skin cancer is a worldwide problem and millions of people are affected in different continents. In the past decades, great improvements have been achieved in the field of skin cancer research. Knowledge has been gained concerning the biology of skin cancer and risk factors; diagnosis has been improved and novel therapeutic modalities have been developed. As UV-exposure is known as the major risk factor for skin cancer, prevention can be achieved through UV-protection and regular sunscreen use. However, further prevention campaigns are needed to improve general knowledge with regard to skin cancer in the population, aiming for a future decrease in skin cancer incidence and more timely diagnosis. When diagnosed early, skin cancer is curable in the majority of cases and may be treated with simple surgery or non-invasive therapeutical approaches. Furthermore, the skin as our largest organ may be easily examined by simple total body examination, and any new or changed lesion may be easily visualized. Diagnostic tools such as dermoscopy and confocal microscopy may nowadays be used to improve diagnostic accuracy. In the future, these tools may help to achieve earlier diagnoses of the different forms of cutaneous neoplasms, especially malignant melanoma.

Because of the high numbers of patients affected worldwide, dermatologists are no longer the only specialty managing skin cancer patients. In many countries primary care physicians are performing regular skin checks and initiate early treatment, working closely with a dermatologist. Therefore, knowledge regarding diagnosis, appropriate treatments including recommended excision margins, the performance of sentinel lymph nodes biopsies, and the ability to use novel topical treatment modalities are of importance for all physicians involved.

Managing Skin Cancer has been designed to combine all relevant up to date information with regard skin cancer and to facilitate practical management of skin cancer patients by dermatologists as well as other medical disciplines. Thereby, the book mainly focuses on diagnosis, treatment and prevention of skin cancer with reference to recent international guidelines.

We hope that this book will guide clinicians in their daily practice and help them make the most appropriate decisions for their skin cancer patients.

Berlin, Germany  Eggert Stockfleth
Houston, USA  Theodore Rosen
Sydney, Australia  Stephen Shumack
Worldwide, millions of patients are affected by skin cancer. Therefore, many medical specialties are involved in the management of this global public health problem. Skin cancer represents an interdisciplinary disease starting with the primary diagnosis, followed by a diagnostic work-up, and then treatment. This publication will serve all physicians dealing with these patients. The clinician will find this book a practical guide for the management of skin cancer patients based on the experience of the authors, with reference to international guidelines for diagnosing and treating skin cancer.

This textbook would not have been finished without the enthusiasm and dedication of many people who have contributed a lot of their time and effort to this project.

The editors would like to thank all authors for their outstanding contributions to this book and for their interest and endeavour in the field of cutaneous oncology. All authors worked to a tight publication schedule for this book, and this helped ensure that up to date information has been included.

Furthermore, we thank the project coordinators, Birgit Hinrichs and Martina Ulrich, who have put a lot of hard work and dedication into this project.

Finally, we also thank our patients who inspire us to provide the best possible care. Many ideas and practical approaches were developed during the interaction with these patients.

Current and future developments may aid in the better prevention, diagnosis and treatment of skin cancer, and we hope that this textbook will be part of this important process.

Berlin, Germany                Eggert Stockfleth
Houston, USA                   Theodore Rosen
Sydney, Australia              Stephen Shumack
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Diagnosis of Skin Cancer

Astner S and Ulrich M

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Core Messages

› Skin cancer diagnosis is based on clinical evaluation and histological exam of biopsy specimens represents the current diagnostic gold-standard. Recently non-invasive imaging techniques have emerged which may aid in the diagnosis and differential diagnosis of skin cancer.

› Dermoscopy has been well established for the evaluation of pigmented lesions. As a novel diagnostic tool, reflectance confocal microscopy (RCM) has been applied for diagnosis of skin cancer and allows the evaluation of the skin at near histological resolution.

1.1 Clinical Evaluation and Risk Assessment

Diagnosis of cutaneous malignancies is based on the clinical evaluation of the patient, a detailed history, and ultimately, histological analysis. As the majority of epithelial skin tumors may already have been identified by clinical evaluation, the total body skin exam is of utmost importance and should forego any invasive procedures. Lesion type, shape, demarcation, color, arrangement, and distribution should be recorded, with particular attention to aspects of asymmetry with respect to color and shape in pigmented lesions. Complete evaluations should include the palms and soles, the genital area, the scalp, and the lymph nodes.
A detailed history allows the assessment of the individual’s skin cancer risk with regard to carcinogen exposure and familial cancer syndromes or risk factors. It should include a record of occupational and recreational sun exposure, a history of sunburns, the general health status, and a personal and family history of cancer. Congenital nevi, familial atypical moles, actinic damage, and Fitzpatrick skin type should be documented in each patient. By considering all aspects of history and clinical exam, patients at risk can be reliably identified for regular screening and prevention (Table 1.1).

<table>
<thead>
<tr>
<th>Table 1.1</th>
<th>Assessment of predisposing risk factors of skin cancer development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factor</td>
<td>Differentiating criteria</td>
</tr>
<tr>
<td>Fitzpatrick skin phototype I–III/IV</td>
<td>Based on the ability to tan/burn none-(minimal-moderate-profuse)</td>
</tr>
<tr>
<td>Sunbathing habits</td>
<td>Use of sunscreen Summer vs. winter</td>
</tr>
<tr>
<td>Area of residence</td>
<td>Latitude (proximally to equator), Altitude, urban vs industrial, Climatic conditions</td>
</tr>
<tr>
<td>Personal and family history of skin cancer</td>
<td>Ask for: NMSC, MM, NBCCS</td>
</tr>
<tr>
<td>Common moles</td>
<td>Risk for melanoma increases with increasing number of moles (&gt;100)</td>
</tr>
<tr>
<td>Atypical moles</td>
<td>Risk for melanoma; &gt;5 or more atypical moles; familial dysplastic moles</td>
</tr>
<tr>
<td>Changing mole</td>
<td>History</td>
</tr>
<tr>
<td>Congenital moles</td>
<td>History</td>
</tr>
<tr>
<td>Gender of the patient</td>
<td>Male &gt; female</td>
</tr>
<tr>
<td>Specific risk factors</td>
<td>Arsenic, tar, radiotherapy, Use of photosensitizers, PUVA therapy or other phototherapies.</td>
</tr>
<tr>
<td>Other risk factors</td>
<td>History of smoking Chronic/longstanding immunosuppression</td>
</tr>
<tr>
<td>Nevus sebaceous</td>
<td>Clinical appearance of yellow, verrucous growth on the scalp, present since birth.</td>
</tr>
<tr>
<td>Genetic syndromes with increased skin cancer risk</td>
<td>Epidermodysplasia verruciformis (EV) Xeroderma pigmentosum (XP) Gorlin–Goltz Syndrome (NBCCS) Familial multiple mole and melanoma (FAMM) Epidermolysis bullosa (dystrophic/junctional variants)</td>
</tr>
</tbody>
</table>

An outline of risk factors to be assessed in a detailed evaluation of patients presenting for skin cancer screening and its practical implications

NMSC Nonmelanoma skin cancer; NBCCS nevoid basal cell carcinoma syndrome; HPV human papilloma virus; AK actinic keratosis; SCC squamous cell carcinoma; BCC basal cell carcinoma; MM malignant melanoma
**1.1.1 Actinic Keratosis and Squamous Cell Carcinoma**

Actinic keratoses (AK) present as multiple, erythematous to brown papules and plaques with adherent hyperkeratotic scales. In patients with extensive sun-exposure, entire fields of AK can be identified (Fig. 1.1a). Hypertrophic variants may exhibit primarily focal hyperkeratosis, which may result in presentation as cornu cutaneum. Pigmented variants may have a history of superficial spreading (superficial pigmented actinic keratosis, SPAK) and may be difficult to differentiate from superficial spreading melanoma (SSM), pigmented basal cell carcinoma (BCC), or pigmented seborrheic keratoses (Table 1.2). Actinic cheilitis of the lower lip presents in the form of dry, fissured lips with marked atrophy, which may disrupt the vermilion border. Actinic cheilitis should be differentiated from allergic/toxic eczema of the lip, granulomatous cheilitis, erosive lichen planus, factitial processes, and ultimately, squamous cell carcinoma (SCC), on the basis of the history and clinical appearance.

SCC present as erythematous, hyperkeratotic papules and plaque with adherent scales, and history of enlargement, bleeding, or frequent irritation. Serohemorrhagic crusting and perilesional cutaneous erythema and edema may be present in the clinical evaluation, representing the cutaneous inflammatory response in immunocompetent individuals.

**Table 1.2 Extended differential diagnosis of actinic keratosis**

<table>
<thead>
<tr>
<th>Lesions that may mimic actinic keratoses</th>
<th>Diagnostic differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Lichenoid) seborrheic keratosis</td>
<td>Light brown papules or thin plaques with regular, well-defined borders on sun-exposed areas. Dermoscopic evaluation reveals the presence of pseudohorn cysts. May require histological evaluation for definite differentiation</td>
</tr>
<tr>
<td>Psoriasis vulgaris</td>
<td>Characteristic erythematous plaques with scale, on extensor surface of extremities. Check for other clinical features (nail findings, anal pinking) ask for family history</td>
</tr>
<tr>
<td>Chronic discoid lupus erythematoses (CDLE)</td>
<td>Salmon colored, discoid plaques with scarring and marked atrophy on face, neck and sun exposed areas of trunk and extremities. Confirm by histology, immunofluorescence, labs: ANA, dsDNA</td>
</tr>
<tr>
<td>DSAP (disseminated superficial actinic porokeratoses)/Porokeratosis of Mibelli</td>
<td>Numerous (&gt;100) skin colored to light brown centrally atrophic papules and plaques with discrete hyperkeratotic ridge surrounding all lesions. Histology: cornoid lamella</td>
</tr>
<tr>
<td>Stucco keratosis</td>
<td>Multiple brown to skin colored verrucous papules on the lower legs with stuck-on appearance. Confirm by histology</td>
</tr>
<tr>
<td>Acrokeratosis verruciformis (Hopf) Darier white disease (DWD)</td>
<td>Numerous round to lenticular verrucous papules dorsa of hand and feet; punctuate palmar keratoses. Check for signs of DWD. Diagnosis confirmed by histology</td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis</td>
<td>Fields of confluent verrucous papules and plaques on hands and forearms. Genetic predisposition, increased susceptibility of HPV Type 5/8. CAVE: Transformation into SCC! Requires histological evaluation. HPV-typing by PCR from isolated DNA</td>
</tr>
<tr>
<td>Lentigo senilis</td>
<td>Round to oval, light brown macule or path on sun exposed areas with regular borders and sharp demarcation. Hyperkeratosis generally absent or mild. Histology needed if LMM is suspected</td>
</tr>
</tbody>
</table>
Fig. 1.1 (a) Corresponds to clinical image of 67-year-old male, with a long standing history of sun-exposure. Clinical evaluation reveals numerous and confluent hyperkeratotic papules and plaques on sun-exposed areas of the balding scalp, consistent with actinic field cancerization. Normal skin is difficult to distinguish from clinically affected skin sites. Histology confirmed the diagnosis of actinic keratoses (AK). (b–e) Correspond to representative RCM images of AK. (b) RCM image obtained at the level of the stratum corneum with noted scaling and demarcation of individual corneocytes, seen as detached bright, polygonal structures (white arrows). (c) RCM image illustrating parakeratosis, identified by the dark nucleus placed centrally within the bright appearing corneocytes. The irregularities of the epidermal architecture are seen as dark hollow between bright rims of keratinocytes. (d) RCM image illustrating keratinocyte pleomorphism, with atypical nuclei seen as dark round to oval, to polygonal structures (white arrows) of variable size and orientation. (e) RCM image obtained at the level of the mid-to-upper dermal layer illustrating solar elastosis. Irregular bundles of bright appearance and somewhat haphazard distribution correspond to irregular dermal elastic fibers. (RCM images obtained by VivaScope 1500, image dimensions 500x500 µm)
1.1.2 Basal Cell Carcinoma

BCC is considered the most common cutaneous malignancy, with an incidence of up to 1,000,000 per year, making early detection the mainstay of effective therapy and management. Subtypes of BCC have been classified into nodular, micronodular, superficial, and morpheaform BCC. In addition, variants of infiltrating BCC, pigmented BCC, and metatypical BCC have been described, of which the latter has a more aggressive course and may even metastasise. Clinically, BCC may present as dome-shaped, erythematous shiny papules with translucent borders (Fig. 1.2a), or more or less erythematous plaques or patches with some atrophy and elevated borders. Morpheaform variants appear as skin-colored or light pink, indurated and atrophic plaques mimicking a scar or a small patch of scleroderma. Pigmented BCC may mimic SSM or other pigmented cutaneous neoplasms (Fig. 1.2b) and a number of differential diagnoses are to be considered (Table 1.3). BCC is most commonly present in anatomic areas with high density of pilosebaceous units, and is more prevalent in sun-exposed areas. In addition, BCC has a reported incidence rate of 10% in patients with nevus sebaceous, and therefore, early excision is recommended.

Table 1.3 Extended differential diagnosis of basal cell carcinoma

<table>
<thead>
<tr>
<th>Lesions that may mimic basal cell carcinoma</th>
<th>Diagnostic differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial BCC vs. actinic keratoses</td>
<td>Clinical exam: AK more hyperkeratotic; may require histological evaluation</td>
</tr>
<tr>
<td>Small nodular BCC vs. sebaceous hyperplasia</td>
<td>Clinical exam: sebaceous hyperplasia with characteristic yellow color, central umbilication</td>
</tr>
<tr>
<td>Nodular BCC vs. Compound melanocytic nevus</td>
<td>By history. Dermoscopy may show pigment network in melanocytic nevus, no arborising bloodvessels; may require histological evaluation</td>
</tr>
<tr>
<td>Superficial BCC vs. M. Bowen</td>
<td>M. Bowen more hyperkeratotic; in situ SCC, requires histological evaluation</td>
</tr>
<tr>
<td>Superficial BCC vs. Eczema</td>
<td>Eczema has benign course; may disappear after few weeks, if lesions persist: histological evaluation</td>
</tr>
<tr>
<td>Superficial BCC vs. Psoriasis</td>
<td>History of Psoriasis vulgaris with pathognomonic findings. Benign course; may disappear after few weeks, if lesions persist: histological evaluation</td>
</tr>
<tr>
<td>Pigmented BCC vs. pigmented seborheic keratoses</td>
<td>Dermoscopic evaluation showing pseudohorn cysts</td>
</tr>
<tr>
<td>Pigmented BCC vs. superficial spreading melanoma</td>
<td>Dermoscopic evaluation showing pigment network/irregularities, blue–white veil. Requires histological evaluation</td>
</tr>
<tr>
<td>Morpheaform BCC vs. flat scar</td>
<td>By history; if in doubt: requires histological evaluation</td>
</tr>
<tr>
<td>Morpheaform BCC vs small patch of scleroderma</td>
<td>By history; if in doubt: requires histological evaluation</td>
</tr>
<tr>
<td>Nodular BCC vs dermal melanocytic nevus</td>
<td>Palpation: softer in consistency; may require histological evaluation</td>
</tr>
<tr>
<td>BCC in nevoid basal cell carcinoma syndrome vs. skin tags</td>
<td>Positive family history of NBCCS; palmoplantar pits. Skin tags are soft; snip-excision allows histological analysis</td>
</tr>
</tbody>
</table>
Fig. 1.2 (a) Left mandibular region of a 67-year-old female with a history of longstanding sun exposure and a lesion of about 6 months duration, slowly enlarging in size. Clinical examination revealed the presence of marked dermatoheliosis (dyspigmentation, epidermal atrophy, and increased wrinkling with solar elastosis) and a 1.5 cm erythematous nodule with central ulceration, hemorrhagic crusting, and sharp demarcation. Dermoscopy reveals the presence of arborising telangiectasias. Histology confirmed the presence of nodular BCC with ulceration, and the lesion was completely excised with a margin of 3 mm.

(b) Mid-upper back of a 56-year-old female with a history of long-standing sun-exposure and a lesion of approximately 4 months duration. Patient was referred to rule out melanoma. Clinical examination revealed a 2.3 cm flat hyperpigmented plaque with some nodular-cystic aspects, an irregular surface, and borders with relatively sharp demarcation. Histology confirmed the presence of a microcystic, pigmented variant of basal cell carcinoma.

c–e) Correspond to RCM images of micronodular BCC. (c) RCM image obtained at the level of the upper dermal layer, illustrating lobulated tumor formations. Extensive, peritumoral cleft-like spaces with dark appearance are partially separated by collagen bundles with bright appearance. Surrounding plump bright cells (white arrows) may correspond to melanophages. (d) RCM image obtained at the level of the upper dermal layer reveals islands of tumor composed of tightly packed cells with bright appearance (white asterisk) extending from the lower epidermis; peritumoral cleft-like spaces of dark appearance are indicated by white arrowheads. Periphery corresponds to bright appearance of pleomorphic keratinocytes. (e) RCM image obtained at mid-upper dermal layer, with irregular streaming (dotted lines) in the periphery. Fibrous septae of bright appearance are shown between tumor formations (white arrows), which themselves appear as hollow spaces of variable density and reflectance. (f) Corresponds to RCM image obtained at the level of the lower stratum spinosum, where elongated nuclei of dark appearance are oriented along the same axis, giving the epidermis a grid-like appearance. (RCM images obtained by VivaScope 1500, image dimensions 500×500 µm)
1.1.3 Melanocytic Nevi

While common acquired nevi are identified by their homogenous appearance (Figs. 1.3a and 1.4a), the differential diagnosis from dysplastic nevi may be challenging on the basis of clinical evaluation alone. Thus, in recent years, a variety of adjunct diagnostic devices have emerged to aid in the differentiation of congenital and acquired melanocytic lesions.

**Fig. 1.3** (a) Showing the clinical image of a common acquired melanocytic nevus on the trunk of a 33-year-old female. Dermatologic examination reveals a discretely elevated, symmetric, well-demarcated plaque with homogenous pigmentation. (b) Corresponding to RCM images obtained at the level of the dermo-epidermal junction, revealing homogenous appearance of dermal papillae (*), with regular distribution of brightly pigmented cells (arrowheads). Dark nuclei are placed centrally within the cell. Characteristic RCM feature of common acquired nevi includes the presence of well-demarcated, “edged” papillae (dashed red line) as shown in (b). The presence of clusters of bright cells in contiguity with the basal layer corresponds to homogeneous nevus nests at the level of the dermo-epidermal junction as illustrated in (c) (dashed red line). (RCM images obtained by VivaScope 1000, image dimensions 200×250 μm)
Fig. 1.3 (continued)

Fig. 1.4 (a) Showing representative clinical image of a dysplastic nevus on the trunk of a 27-year-old male. Dermatologic examination reveals a large oval plaque with 1.8×1.5 cm in diameter and slightly inhomogenous pigmentation. (b) Corresponds to RCM image of dysplastic nevus, obtained at the level of the dermo-epidermal junction. RCM evaluation reveals a distortion of the normal architecture, with variations in size/shape of the dermal papillae (dashed red line) and somewhat ill-defined demarcation of “nondged papillae.” (c) RCM image is obtained at the level of the suprapapillary plate; RCM reveals an atypical cobblestone pattern (red arrowheads). (d) Illustrates junctional thickening (asterisk) which corresponds to “bridging of epidermal papillae” on routine histology (RCM images obtained by VivaScope 1000, image dimensions 200×250 μm)
1.1.4 Malignant Melanoma

While early diagnosis is most essential for effective management of melanoma, the incidence and number of deaths related to malignant melanoma have continued to rise, despite screening efforts and improved technical screening tools. Four classical subtypes can be differentiated: superficial spreading melanoma (SSM), nodular melanoma (NM), acrolentiginous (including subungual) melanoma, and lentigo maligna melanoma (LMM). Rare subtypes include mucosal and desmoplastic melanomas, or the entity of melanomas arising in congenital nevi.

Clinically, SSM may appear as brown macules, flat papules, or plaques with raised borders on palpation or inspection and various shades of pink, white, gray, and blue. Lesion asymmetry is most commonly noted with respect to color distribution and shape/configuration.
SSM may occur on any site of the body, with high prevalence on lower legs in women. Acrolentiginous melanoma (ALM, including subungual melanoma) and LMM appear as predominantly brown to dark brown/black macular lesion with variations in pigment pattern; highly irregular borders with areas of regression. Detection may be delayed further if lesions are amelanotic. NM may appear as brown to dark brown/black nodule on previously normal skin. Early detection is most critical since NM does not exhibit a radial growth phase.

1.2 Noninvasive Imaging Techniques

1.2.1 Dermoscopy

Dermoscopy has been developed as an adjunct noninvasive tool for the diagnosis of skin cancer and has widely been used for the differential diagnosis of melanocytic lesions for the past 20 years, especially around Europe [1–4]. The terms dermatoscopy, epilumence microscopy (ELM), and skin surface microscopy have been used synonymously.

Dermoscopy allows the visualization of skin structures (e.g., blood vessels or pigment), which would otherwise not be visible to the naked eye. The basic principle of dermoscopy is shown in Figure 1.7.

a. The principle of dermoscopy is the use of cross-polarized light in combination with an immersion medium (alcohol, immersion oil), thereby minimizing surface reflection. Subsurface structures in the epidermis, at the dermo-epidermal junction and in the upper dermis, can be visualized and analyzed in correlation with established scoring schemes (Tables 1.4 and 1.5). Stolz et al. established the ABCD rule as the first diagnostic algorithm after the evaluation of 31 dermoscopic criteria using a semiquantitative scoring scheme: A (asymmetry), B (border), C (color), and D (dermoscopic structures) [5–6]. Total dermatoscopic score (TDS) is calculated by multiplying individual scores with different weighting factors (weighting coefficients) according to the importance of individual criteria. In an effort to simplify the diagnostic process, a number of scoring schemes have since been described; among them is the Menzies’ method, which employs 11 criteria and the 7-point checklist by Argenziano and his coworkers (Tables 1.4 and 1.5) [7–8].
Most hand-held devices used in clinical practice have a magnification of 6–10 fold (Fig. 1.7b). Newer devices may allow a magnification of up to 100-fold and have been equipped with image analysis software. Computer-assisted dermatoscopic image analysis permits the monitoring of complex lesions or the observation of patients with numerous moles whereby extensive or serial excisions may be avoided. In the evaluation of melanocytic skin lesions, dermoscopy has been shown to improve the diagnostic accuracy if used by a trained and experienced observer. However, studies have shown that the diagnostic accuracy may also decrease if dermoscopy is used by untrained physicians [9].

### 1.2.2 Ultrasound

In ultrasound, skin morphology is visualized by the use of ultrasound waves that are reflected from the tissue. In dermatologic oncology, two main devices are used, mid frequency ultrasound (MFUS) and high frequency ultrasound (HFUS).

MFUS employs frequencies between 7.5 and 15 MHz and has been established for the evaluation of lymph nodes and cutaneous metastasis in the follow-up of melanoma. It is often used in combination with ultrasound guided fine needle biopsies for cytologic confirmation of suspicious findings. The penetration depth of MFUS reaches 6 cm.

Advantages of ultrasound include the high penetration that allows the measurement of tumor thickness and the evaluation of lymph nodes. At present, the clinical application of ultrasound is limited by the low resolution, which does not allow the histomorphologic distinction between different skin tumors.

HFUS employs frequencies between 20 and 100 MHz and may be used for the preoperative assessment of tumor thickness. Sonography at 20 MHz reaches a penetration depth of 3.8 mm with an axial resolution of 39 μm and a lateral resolution of 210 μm. Devices with 100 MHz provide an increased resolution of 9.9 μm (axial) and 84 μm (lateral), but yield an overall lower penetration of 1.1 mm [10–11].

### 1.2.3 Optical Coherence Tomography

Optical coherence tomography (OCT) is a novel non-invasive imaging technique that is based on interferometry. The images obtained by OCT are 2 dimensional, cross-sectional, and have a lateral dimension of 4–6 mm. The axial and the lateral resolution reach about 15 μm and the penetration depth is 500–1,000 μm [12]. With OCT, the macromorphology of the skin as well as adnexal structures and blood vessels can be differentiated. However, cellular and subcellular details as well as the basement membrane cannot be visualized. Therefore, early tumor invasion cannot reliably
be detected. OCT has been evaluated for different inflammatory skin diseases, including contact dermatitis and psoriasis [13], and preliminary studies have described the features of nonmelanoma skin cancer including BCC and AK [14–16]. However, there is a lack of systematic studies evaluating the sensitivity and specificity of OCT for the diagnosis of Nonmelanoma skin cancer (NMSC) to date.

1.2.4 Reflectance Confocal Microscopy

Reflectance mode confocal microscopy (RCM) is a novel noninvasive imaging technique that has first been described for imaging of human skin in 1995 [17]. Since then, it has been evaluated for a variety of inflammatory and neoplastic skin conditions including BCC, AK, and malignant melanoma [18–25]. In contrast to conventional diagnostic biopsy, RCM evaluation is noninvasive, painless, and enables the visualization of cellular details in the skin in vivo without processing artifacts. Since tissue is not removed, the same lesion can be evaluated over an extended period of time, and disease evolution as well as therapeutic effects may be monitored by RCM [26–27].

The optical principle of RCM is the detection of skin chromophores (melanin, hemoglobin, and water) based on the differences in their refraction indices (Fig. 1.8a) [17]. In RCM, a point light source is used to illuminate a small spot within the tissue. The light is reflected from the tissue and conducted through a small pinhole onto a detector. For imaging of larger horizontal planes within the tissue, individual maps can be obtained by scanning the light source in the X–Y direction, whereby areas between 1 and 8 mm² can be evaluated. The resolution of reflectance confocal microscopy depends on the wavelength of the light source, the size of the pinhole, and the objective lens. The commercially available confocal microscope (Vivascope 1500, Lucid Inc. Rochester, NY, USA, MAVIG GmbH Munich, Germany) uses an 830 nm diode laser, a 30x objective lens with a numerical aperture of 0.9. The system provides an axial resolution of 3–5 μm and a lateral resolution of 0.5–1 μm, which is comparable to routine histology sections. The penetration depth reaches 250 μm, which corresponds to the level of the upper reticular dermis (Fig. 1.8b) [17].
1.2.4.1 RCM Imaging of Actinic Keratosis (AK) and Squamous Cell Carcinoma (SCC)

AK have been classified as in situ SCC [28]. On cellular and morphological level, they show similar changes to invasive SCC. RCM has been used for the evaluation of AK [20] and recent studies have shown that the correct diagnosis of AK can be obtained in 97.7% of cases when compared with normal skin [21, 23]. On RCM, AK show characteristic features including parakeratosis, cellular/nuclear polymorphism, and architectural disarray (Fig. 1.1b–e) [21, 29].

So far, it has been difficult to distinguish AK from invasive SCC by reflectance confocal microscopy. The horizontal sectioning mode impedes the detection of single invasive cells. Furthermore, optical penetration is limited in hyperkeratotic lesions. However, superficial curettage of the hyperkeratotic scale enhances penetration and resolution at deeper levels. Preliminary data indicate that involvement of the entire epidermal thickness correlates with severe AK and may be a feature of early invasive SCC.

1.2.4.2 Imaging of Basal Cell Carcinoma (BCC)

The features of BCC have been defined and a recent study has evaluated the sensitivity and specificity of reflectance confocal microscopy for the diagnosis of BCC [22]. In this study, the presence of two or more RCM criteria of BCC showed a sensitivity rate of 100%. The most important criterion was the presence of polarized, monomorphic nuclei, with a sensitivity of 91.6% and a specificity of 97%. Other characteristic features of BCC include elongated nuclei, orientation of the nuclei along the same axis, palisading of tumor cells, dilated/elongated blood vessels and increased vascularity with inflammatory infiltrate (lymphocyte rolling), and disruption of the epidermal architecture in the overlying epidermis [29]. The typical tumor nests with surrounding stroma can also be visualized by RCM, and may present as moderately refractile lobulated tumor nodules (Fig. 1.2c–e).

1.2.4.3 Melanocytic Nevi and Melanoma

Reflectance confocal microscopy has most extensively been used for the evaluation of melanocytic lesions in vivo. Melanocytic lesions are particularly suitable for evaluation with RCM because melanin provides strong contrast [17]. Benign nevi characteristically show the presence of small, monomorphous round to oval cells at the dermo-epidermal junction (junctional nevi) or at the dermo-epidermal junction and in the superficial dermis (compound nevi) [24–25]. RCM features that are consistently found in benign nevi are regular and well-demarcated papillae (edged papillae), regular nests of melanocytes at the junction and regular architecture of the epidermis, described as honeycomb or cobblestone pattern (Fig. 1.3a–c) [29–31]. The differentiation of dysplastic nevi relies in large parts on the presence of irregular shapes of dermal papillae, with altered contours of the rete ridges and the presence of atypical aggregates of junctional melanocytes. RCM evaluation may reveal the presence of irregular, dense clusters, some of which may assume a pseudopod-like appearance. The overlying epidermis may be normal, but a significant proportion of dysplastic nevi may show disruption of the normal honeycombed pattern and the presence of single, bright cells interspersed within the keratinocytes corresponding to pagetoid melanocytes (Fig 1.4a–d).

RCM evaluation of malignant melanoma reveals dermal papillae without a rim of bright basal cells, which are referred to as nonedged papillae, irregular nests of atypical melanocytes, marked distortion of the epidermal architecture, and the presence of large nucleated cells in the epidermis corresponding to pagetoid spread [29–31]. RCM features of malignant melanoma also include the presence of large dendritic melanocytes with long irregular branches, increased number of bright cells, and may reveal atypical nests (clusters) in the dermis of inhomogeneous, sparse, or cerebriform morphology (Fig. 5a–c) [32–34]. Good correlation between RCM and dermoscopy has been shown in several reports [32, 33]. Presently, technical limitations do not permit the evaluation of tumor thickness or level of invasion; therefore, routine excisional biopsies remain the gold standard for diagnosis and assessment of melanocytic skin lesions. However, RCM may aid in the diagnostic process by minimizing sampling errors, increasing diagnostic accuracy, or avoiding unnecessary re-excisions. Large clinical studies are currently on the way to evaluate the applicability of RCM in dermatology.
1.3 Biopsy

Although many skin tumors may be diagnosed by clinical diagnosis alone or with the help of adjunctive diagnostic tools, the histological examination of skin biopsies remains the gold standard in the diagnosis of skin cancer. Histological examination is the only method to exclude malignancy or obtain the definitive diagnosis. The histological features of different skin cancer are described in Chap. 2.

Many different techniques can be used for obtaining a skin sample. While an excisional biopsy is the best technique for diagnosis of melanocytic neoplasms, the diagnosis of nonmelanoma skin cancer may be also obtained by the use of less invasive techniques. Prior to excision, local anesthesia is administered using lidocaine or xylocaine 1/2%, with or without the addition of epinephrine. The addition of epinephrine has to be avoided in acral lesions and patients with a history of increased hemodynamic/cardiac or immunologic sensitivity to epinephrine. Hypersensitivity to local anesthetics may require the testing for suspected allergies and alternatives, and an adaptation of the anesthetic used in subsequent procedures. The anesthetic is infiltrated intradermally using a small gauged syringe. The onset of action starts immediately after injection and lasts for 1–2 h. Relative contraindications to skin biopsy include the use of blood thinners like aspirin or warfarin. However, small biopsies may be performed with caution.

1.3.1 Punch Biopsy

Punches are available in different sizes ranging usually from 2 to 8 mm. After anesthesia, the skin is pulled across the skin tension lines in order to get an elliptic defect rather than a circular defect which facilitates wound closure and yields better cosmetic results. The punch is rotated through the full thickness of the dermis into the subcutaneous fat, from which the specimen is cut on the base. Grasping the forceps has to be avoided in order to minimize crush artifacts. Usually, closure is performed with single interrupted or vertical mattress stitches.

1.3.2 Shave Biopsy

Shave biopsies are used for the removal of superficial, elevated lesions in the epidermis and dermis (seborrheic keratoses, AK) where histological evaluation of the epidermal part of the tumors is sufficient for diagnosis and depth of penetration is not required for further management. It can be performed with a scalpel, a dermablade, or a razors blade, followed by the local application of pressure, hemostyptic sponges, or Iron(III) chloride.

1.3.3 Excisional Biopsy

With an excisional biopsy, the suspicious lesion is completely removed with a small margin of clinically normal tissue. It is the method of choice for the removal of pigmented lesions. Sutures are required.

1.3.4 Incisional Biopsy

Incisional biopsies are performed in order to remove a larger part of the suspicious lesion in patients where primary excisional biopsy cannot be performed due to the size or location of the lesion. Incisional biopsies are most commonly used for nonmelanoma skin cancers. For melanocytic lesions, incisional biopsy should preferably be performed in those areas with either the most intense (darkest) pigmentation or in the nodular aspects of the suspicious lesion. Incisional biopsies are followed by immediate wound closure using single interrupted stitches.

References


2.1 Basal Cell Carcinoma

G. Goldenberg, L.E. Golitz, and J. Fitzpatrick

Basal cell carcinoma (BCC) is an epithelial neoplasm that is believed to derive from the basal layer of the epidermis or follicular epithelium. The classic histologic presentation of BCC is that of nodules and/or strands of atypical basaloid cells that show nuclear palisading, cellular apoptosis, and scattered mitotic activity. Artifactual cleft formation may be seen between the tumor lobules and its surrounding stroma, which may be mucinous. Solar elastosis, a manifestation of chronic actinic damage, is usually present in the dermis. Tumor calcification may be seen, especially in long standing tumors, although this phenomenon has been reported to be more commonly associated with more aggressive BCC subtypes [1]. Multiple growth patterns of BCC have been described, and these act as prognosticators of biologic behavior [2].

Superficial basal cell carcinoma presents with nodules and strands of basaloid cells that proliferate parallel to the epidermis and demonstrate slit-like retraction.
Fig. 2.1 (continued)
from the surrounding stroma (Fig. 2.1a, b) [3]. Tumor cells may also proliferate along follicular structures.

Nodular basal cell carcinoma (NBCC) presents with discrete, well-defined nodules and strands of basaloid cells in the papillary and reticular dermis, which may focally show a connection to the overlying epidermis (Fig. 2.1c, d). Roughly one-third of NBCC’s will show a coexistent superficial component [2]. Artifactual stromal retraction is usually present in these cases. Central tumor necrosis and/or mucin deposition may be seen within the individual nodules, giving the neoplasm a “cystic” appearance.

Morpheaform (sclerosing) basal cell carcinoma presents with thin strands of atypical basaloid cells in the dermis (Fig. 2.1e, f). These neoplastic strands are usually one-to-two strands thick and are enmeshed in a densely collagenized stroma with proplastic fibroblasts [2]. Individual tumor cell necrosis and mitotic activity may be more common with this growth pattern. Stromal retraction may still be seen, but is less common than in other types of BCC. This neoplasm is usually poorly circumscribed and shows an infiltrating growth pattern, invading into reticular dermis and subcutaneous fat.

Fibroepithelioma of Pinkus is a rare type of BCC that typically presents above the natal cleft or on the lower trunk with a pink or flesh colored nodule that may mimic seborrheic keratosis [4]. This tumor presents with elongated basaloid epithelial strands, which usually show multiple connection points to the overlying epidermis (Fig. 2.1g, h). Retraction from the distinct fibromyxoid stroma is usually seen. Histologically, the most important differential diagnosis is eccrine syringofibroadenoma of Mascaro, which presents with
elongated basaloid strands containing central eccrine ductal cells with a well-defined cuticle [5].

Immunohistochemical staining is rarely required in order to diagnose a BCC. Ber-EP4, a monoclonal antibody which recognizes two glycopolypeptides (34 and 39 kDa) found in most human epithelial cells, has recently been utilized to distinguish BCC from squamous cell carcinoma (Fig. 2.1i) (SCC) [6–10]. All BBCs, regardless of the subtype, stain positive with Ber-EP4, whereas SCC do not show positive staining. This marker can also be reliably used to differentiate BCC from microcystic adnexal carcinoma [11].

2.2 Squamous Cell Carcinoma In Situ

J. Roewert-Huber

SCC in situ has many diverse clinical presentations (see Table 2.1) and includes numerous distinct subtypes with a wide range of clinical manifestation. Histologically, squamous cell carcinoma in situ is composed of atypical keratinocytes, which can be identified throughout the full thickness of the epidermis. The atypical keratinocytes exhibit eosinophilic, sometimes pale or vacuolated cytoplasm, a sign of faulty cornification, as well as whorls of parakeratosis within aggregates of neoplastic cells (“horn pearls”). An increased number of atypical mitoses and dyskeratotic or necrotic keratinocytes can be found throughout the epidermis. The nuclei of the atypical keratinocytes are crowded, pleomorphic, and often large and hyperchromatic. By definition, the atypical keratinocytes throughout the epidermis do not penetrate into the dermis. SCC in situ may develop into invasive SCC.

Histologically, the different types of SSC exhibit the same morphology; however, their architectural patterns are different. It is very important to differentiate between these lesions because they present with a wide range of different clinical manifestations covering benign types of bowenoid papulosis, as well as tumors with possible invasive growth potential. Examples of the more aggressive of the latter tumor types are actinic keratosis and Bowen’s disease with a tendency towards invasive, and frequently metastatic, growth.

<table>
<thead>
<tr>
<th>Squamous cell carcinoma in situ</th>
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<tbody>
<tr>
<td>Actinic keratosis</td>
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<tr>
<td>Bowen’s disease</td>
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<tr>
<td>Bowenoid papulosis</td>
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<td>Erythoplasia of Queyrat</td>
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2.2.1 Actinic Keratosis (AK)

For the last approximately 100 years, a controversial discussion regarding the terminology of actinic keratosis has been ongoing. Actinic keratosis lesions are categorized by some authors as precancerous because a subset appears to have low individual potential for invasive malignancy or for spontaneous regression.
However, other authors have postulated that AK lesions have to be regarded as early squamous cell carcinomas. The reason for this is that the morphology of atypical cells in the epidermis in both actinic keratosis and cutaneous squamous cell carcinoma is identical and represents histological aspects of the same disease. Today, AK is considered as early squamous cell carcinoma. Recent studies of molecular, biochemical pathogenesis confirm this pathogenetic classification.

### 2.2.1.1 Histology Appearance

Histologically, AK is characterized by the loss of orderly cell maturation with atypical keratinocytes in the epidermis. The atypical keratinocytes reveal a loss of polarity, and the nuclei of the atypical keratinocytes are crowded, pleomorphic, and often large, hyperchromatic with cytologic atypia. These cells are characterized eosinophilic, sometimes pale or vacuolated cytoplasm. The number of mitosis is increased. Dyskeratotic or necrotic keratinocytes are found in the epidermis. The presence of atypical keratinocytes varies from very few atypical cells in size and amount at the basal cell layer of the epidermis to more advanced lesions with moderate keratocytic atypia in the epidermis that does not involve the granular cell layer. Fully developed lesions contain atypical keratinocytes, which involve the entire epidermis reaching the granular cell layer. These histological changes are equivalent to previously called SCC in situ. The epidermal keratinocytes of the acrosyringia and acrotrichia are spared, showing normal appearance and keratinization patterns, thereby reflecting a normal orthokeratotic cornified layer. The cytoplasm of keratinocytes of the acrosyringia and acrotrichia is more basophilic or blue and shows a sharp demarcation to the atypical epidermal keratinocytes, which have a more eosinophilic or pink cytoplasm. There are often small round buds at the basal layer which protrude into the papillary dermis. The epithelial keratinocytes are immature, thereby contributing to parakeratosis alternating with hyperkeratosis. Actinic keratoses almost always show solar elastosis in the dermis and often contains a cell infiltrate, composed mostly of lymphocytes and plasma cells.

AKs can be divided into the following six histological types: hypertrophic, atrophic, Bowenoid, acantholytic, lichenoid, and pigmented. Overlapping between these subtypes may be noticed within the same lesion.

The hypertrophic type shows prominent hyperkeratosis and acanthosis. The atrophic variant has a thinned epidermis, rete ridges are missing. The Bowenoid type of actinic keratosis is difficult to distinguish from Bowen’s disease. In contrast to actinic keratosis, Bowen’s disease shows parakeratosis, which may be strikingly predominant, and no distinct alternation of orthokeratosis and parakeratosis. The process spares acrosyringia, but not acrotrichia; suprabasal clefts or acantholytic cells are not found. The acantholytic variant reveals focal acantholysis, sometimes being accompanied by clefts similar to other acantholytic diseases. The lichenoid type shows a dense band-like infiltrate of lymphocytes in the papillary dermis and vacuolar alteration at the dermoeipidermal junction. The pigmented variant has increased melanin pigmentation in the epidermis.

In 2007, Roewert-Huber et al. [1] published a classification of actinic keratoses, which categorizes the AK into three histological types based on the extent of atypical keratinocytes in the epidermis.

**Early In Situ SCC-Type I (Mild)**

Atypical keratinocytes are found in the basal and suprabasal layer of the epidermis, and could extend to the lower one-third of the epidermis.

The nuclei are hyperchromatic, variable in size, and have mild irregularities in nuclear outline. Often, a loss of nuclear polarity occurs, with many of the cells that have oval nuclei oriented at obtuse angles, instead of perpendicular to the epidermis. The follicular infundibulum is not involved.

**Early In Situ SCC-Type II (Moderate) (Fig. 2.2a)**

Atypical keratinocytes extend to the lower two-thirds of the epidermis alternating with zones of normal epidermis of the acrotrichia and acrosyringia in particular. Buds of keratinocytes in the upper papillary dermis can be found.

**In Situ SCC-Type III (Severe) (Fig. 2.2b)**

Atypical keratinocytes extend more than two-thirds to full thickness within the epidermis including involvement of the epithelia of the hair follicle
Buds of keratinocytes can also be found in the upper papillary dermis. Grade III lesions are equivalent to lesions previously called SCC in situ.

This creation of a grading system for epithelial tumors, similar to that for other neoplasms, was warranted and long overdue. Tumor classifications according to severity and extent are important. The classification of AK will provide the clinician with a very improved prognostic tool of the malignant potential of the lesion, helping him with the selection of the most specific therapeutic option. Without a grading system, the clinician does not have the tools to accurately judge the amount of atypical keratinocytes in the epidermis; with this information, the physician has the information to choose more precisely the appropriate therapy for these types of early squamous cell carcinomas.

Reference


Fig. 2.2 (a) Early in situ SCC-type II (moderate) with atypical keratinocytes extending to the lower two thirds of the epidermis alternating with zones of normal epidermis of the acrotrichia and acrosyringia in particular. Alternation of pink parakeratosis and blue orthokeratosis. (b) In situ SCC-type III (severe) with atypical keratinocytes extending more than two thirds to full thickness of the epidermis including involement of the epithelia of the hair follicle infundibula and acrosyringia as seen in SCC in situ.

infundibula and acrosyringia as seen in SCC in situ. Buds of keratinocytes can also be found in the upper papillary dermis.

Grade III lesions are equivalent to lesions previously called SCC in situ.

This creation of a grading system for epithelial tumors, similar to that for other neoplasms, was warranted and long overdue. Tumor classifications according to severity and extent are important. The classification of AK will provide the clinician with a very improved prognostic tool of the malignant potential of the lesion, helping him with the selection of the most specific therapeutic option. Without a grading system, the clinician does not have the tools to accurately judge the amount of atypical keratinocytes in the epidermis; with this information, the physician has the information to choose more precisely the appropriate therapy for these types of early squamous cell carcinomas.
2.2.2 Bowen’s Disease

J. Röwert-Huber

The term Bowen’s disease refers to a particular type of intraepidermal squamous cell carcinoma, the so-called squamous cell carcinoma in situ. Nevertheless, it is a clinical and histopathological distinct entity.

The lesion may occur on any skin surface.

The epidermis shows acanthosis with increased cellularity and hyper – and parakeratosis as signs of aberrant cornification. The keratinocytes are crowded and are arranged in complete disorder, reflecting a “windblown” appearance. The specific histological features of Bowen’s disease are cells with more prominent cytologic atypia characterized by large, pleomorphic and hyperchromatic nuclei. By loss of normal polarity, and by absence of maturation to the surface in together with dyskeratotic and occasionally multinucleated cells. Numerous mitoses including atypical bizarre forms are noted. Below the otherwise intact dermoeidermal basement membrane, there is a chronic inflammatory infiltrate in the upper corium (Fig. 2.3).

In the pigmented variant of Bowen’s disease, is characterized by the presence of more pigment in the atypical keratinocytes along with numerous melanophages.

2.2.2.1 Erythroplasia of Queyrat

Similar lesions located on the glans penis are referred to as Erythroplasia of Queyrat. They have the identical histological features as does Bowen’s disease. The term Bowen’s disease has been replaced in gynaecological pathology by the term vulvar interepithelial neoplasia (VIN) and is equivalent to VIN grade III.

2.2.2.2 Bowenoid Papulosis

Bowenoid papulosis is characterized by the same cytopathological changes as Bowen’s disease, except that in low power the lesions resemble condylomata acuminata. In contrast to Bowen’s disease, Bowenoid papulosis exhibits multiple verrucous papules, which are frequently pigmented.
2.3 Invasive Squamous Cell Carcinoma

J. Roewert-Huber

Invasive Squamous cell carcinoma is an epithelial tumor infiltrating into the dermis, characterized by signs of cornification. The histological picture of squamous cell carcinoma reveals proliferation of anastomosing nests, sheets, and strands of atypical keratinocytes originating in the epidermis and infiltrating into the dermis. Prominent intercellular bridges are characteristic. Epithelial cells exhibit glassy eosinophilic cytoplasm and frequently a large nucleus. Dyskeratotic cells, parakeratosis, and horn pearl formation are sign of abnormal cornification (Fig. 2.4). These morphologic features of squamous cell differentiation are variably present in the tumor. Sometimes, in lesions with complete anaplastic transformation, it may be difficult to determine the tumor origin. Immunohistochemical examinations play an important role, because these transformed cells will characteristically show a type of keratin expression with higher molecular weight and particular epithelial membrane antigen (EMA).

SCC is categorized into well-differentiated, moderately, or poorly differentiated subtypes. The extent of differentiation varies with the extent of keratinization. In well-developed, well-differentiated SCC the majority of the tumor cells are highly differentiated and exhibit squamous eddies or horn pearls and show minimal pleomorphism. Poorly-differentiated SCC, which is a more aggressive tumor type, contains very few keratin horn pearls in comparison and exhibits a more advanced anaplastic appearance. The moderately differentiated SCC exhibits a histopathology pattern with features of both the well-differentiated and the more anaplastic type.

Broders’ classification, originally published in 1932, devises a four-tiered system: grade I, tumors in which more than 75% of cells are differentiated; grade II, tumors with 50–75% differentiation; grade III, tumors with 25–50% differentiation; and grade IV, tumors with less than 25% differentiation. This classification was never really accepted and used by pathologists, because it was perceived as being rather subjective. Clinically, the most important are the two extremes of well vs. poorly differentiated squamous cell carcinoma. Today, the TNM classification system (see Table 2.2) is used for squamous cell carcinoma of the skin. Together with the clinical staging grouping, the TNM classification system allows physicians to compare tumor stages across patients, assess prognosis, and design appropriate treatment regimens.

An important additional prognostic factor besides tumor size and histological differentiation is the depth of infiltration. With increasing depth of invasion of the primary tumor, the risk of metastatic spread increases significantly. In addition, anatomic site, perineural invasion, as well as histological variants are important influencing contributors toward a more aggressive course of tumor progression. If signs of spindle-cell differentiation, glandular differentiation, or basal-cell differentiation are present as part of the squamous cell tumor, these will be described appropriately and thus

![Invasive squamous cell carcinoma: Proliferation of anastomosing nests, sheets and strands of atypical keratinocytes originating in the epidermis and infiltrating into the dermis. Epithelial cells exhibit glassy eosinophilic cytoplasm and frequently a large nucleus. Dyskeratotic cells, parakeratosis and horn pearl formation are also observed.](image)
recognized as distinctive features. The major variants are listed in Table 2.3.

### Table 2.2 TNM clinical classification

<table>
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<th>Distant metastases (M)</th>
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### Table 2.3 The major variants of squamous cell carcinoma

- Acantholytic squamous cell carcinoma/Pseudovascular squamous cell carcinoma
- Spindle cell (Sarcomatoid) carcinoma
- Verrucous squamous cell carcinoma, Keratoacanthoma
- Adenosquamous carcinoma

2.3.1 **Acantholytic Squamous Cell Carcinoma**

It is also named adenoid SCC (pseudoglandular) based on its gland-like pattern related to prominent acantholysis. Acantholyse is characterized by a loss of cohesion (desmosomes) between cells. These cells typically are round and can contribute to the formation of clefts, gland-like cell aggregates, or tubular spaces. The acantholytic areas may mimic types of adenocarcinoma or sweat gland carcinoma or may be forming a pseudo-vascular pattern resembling angiosarcoma. Clinically, this type of tumor is indistinguishable from other SCCs. In the literature, discussion is controversial whether this variant may be more aggressive than conventional SCC.

2.3.2 **Spindle Cell Squamous Cell Carcinoma**

It is an uncommon variant of SCC, also named spindle-cell carcinoma, carcinosarcoma, or sarcomatoid carcinoma. This tumor variant appears almost always on sun-damaged or irradiated skin of elderly patients. The incidence is increased in immunosuppressed patients. Histologically, the tumor is composed of atypical spindle cells with no or minimal components of keratinization and no evidence of epidermal origin. The spindle cells show scant eosinophilic cytoplasm and large nuclei. Many Mitotic figures and bizarre pleomorph giant cells are usually found. Distinction between this tumor type, sarcomas, or other spindle cell tumors may be difficult. Thus, in cases of doubt, immunohistochemistry is helpful because it allows identification of particularly high-molecular keratin and EMA antibodies.

2.3.3 **Verrucous Squamous Cell Carcinoma**

It has been described under different synonyms. In the skin, it is named epiderthelioma cuniculatum, or in ano-genital region, Buschke-Löwenstein tumor, and the oral cavity, Ackermann tumor. It is extremely rare, and a well-differentiated variant of SCC with low malignant potential. All the different kinds of verrucous squamous cell carcinoma have the same histologic features, exhibiting endo-oxophytic growth with hyperkeratosis, papillomatosis, and acanthosis resembling a verruca vulgaris. The well-proliferating keratinocytes in these lesions are more pushing with broad, rounded borders, rather than infiltrating the tissue.
Only very little atypia and no atypical mitotic figures are present in this tumor. Draining sinuses and crypt-like spaces as well as interaepidermal neutrophils usually forming an intraepidermal abscess are also an important diagnostic clue.

2.3.4 Adenosquamous Carcinoma

It is a rare variant of squamous cell carcinoma related to acrosyringia. These lesions are characterized by the formation of mucin secreting true glandular differentiation within well-differentiated squamous cell nest. A moderate number of mitosis can be found. The tumor cells might have their origin in pluripotent epithelial cells near or within the acrosyringial portions of sweat ducts because they secrete diastase resistant mucins of sweat gland tumors. The glands forming cells express also carcinoembryonic (CEA) antigen, which are normally found in eccrine and apocrine glands.

The tumor occurs on the head, neck, and penis in elderly patients. The behavior of this tumor is aggressive and is associated with a high rate of recurrence and metastasis rate.

2.3.5 Keratoacanthoma (KA), Variants of SCC

Keratoacanthoma (KA) is considered by most physicians as a variant of SCC. The morphological appearance, clinical course, and the potential for spontaneous regression are unique features of Keratoacanthoma. Histologically, many features overlap with SCC. Definitive histologic distinction from a well-differentiated SCC could be very difficult or may be impossible to achieve with confidence if the lesion is incompletely excised.

The architecture of the fully developed lesion is symmetrical, well circumscribed with a central keratin-filled crater. The epidermis consists of exo-endophytic nodules, which infiltrate the dermis. The tumor is poorly demarcated and is usually surrounded by a mixed inflammatory infiltrate. Neutrophils may be seen in the epidermis producing small microabscesses. The keratinocytes have an abundant hyalinated cytoplasm. Typical mitotic figures, perineural invasion, and intravenous growth may be seen incidentally.

2.4 Malignant Melanoma

G. Goldenberg, L.E. Golitz, J. Fitzpatrick

The histologic diagnosis of malignant melanoma (MM) requires a constellation of specific architectural and cytologic findings. The atypical architectural features seen in MM are listed in Table 2.4 and atypical cytologic features are listed in Table 2.5. MM may develop de novo or within a preexisting melanocytic nevus, which is present in approximately one-third of MM. It has also been demonstrated that almost all primary MM begin as proliferations of melanocytes initially present at the dermoepidermal junction (DEJ) [12]. This stage or phase of MM progression has been termed “nontumorigenic” or radial growth phase [13]. MM becomes invasive as atypical melanocytes invade into the papillary dermis, as single cells or atypical nests. This phase of tumor progression has been termed as “tumorigenic” or vertical growth phase (VGP). Some have described the VGP as invasion of melanoma cells in cohesive aggregates [14]. The depth of invasion of MM into the dermis can be measured by Clark’s level.

<table>
<thead>
<tr>
<th>Table 2.4 Atypical architectural finding seen in malignant melanoma</th>
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<tr>
<td>Large size</td>
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<tr>
<td>Predominance of single cell melanocytes over nests of melanocytes along the dermoepidermal junction</td>
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<tr>
<td>Pagetoid (upward) migration of single cell melanocytes</td>
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<tr>
<td>Confluent spread of melanocytes</td>
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<tr>
<td>Cellular dyscohesion</td>
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<tr>
<td>Lack of uniform melanin distribution</td>
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<td>Lack of melanocyte maturation with descent in the dermis</td>
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<td>Dermal regression</td>
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<tr>
<th>Table 2.5 Atypical cytologic findings seen in malignant melanoma</th>
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<tr>
<td>Nuclear hyperchromasia with coarse chromatin</td>
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<tr>
<td>Nuclear enlargement</td>
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<td>Nuclear pleomorphism</td>
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<td>Prominent nucleoli</td>
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<td>Mitosis, dernal, including atypical mitosis</td>
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<td>Cellular necrosis</td>
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<tr>
<td>Dusty melanin</td>
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<tr>
<td>High nuclear to cytoplasmic ratio</td>
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<tr>
<td>Thickened nuclear membrane</td>
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Table 2.6 Clark’s level of invasion

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>I</td>
<td>Melanoma in situ</td>
</tr>
<tr>
<td>II</td>
<td>Microinvasion into papillary dermis</td>
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<tr>
<td>III</td>
<td>Expansion into papillary dermis</td>
</tr>
<tr>
<td>IV</td>
<td>Invasion into reticular dermis</td>
</tr>
<tr>
<td>V</td>
<td>Invasion into subcutaneous fat</td>
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Table 2.7 Selected stains utilized in MM

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<th>Stain</th>
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<tr>
<td>S100</td>
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<tr>
<td>HMB-45</td>
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<td>Melan-A/MART-1</td>
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(Table 2.6) and Breslow’s depth, which is measured in millimeters. Multiple special stains have been utilized in MM, and these are listed in Table 2.7.

Malignant melanoma in situ (MMIS), including lentigo maligna (LM) type, presents with atypical melanocytes confined to the epidermis (Fig. 2.5a, b). The epidermis is typically atrophic in LM type of MMIS. The presence of single cell melanocytes, junctional nests of atypical melanocytes, extension of melanocytes above the basal layer of the epidermis, confluent spread of atypical basal cells, and follicular extension have been used as criteria for diagnosis of MMIS [15, 16]. Solar elastosis and melanophages are often found in the dermis. Lentigo maligna melanoma (LMM) arises from LM, and is characterized by the same findings within the epidermis as LM, with dermal invasion by atypical melanocytes.

Superficial spreading malignant melanoma (SSMM) presents with atypical melanocytes at all levels of the epidermis, with significant pagetoid spread (Figs. 2.5c–e). Atypical melanocytes found in the dermis may be present singly and in nests. Atypical dermal melanocytes show failure of maturation with descent. While the majority of atypical melanocytes are epithelioid, spindle cell melanocytes may also be seen.

Nodular malignant melanoma (NMM) presents with atypical melanocytes within the epidermis, with pagetoid spread, and in the underlying dermis (Fig. 2.5f–h). This MM subtype is characterized by the lack of atypical melanocytes within the epidermis adjacent to the dermal component. Dermal melanocytes fail to mature and may show significant mitotic activity.

Acral lentiginous malignant melanoma (ALMM) initially presents with a lentiginous radial growth phase of melanocytes within the epidermis, but as the tumor becomes thicker, nests on melanocytes with pagetoid spread may be seen (Fig. 2.5i, j) [17]. Halos surrounding melanocytes may be seen, giving the atypical cells a lacunar appearance. Invasive dermal melanocytes may be seen singly or in nests, composed of epithelioid or spindle-shaped cells.

Desmoplastic malignant melanoma (DMM) is a rare type of MM that presents with dermal elongated spindle-shaped melanocytes, which may show nuclear hyperchromasia, bizarre nuclei, and lack melanin pigment (Fig. 2.5k, l). Melanocytes in DMM usually lack pigment and may be highlighted by immunochemical stains (Fig. 2.5m). Fascicles of atypical melanocytes may show an infiltrative growth pattern, extending into subcutaneous fat. Abundant desmoplastic collagen bundles are usually present in the dermis. Lesions which present with less collagen and more spindle-shaped cells are referred to as spindle cell malignant melanoma (SCMM), although it has been shown that SCMM and DMM form a continuum without discrete separation [18]. An intraepidermal atypical melanocytic proliferation is also observed in the majority of DMM [19].
Fig. 2.5 Malignant melanoma. (a, b) Lentigo maligna type showing single cell spread of melanocytes along the dermal-epidermal junction; (c, e) Superficial spreading malignant melanoma showing significant pagetoid spread; (f, h) Nodular malignant melanoma showing dermal invasion without significant later spread along the dermal-epidermal junction; (i, j) Acral lentiginous malignant melanoma showing an atypical melanocytic proliferation on acral skin; (k, l) Desmoplastic malignant melanoma showing atypical melanocytes embedded in a desmoplastic stroma; and (m) S100 stain highlights atypical melanocytes in this Desmoplastic malignant melanoma.
2.5 Merkel cell carcinoma

Martina Ulrich, Jean Kanitakis

The diagnosis of Merkel cell carcinoma (MCC) is usually made by histologic examination as the clinical features are rather nonspecific. Histopathologically, MCC represents a dermal tumor composed of round, small basophilic monomorphous cells with large nuclei, prominent nucleoli, and inconspicuous cytoplasm. Mitotic figures are commonly seen, and necrosis and ulceration may occur. The tumor usually spares the papillary dermis and the epidermis, and extends from the reticular dermis to the subcutaneous tissue. However, spread to the hypodermis and epidermis with pagetoid infiltration might occur [1]. Three pathological subtypes of MCC have been described, i.e., the trabecular, the small cell, and the intermediate type, which is the commonest one [2].

The differential diagnosis includes other tumors made of small cells, namely small cell lung cancer metastasis, lymphoma, or melanoma. Immunohistochemistry is needed for the confirmation of diagnosis. MCC cells express CK20 (and occasionally also neurofilaments) with a typical perinuclear dot pattern (Fig. 2.6), Neuron Specific Enolase, chromogranin A, and synaptophysin. Contrasting with small cell lung cancer, MCC does not express the Thyroid Transcription Factor 1 (TTF-1) (Table 2.8).

References


Table 2.8 Immunohistochemical features of MCC in comparison with other small cell tumors

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<thead>
<tr>
<th></th>
<th>CK20</th>
<th>TTF-1</th>
<th>Vimentin</th>
<th>NSE</th>
<th>Chromogranin</th>
<th>S100 protein</th>
<th>LCA</th>
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<tr>
<td>Merkel cell carcinoma</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+/-</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Small cell lung cancer</td>
<td>+/-</td>
<td>+</td>
<td>–</td>
<td>+/-</td>
<td>+/-</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Melanoma</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+/-</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>–</td>
<td>–</td>
<td>+</td>
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<td>–/+</td>
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<td>+</td>
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</table>

CK20 cytokeratin 20; TTF-1 thyroid transcription factor-1; NSE neuron-specific enolase; LCA leucocyte common antigen

Fig. 2.6 (a) Pathology of Merkel cell carcinoma: the tumour is made of uniform, large round cells with basophilic nuclei, invading diffusely the dermis (haematoxylin-eosin stain). (b) Merkel cell carcinoma: tumor cells express CK20 in a dot-like or signet-ring-like pattern (immunoperoxidase)
2.6 Kaposi’s Sarcoma

G. Goldenberg, L.E. Golitz, J. Fitzpatrick

The histologic presentation of Kaposi’s sarcoma (KS) is similar, regardless of the clinical disease presentation [20, 21]. The unifying histologic features of KS are the presence of atypical, irregular, and angulated vascular channels (Fig. 2.7a,b). The promontory sign is often described in KS and refers to irregular vascular channels that partially surround preexisting blood vessels. The presence of plasma cells in the surrounding stroma is also a classic finding.

The histologic presentation of KS evolves through patch, plaque, and tumor stages, similar to clinical disease [22]. Patch stage KS present with irregular, angulated vascular channels in the reticular dermis. While ectatic vascular channels may be seen in this stage, the vessels may be very subtle and present with slit-like spaces and spindle-shaped cells. Plaque stage KS presents with obvious vascular channels filling the entire dermis and extending into the superficial subcutaneous fat. The presence of a significant spindle cell component is the most characteristic feature of this stage of KS. These cells intercalate between collagen bundles, forming slit-like, irregular vascular channels. Hemosiderin deposits and PAS-positive hyaline globules are commonly seen in this stage of KS. Fascicles and sheets of spindle-shaped cells characterize the tumor stage of KS, along with a variable number of slit-like vascular channels. Mitotic figures vary in number, but may be frequent in this stage of KS.

Evidence of human herpesvirus 8 (HHV-8) has been found by polymerase chain reaction in approximately 95% of KS lesions, and appears to be independent of the type of the disease (i.e., endemic type vs. AIDS-associated type and etc.) [23]. An immunohistochemistry stain for HHV-8 is available, and has been shown to be 99% sensitive and 100% specific for KS lesions (Fig. 2.7c) [24]. Immunohistochemical staining with CD-31, CD-34, factor VIII antigen, and CD-40 has also been found useful.

Fig. 2.7 Kaposi’s sarcoma. (a, b) Numerous atypical, irregular, and angulated vascular channels; (c) positive staining with human herpesvirus 8 immunohistochemical stain
2.7 Dermatofibrosarcoma Protuberans

G. Goldenberg, L.E. Golitz, J. Fitzpatrick

Dermatofibrosarcoma protuberans (DFSP), which is associated with the rearrangement of chromosomes 17 and 22 with the fusion between the collagen type I1 gene and the platelet-derived growth factor β-chain gene, is a spindle cell neoplasm that shows an infiltrative growth pattern (Fig. 2.8a, b) [25]. The main portion of this neoplasm shows a storiform arrangement with extension into the subcutaneous fat, with fat entrapment creating a honeycomb pattern [26]. Cytologically, there is usually little nuclear pleomorphism and a low-to-moderate mitotic index. DFSP is a highly cellular malignancy with scant collagen. Several histologic variants of DFSP have been reported, including myxoid, granular cell, and pigmented types.

Expression of CD-34 antigen (human progenitor cell antigen) in DFSP (Fig. 2.8c) is well described and has been used to support the view that these lesions are variants of nerve sheath tumors, which are distinct from benign fibrous histiocytomas that do not express CD-34 [27]. Immunohistochemical staining with vimentin, and more recently CD-10, has also been reported [28, 29].

Fig. 2.8 Dermatofibrosarcoma protuberans. (a, b) Atypical spindle cells show an infiltrative growth pattern and storiform arrangement, with extension into the subcutaneous fat; (c) Positive CD-34 immunohistochemical stain
2.8 Atypical Fibroxanthoma

G. Goldenberg, L.E. Golitz, J. Fitzpatrick

Atypical fibroxanthoma is a dermal neoplasm usually separated from the overlying epidermis by a thin Grenz. It is composed of multiple cell-types, including spindle, polyhedral, giant, clear, granular and osteoid cells (Fig. 2.9a, b) [30]. Spindle cells may predominate, show pleomorphism, contain vesicular nuclei, and often form fascicles. Polyhedral cells usually show a vacuolated lipid-containing cytoplasm, and are large and haphazardly arranged. Giant cells are multinucleated and pleomorphic, and bizarre mitosis are common in this variant. By definition, this is a superficial neoplasm, without the involvement of the deep dermis and subcutis. The overlying epidermis is usually effaced and the surrounding dermis usually shows solar elastosis.

Immunohistochemically, AFX stains positive with vimentin, and staining with CD10 and procollagen-1 (Fig. 2.9c) has also been recently described [31, 32].

Fig. 2.9 Atypical fibroxanthoma. (a, b) Spindle cells showing pleomorphism, nuclear hyperchromasia, numerous mitosis, and arranged in fascicles; (c) Positive Procollogen I immunohistochemical stain
2.9 Malignant Fibrous Histiocytoma

G. Goldenberg, L.E. Golitz, J. Fitzpatrick

The term “malignant fibrous histiocytoma” (MFH) has fallen out of favor, and most of these tumors have been reclassified in the latest World Health Organization Classification of soft tissue tumors [33]. A recent study that utilized comparative genomic hybridization demonstrated that most MFHs do not constitute a homogeneous entity, but could correspond to other sarcomas, particularly leiomyosarcoma and liposarcoma [34, 35]. The classic histologic presentation of MFH has been divided into five types: pleomorphic, angiomatoid, myxoid, giant cell, and inflammatory. Architecturally, MFH is a dermal neoplasm with an infiltrative border. The pleomorphic type is most common, and presents with plump, atypical spindle cells that may be arranged in a storiform pattern, bizarre giant cells, and nodules and sheets of histiocytes. The angiomatoid variant shows large blood filled spaces, admixed with atypical spindle-shaped cell.

Immunohistochemical staining is usually positive with vimentin, and staining with CD74 and CD68 has also been described [36–38].

References


3.1 Introduction/Epidemiology

In the past decade, Australia, Europe, and North America have seen significant increases in the incidence of basal cell carcinomas (BCCs) [1–4]. Basal cell carcinoma (BCC) is the most common malignancy found in humans [5, 6]. Australia has the highest incidence of BCC with an annual incidence of 726 per 100,000 [3, 7]. More than one million cases of non-melanoma skin cancer occur annually in the United States [8]. However, the lack of systematic reporting to official registries in many countries makes determining...
the incidence and prevalence difficult and dependent upon mathematical modeling [9].

BCC is a slow growing, locally invasive malignancy that causes significantly greater morbidity than mortality. It most often occurs in the sun-exposed areas, with greater than 85% of nodular and morpheaform BCCs arising on the head and neck, whereas the trunk is the most common location for the superficial type (45.9%) [10].

Growth of BCC is usually localized to the area of origin; however, it has been estimated that 0.0028–0.1% of BCCs will subsequently metastasize [11, 12]. Metastatic BCC carries a 5-year survival rate of 10% and a mean survival of 8 months [13–15]. Giant BCCs account for 80% of metastatic BCCs, and the risk of metastasis is directly associated with the increasing diameter of the primary BCC [16].

The incidence of BCC is much higher in fair-skinned than in dark-skinned individuals. Darkly pigmented individuals and those who tan well are significantly less likely to develop such tumors [17–24]. The protective role of skin color is highlighted in Blacks with albinism. Individuals with albinism develop BCCs at an early age [25–27] when compared with Black individuals without pigmentary conditions who rarely develop nonmelanoma skin cancer [28–30].

For BCC, the highest incidence occurs when fair-skinned people inhabit equatorial regions. The closer one lives to the equator, the greater the risk of developing BCC. According to estimates based on the power model of Fears and Scotto, if the amount of exposure to UVB increases by 30%, the incidence of skin cancer will increase by 60% in males and 45% in females [31]. This environmental factor partially accounts for the variations in incidence seen in fair-skinned populations, for example, in Finland and Australia [9]. Other environmental factors include ionizing radiation, arsenic exposure, and topical nitrogen mustard. Finally, genodermatoses including xeroderma pigmentosum and basal cell nevus syndrome (Gorlin’s disease) and other syndromes Bazex-Dupre-Christol (atrophodera vermiculatum, BCC, hypohidrosis, hypotrichosis) and Rombo (BCC, milia, atrophodera vermiculatum, acral cyanosis, hypotrichosis) have been associated with increased development of BCC.

Based on these findings, one can conclude that the risk of developing BCC depends on a combination of genetic predisposition and exposure to carcinogenic agents.

### 3.2 Pathogenesis

Malignancy results from a single altered cell, which grows and gives rise to a population of abnormal clones. Transformation of a normal cell to a dysplastic clone occurs when the regulatory machinery controlling the cell cycle is disturbed. Damage to the deoxyribonucleic acid (DNA) must be adequate to alter the cell and initiate dysplasia, but only to the extent that the cell is viable [1, 9].

Ultraviolet light (UVL) serves as a well-known mutagen in the development of BCC and instigates keratinocyte malignant transformation. UVL is a complete carcinogen in that it is able to initiate, promote, and enhance the progression of skin cancer. Most of the evidence for implicating sunlight in BCC depends on epidemiologic data and the frequent occurrence of UV signature mutations such as C→T and C-C→T-T [32]. UVL may mediate its carcinogenic effect not only by damaging DNA, but also by creating an immune tolerant state in the skin [33–43]. Mutations in p53, tumor suppressor gene, have been found in 50% of BCCs [44]; however, the causal relationship has not been elucidated. In fact, evidence against its role in BCC production is seen in people with LiFraumeni syndrome who inherit defective p53 and are prone to many cancers, but not to BCC [45]. This clinical evidence, coupled with the recognition that P53 is not noted to be much higher in BCC than in sun-damaged skin nearby, probably relegates it to a supporting role in tumor development [46].

In Xeroderma pigmentosum, patients lack the ability to repair UVL-induced DNA damage [47–50], leading to the development of numerous nonmelanoma skin cancers at an early age. However, this model has not consistently explained the development of BCCs in non-XP patients [45, 51].

The best-studied genetic transformation involved in BCC is the sonic hedgehog (SHH) signaling pathway [1, 52]. Irreversible damage that either empowers growth stimulation (SHH, Smo) or weakens growth suppression (PTCH) may lead to BCC formation [9, 53]. Loss of function mutations of PTCH1, including the germ line mutation found in patients with nevoid basal cell carcinoma (or Gorlin’s) syndrome, has been identified in 30–40% of sporadic cases of BCC [51, 54].

Environmental factors other than UVL that are associated with BCC include ionizing radiation [55–57] – such as that used to treat acne and arsenic
exposure – in well water, pesticides, medications, and industry (mining, smelting) [58–60].

Other clinical settings in which there is an increased risk of BCC development include the use of topical nitrogen mustard, scars [61–64], and nevus sebaceous [65, 66].

### 3.3 Clinical/Histological Variants

A number of distinct clinical and histological subtypes of BCC exist. Several histological subtypes have distinctive clinical morphologies. Distinct clinical morphologies include nodular (Fig. 3.1), superficial, morpheaform (Fig. 3.2a, b), ulcerated/rodent ulcer (Fig. 3.3), pigmented, and Pinkus tumors (Fig. 3.4).
Histological subtypes include nodular, micronodular, superficial, infiltrating, sclerosing/morpheaform, and fibroepithelioma of Pinkus (See Chap. 3).

3.4 Diagnosis/Work Up/Risk Factor Assessment

In an ideal case scenario, all potential BCCs would be biopsied before definitive therapy is performed to allow for the most appropriate therapeutic option to be selected based on histological subtype. The choice of biopsy technique depends on the presumed depth of the lesion and the potential definitive treatment choice. For example, a punch biopsy should be avoided for BCCs that are being considered for curettage and electrodesiccation (CE) because the curette will fall into the hole created by the punch biopsy and make curettage difficult and unreliable [67, 68]. Utilizing the curetting technique for biopsy may yield a specimen that confirms the diagnosis of BCC; however, it does not allow evaluation of histological subtype and therefore, should be used cautiously. If an infiltrating BCC or deep recurrent BCC is suspected, a deep punch or incisional biopsy would be the preferred technique so as not to miss the deep component.

When a biopsy is not feasible due to extenuating patient circumstances (i.e., comorbidities, advanced patient age limiting subsequent treatment, logistical obstacles, or patient refusal), the clinician is justified in carrying out appropriate therapy when clinical suspicion is high. It is recommended that a pathologic specimen be submitted at the time of definitive treatment for confirmation and posttreatment consideration of further adjuvant therapies.

Posttreatment biopsies can aid in determining treatment efficacy when therapeutic modalities that do not produce a pathological specimen are utilized, such as cryosurgery, radiation, and use of topical immunomodulators.

After careful clinical examination and confirmation of histological subtype, one may have to consider MRI studies for potential extensive disease involving underlying structures, as involvement of underlying structures will narrow down the therapeutic options and increase the need for adjuvant therapies. In certain patients at high risk for multiple primary tumors, increased surveillance and consideration of prophylactic measures may be indicated [69].

3.5 Treatment

The increased incidence of BCC has prompted many countries and dermatology associations to develop guidelines for the management of BCCs. These guidelines aim to aid in the selection of the most appropriate treatment for individual patients. Maize clearly defines the overriding concepts in the management of a patient with a BCC with four goals: (1) Complete eradication of the cancer, (2) Preservation of normal tissue, (3) Restoration of normal function, and (4) Cosmetic outcome [70].

All treatment decisions should be customized to account for the particular factors present in the individual case and for patient’s preferences, thereby altering the customary age and size parameters [69]. Selection of the optimal treatment course is dependent upon multiple variables. These include location, size, tumor subtype, primary vs. recurrent tumors, history of prior radiation, and patient age. In addition, patient refusal of surgical options and medical comorbidities may narrow or limit therapeutic options. Table 3.1 reviews the variables which should be considered when selecting the appropriate therapy. Each biopsied tumor should be stratified into a low or high-risk category based on the risk of recurrence (Table 3.2).

Surgical approaches offer the most effective and efficient means for cure, but patient factors such as preservation of function, cosmesis and patient preference may lead to choosing radiation and alternative therapies in order to achieve optimal overall results [69].

In patients with low-risk, superficial BCCs, where surgery or radiation is contraindicated or impractical

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<th>Table 3.1 Variables to consider in BCC management</th>
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<td>Age of patient</td>
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<td>Number of lesions to be treated</td>
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<td>Size of lesion</td>
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<td>Distinctness of the tumor border</td>
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<td>Primary vs. recurrent BCC</td>
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<td>Anatomic location</td>
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<td>Histological subtype</td>
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<td>History of prior radiation</td>
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M. J. Patel et al.
3 Basal Cell Carcinoma

3.5.1 Methods of Treatment

3.5.1.1 Destructive

Curettage and Electrodesiccation (CE)

CE is a common, simple, cost-effective technique for the treatment of low-risk BCC. Efficacy of this modality is highly dependent upon how this technique is performed (type of curette used, number of cycles), experience of the provider, and appropriate selection of cases. It is best used for selected low-risk lesions (small, well-defined primary lesions with nonaggressive histology usually in noncritical sites) where the 5-year cure rates of up to 97% are possible [71].

CE is generally not recommended for the management of recurrent or morpheaform tumors, and for tumors in high-risk mask areas of the face [72]. Tumor size is an important factor as recurrence rate rises dramatically with increasing tumor size [73]. Many studies on CE have suggested that lesions as large as 2 cm in diameter can be successfully treated [71, 74, 75]. Salasche proposed that the upper limit should be 1 cm for nodular tumors as those greater than 1 cm may penetrate deeply and extend beyond the clinically apparent margin, especially in the high-risk areas [76].

With regard to technique, some authors have suggested that CE should be performed a fixed number of times [75, 77, 78], while others [71] feel the procedure should be done only until a healthy base has been reached. In addition, several investigators have omitted electrodesiccation in an effort to improve hypertrophic scarring with only a slightly lesser cure rate when compared with CE [79–82].

Cryosurgery

Cryosurgery is a cytotoxic technique that utilizes a liquid nitrogen spray or probe to induce cell necrosis. It is reserved for low-risk tumors with well-defined borders.

A systematic review of recurrence rates in studies (>50 patients) published between 1970 and 1997 indicated that cryotherapy in the treatment of primary BCC resulted in a cumulative 5-year recurrence rate of 4–17% [83]. Many large series evaluating cryosurgery for BCC specifically exclude very high-risk BCCs,
emphasizing the importance of careful selection of appropriate lesions with nonaggressive histology and noncritical facial sites in order to achieve high cure rates [84–88]. Thorough curettage immediately prior to cryosurgery may help to increase the cure rate [89]. Adverse events include peri-operative pain, bulla, erythema, sloughing of necrotic tissue, and localized edema. Ultimately, the procedure can result in hypertrophic scarring, local hypopigmentation, and peripheral hyperpigmentation, similar to CE.

Radiation Therapy (RT)

RT remains a useful modality for the management of certain BCCs. It serves as a primary alternative to surgical treatments, but faces the same problem of accurately identifying tumor margins as cryosurgery. It has the advantages of sparing normal tissue and is used in patients too frail for surgery or those unwilling to undergo surgical procedures. Operator experience and the specifics of the approach to each tumor are critical to the technique’s success rate.

Recommendation from the national comprehensive cancer network (NCCN) is based on category 2B evidence: nonuniform consensus (but no major disagreement) based on lower-level evidence including clinical experience that the recommendation is appropriate. According to the NCCN guidelines, it serves a role as primary treatment for low-risk BCC in patients greater than 55 years of age with tumors in the mask area of the face (central face, eyelids, eyebrows, periorbital region, and nose), lips, chin, mandible, pre and postauricular skin and cheeks, forehead, scalp, and neck [69]. For the primary treatment of high-risk BCCs, the NCCN recommends the selection of patients greater than 55 years of age with <15 mm tumors in the mask area of the face (central face, eyelids, eyebrows, periorbital region, and nose), lips, chin, mandible, pre and postauricular skin or <20 mm on the cheeks, forehead, scalp, and neck, if no other high-risk factors are present.

A study of BCC irradiated by a “standard” X-ray therapy schedule indicated an overall 5-year recurrence rate of 7.4% for primary (n = 862) and 9.5% for recurrent (n = 211) BCC [90, 91]. There is a decrease in cure rate as the size of the lesion increases [92, 93]. RT is also useful as adjuvant therapy when tumor margins are positive after surgery and for extensive perineural or large nerve involvement. It is contraindicated in genetic disorders which predispose patients to skin cancer such as Gorlin’s syndrome, xeroderma pigmentosum, and connective tissue disorders such as lupus erythematosus and scleroderma.

Photodynamic Therapy (PDT)

PDT involves the use of light to activate a photosensitizer, localized to diseased tissues, which results in the formation of cytotoxic reactive oxygen species. Methyl aminolevulinate (MAL), marketed as Metvix® in Europe, Australia, and New Zealand, and 5-aminolevulinic acid, marketed in the United States and Canada as Levulan®, are topical photosensitizer precursors used to treat NMSC.

In January 2007, the International Society for PDT in Dermatology published a consensus on guidelines for the use of PDT in NMSC based on a systematic literature review. Initial efficacy for superficial BCC is consistently high. Three-month clearance rates with MAL-PDT range from 80% (in complex cases with recurrent or large lesions, or H-zone lesions) to 97% in primary sBCC. These included histologically controlled studies [94, 95]. Four-year follow-up of a phase III study suggests that recurrence with MAL-PDT is comparable with cryotherapy (22% for MAL-PDT vs. 19% for cryosurgery at 48 months) [96, 97]. Recurrence rates were even lower for lesions 1 cm or less in diameter (with a 36-month recurrence rate of only 6%) [96].

PDT was generally well tolerated with some pain and erythema experienced by most patients, which was similar to those reported with cryosurgery [98].

For nodular BCC, delivery of sufficient photosensitizer and light to the full depth of the lesion is critical. Topical MAL has superior tissue penetration over ALA because of its decreased charge and increased lipophilicity, although these agents have not been compared directly in clinical studies of nBCC [99]. The strongest evidence for topical PDT in nBCC comes from 5 phase III studies with MAL-PDT, in which a total of 220 nBCC lesions were treated [94, 95, 100, 101]. Efficacy is consistently high, with 3-month complete response rates of 73–94%, which has been confirmed with histologically controlled studies. A 5-year recurrence rate of 14% was found in patients who took part in a phase III study of MAL-PDT for nBCC [100]. Studies with ALA report variable efficacy rates of 61% [102], 64%
and up to 92% [100, 104]. Recurrence rates with ALA have been quoted as 5% at a median of 17 months [105] and 12% at 1 year (65%).

Current evidence supports the use of MAL rather than ALA for PDT of nBCC. Its use has been approved for the treatment of nBCC in the European Union, Australia, New Zealand, and Brazil.

**Laser Therapy**

Various modes on the carbon dioxide (CO2) laser have been used in the treatment of BCC. The nonablative focused or incisional mode not only yields an intact specimen for histological examination, but also offers the advantage of sealing small blood vessels, lymphatics, and nerves creating both a relatively bloodless field and potentially minimizing postoperative pain [106, 107].

In the defocused ablative mode, the CO2 laser has been used alone and in combination with curettage to manage patients with large or multiple sBCCs. In a retrospective chart review of 61 biopsy-proven superficial and nodular BCCs without prior treatment, clinical recurrence was observed in two cases (3.2%). The patients were followed postoperatively for a period of 15–85 months (mean 41.7 months) [108]. Wheeland et al. report high cure rates with rapid healing and diminished postoperative pain when combining traditional curettage with carbon dioxide laser vaporization in the treatment of 52 patients with 370 sBCC [107]. Hypopigmentation and hypertrophic scarring were reported in both studies.

### 3.5.1.2 Surgical

**Excision with Postoperative Margin Assessment (POMA)**

Surgical treatment of BCC using postoperative histological assessment is routinely practiced around the world. The efficacy of the procedure is closely linked to appropriate case selection by the surgeon – giving close attention to tumor location, size, and histological subtype.

The clinical surgical margin is selected to minimize the incomplete excision rate without sacrificing excessive normal tissue. There is an inverse relationship between these parameters; achieving a 5% incomplete excision rate requires a mean tissue sacrifice of over 4 mm [84, 109–111]. The current recommended margin for low-risk tumors is 3–5 mm [112–114].

BCCs with aggressive growth patterns (high-risk) are more likely to have marginal involvement than nodular BCC. In a study of 1,039 consecutive BCC submitted to a pathology laboratory, micronodular, infiltrative, and morpheaform tumors were more than threefold as likely to be incompletely excised than nodular or superficial tumors [115]. For primary morpheaform/infiltrating BCC, the rate of complete excision with increasing peripheral surgical margins is as follows: 3 mm margin, 66%; 5 mm margin, 82%; and 13–15 mm margin, >95% [116].

Incomplete excision is more common on the head and neck, particularly the central face region [110]. Walker and Hill have postulated that based on studies evaluating inadequate excision vs. surgical margin, and given that BCCs in these high-risk areas have approximately doubled the rate of recurrence, the usual margins should be increased by roughly 1 mm. The higher incomplete excision rate has been explained on the basis of narrower margins being taken in these cosmetically important regions and more extensive subclinical spread attributed to more aggressive histology [116].

Larger tumors have been associated with increased risk of incomplete excision. In addition, previously treated BCC has a recurrence rate two to fourfold higher by all treatment modalities [117]. Curettage prior to excision has been used to supplement the determination of clinical margins on the principle that the curette will reveal subtle subclinical extensions not obvious to the naked eye [118].

Potential drawbacks include scarring, dyspigmentation, infections, and cosmetic deformity.

**Mohs Micrographic Surgery (MMS)**

MMS offers the highest histological accuracy and conservative tissue removal of all surgical modalities available. It is commonly used for patients who present with large (>20 mm) tumors, BCCs in high-risk locations, infiltrating histological subtypes, recurrent tumors, and lesions with perineural invasion [114].

In a review of all studies published since 1947, the overall 5-year recurrence rate was approximately 1% for primary BCC [90] and a review of all studies since 1945 suggested a recurrent rate of 6% for recurrent BCC [117, 119, 120].
Key limitations include the requirement for specialized training (as the surgeon also functions as the pathologist), the time requirement for both the patient and the physician, and the need for specialized equipment for tissue preparation. Cost analysis found that MMS performed on all body locations was similar in cost to office-based surgical excision and less expensive than hospital/facility-based surgeries; however, 39% of the wounds healed by second intention, and the study did not evaluate cost effectiveness [90, 121].

3.5.1.3 Pharmacological Treatments

Surgical procedures remain the mainstay of care in the treatment of BCC; however, pharmacologic modalities are now offering new alternatives particularly in patients where surgery is contraindicated.

Interferon (IFN)

To date, four controlled studies have evaluated the use of IFN therapy in the treatment of nBCC and sBCC [122]. IFN α-2b, 2a, IFN β, and a sustained release preparation of 2b were evaluated. Overall, this pharmacologic option has been successfully employed, with cure rates independent of the lesion type or size [123]. Increased effectiveness was not shown with combination therapy (2a + 2b). The long-term cure rate for this modality appears to be approximately 80% [124].

Side effects include flu-like symptoms (fever, chills, headaches, fatigue, myalgia) and injection site reactions, and these occurred in at least 20% of participants. It is a labor intensive treatment requiring multiple visits, has a higher percentage of early treatment failure, and is relatively expensive.

Topical Chemotherapy

5-Fluorouracil (5-FU) was the first topical agent approved for the treatment of sBCC. It is a chemical ablative agent that inhibits DNA synthesis, prevents cell proliferation, and causes tumor necrosis. Five percent cream and solution formulations have been approved by the FDA in the U.S. for the treatment of sBCC when conventional methods are impractical. The NCCN guidelines reserve this therapy in patients with low-risk sBCC where surgery or radiation is contraindicated or impractical even though the cure rate may be lower [69]. Because the percutaneous penetration of 5-FU is variable and limited [125–127], its use is recommended only for sBCC and not invasive BCCs or BCCs with follicular involvement as this can mask deeper involvement as only the superficial component may be eliminated.

Topical 5-FU is applied twice daily for no less than 6 weeks if not occluded or combined with curettage. Often upward of 3 months is necessary to eradicate the tumor increasing the likelihood of untoward side effects including discomfort, severe inflammation, dyspigmentation, and allergic reactions. In a recent prospective study by Gross et al., a total of 29 patients with 31 biopsy-proven superficial BCC lesions on the trunk or limbs were treated with 5% 5-FU cream twice daily for up to 12 weeks. The lesional site was surgically excised 3 weeks after the end of treatment for histologic evaluation of cure. The histologic cure rate was 90% (28/31 lesions cured) and the mean time to clinical cure was 10.5 weeks [128].

Retinoids

Systemic retinoids in the management of BCCs are limited and have primarily been used for their preventative effects in patients with basal cell nevus syndrome [129–131]. Unfortunately, the relatively high doses needed to induce a positive effect increases intolerance to the side effects, and relapse occurs following the discontinuation of treatment [130, 132].

Immune Response Modifier

Imiquimod 5% cream is the newest addition to the treatment arsenal for BCC. Working via the activation of antigen presenting cells such as monocytes, dendritic cells, and epidermal Langerhans cells, imiquimod binds to toll-like receptor 7 inducing proinflammatory cytokine secretion (e.g., IFN-α and tumor necrosis factor-α) [133].

The efficacy of topical imiquimod 5% in the treatment of adult patients with BCC has been investigated in four randomized, double-blinded, placebo controlled trials. These four trials demonstrated significantly higher rates of histologically confirmed clearance of target BCC lesions with imiquimod 5% applied 5 times
weekly or every day for 6 or 12 weeks than with placebo (sBCC: 79–87% vs. 2–19%, \(p < 0.001\); nBCC: 70 and 76% vs. 13%, \(p < 0.001\)) [134–137]. Decreasing application to 3 times weekly for 12 weeks, although superior to placebo, dropped efficacy rates (histological clearance sBCC: 52%, \(p < 0.01\); nBCC: 60%, \(p = 0.001\)). In an open label trial of low-risk nBCC where imiquimod 5% was applied 3 times weekly for 8 or 12 weeks, histological evidence of residual disease remained in 17% of patients with clinical clearance [138] highlighting the need for posttreatment biopsy.

The European prescribing information reports a sustained clearance rate of approximately 80% after 4-year follow-up from initial treatment in a noncomparative trial [139].

The short-term use of imiquimod 5% as an adjunct to C&E or curettage alone appears to increase efficacy in the treatment of nBCC with histological clearance rates of 90–100% [140–142], with no reported recurrences in the curettage alone cohort after 1 year of follow-up (\(n = 60\)) [141].

**Systemic Chemotherapy**

Chemotherapy has been used both for the management of uncontrolled local disease and for patients with metastatic BCC [143]. For disseminated metastases, systemic chemotherapy alone or in conjunction with RT is indicated. Numerous agents have been used, including cisplatin, bleomycin, cyclophosphamide, 5-FU, and vinblastine [144–146]. Of these, cisplatin appears to be the most effective [146]. For palliation in advanced and unresectable BCCs, cisplatin and doxorubicin, either alone or in combination with radiation are reasonably well tolerated with high response rates and prolonged disease control [147–149].

On the horizon, trials investigating targeting the Sonic Hedgehog pathway are underway.

**Follow-Up**

Approximately 44% of people will develop a second BCC within 3 years of a BCC excision [150]. A review of the recurrence rate reported in studies from 1947 to 1987 after treatment of primary BCC by surgical excision, CE, RT, or MMS found that after treatment by any modality less than one-third of all recurrences occurred in the first year, only 50% of recurrences occur in the first 2 years, and 66% within 3 years [151]. Consequently, most guidelines have recommended long-term, even lifetime follow-up, particularly for patients with high-risk or multiple lesions [151, 152].

**References**

17. Fears TR, Scotto J, Schneiderman MA (1977) Mathematical models of age and ultraviolet effects on the incidence of skin
42. Toews GB, Bergstresser PR, Strelieen JW (1980) Epidermal langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. J Immunol 124:445–453


4.1 Actinic Keratoses

4.1.1 Epidemiology and Ethopathogenesis

Actinic keratoses (AKs) are hyperkeratotic, rough lesions that occur on areas of chronically sun-damaged skin. They have previously been referred to as preneoplastic lesions, but have recently been redefined as carcinoma in situ [1, 2]. AKs are among the most common neoplasm in humans. The incidence of AK has increased worldwide during the past decades, with higher prevalence rates in areas of increased UV indexes. A study from...
the U.K. showed a prevalence rate of 15% in men and 6% in women [3]. In the population older than 70 years, an increase was found with 34% of males and 18% of females developing AKs. Data from the United States show prevalence rates of 11–26% [4] and Australia reports very high prevalence rates of 55 and 37% in men and women between the age of 30 and 70 years, respectively [5].

The most important risk factor for its development is UV radiation. This is reflected in the geographic distribution that shows a correlation of increased prevalence of AK in areas of high UV exposure. Furthermore, the increase of vacational and recreational sun exposure during the past decades has contributed to the current epidemiologic developments. AKs show a male predominance and individuals with fair skin type are predisposed. Other risk factors for AK include advanced age; immunodeficiency, e.g., after organ transplantation; arsenic exposure; and hereditary disorders (xeroderma pigmentosum). Immunocompromised individuals show a significant increase of AK with a 250-fold higher risk for AK and 100-fold increase for invasive SCC when compared to the normal population. Furthermore, AKs show a more aggressive course in organ transplant recipients, with 40% of AKs developing into invasive SCC [6, 7].

To date, AK accounts for the most common carcinoma in situ in humans with millions of people being affected worldwide and the number still seems to increase.

The most important factor in the pathogenesis of AK is chronic UV exposure. UV-B (290–320 nm) has been shown to directly induce DNA mutations via thymidine dimer formation. These DNA changes may lead to the development of AK in the absence of repair mechanisms and depend on the area where the mutation occurs [8]. UV-A (320–400 nm) contributes to the development of AK by inducing oxidative stress that leads to tissue damage. Furthermore, UV is known to have an immunosuppressant effect by depletion of Langerhans cells in the epidermis, an effect that has also been used in the light treatment of psoriasis with PUVA therapy. Patients who have received high dose PUVA therapy have been shown to have an increased incidence of AK and SCC [9]. Human papilloma viruses have been proposed as a cocarcinogen in the ethiopathogenesis of AK. In patients with the hereditary disorder epidermodysplasia verruciformis, the association between special cutaneous HPV types and the development of nonmelanoma skin cancer is well established. In the past decade, cutaneous HPV have also been detected in AKs, especially in organ transplant recipients. The antiapoptotic effect of the E6 protein in HPV has been proposed as a tumor-inducing factor [10, 11]. However, HPV can also be detected in normal sun-exposed skin of healthy individuals [12], and the correlation between HPV and skin cancer is less strong than in cervical cancer. Therefore, it has been proposed that HPV rather acts as a cocarcinogen in skin carcinogenesis that acts via antiapoptotic pathways and delay of DNA repair mechanisms in response to UV [13].

Although AKs may present as a single lesion, they usually affect a whole field of chronic sun-exposed areas (e.g., forehead, hands), an observation that has been described as field cancerization [14].

### 4.1.2 Clinic

AKs present as skin-colored to reddish-brown scaly macules, papules, or plaques occurring in areas of chronic sun exposure, especially on face, forehead, scalp, ears, neck, décolleté, arms, dorsum of hands, and lower lips (Fig. 4.1 and 4.2). Lesions’ size ranges from a few millimetres up to 2 cm or more in diameter. AKs rarely develop as solitary lesions, but occur as multiple lesions in the context of field cancerization.

Fig. 4.1 Typical clinical presentation of actinic field cancerization with multiple hyperkertatotic papules and plaques on the scalp
4 Squamous Cell Carcinoma In Situ

Different clinical subtypes have been described, including keratotic, atrophic, cornu cutaneum, verrucous, pigmented, and lichenoid variants of AK. On clinical grounds, the differentiation between AKs and early invasive squamous cell carcinoma may be difficult to distinguish. However, increased thickness and infiltration may be observed in SCC, and inflammation and pain are a sign for progression of the lesion [15]. The diagnosis of AK is usually made clinically, but confirmation by histology is necessary in doubtful cases and if invasive squamous cell carcinoma is suspected. Noninvasive imaging techniques may aid in the diagnosis of AK. Dermoscopy can be used to distinguish pigmented AK from melanocytic lesions or pigmented basal cell carcinoma. Reflectance confocal microscopy (RCM) is a novel noninvasive diagnostic technique with cellular resolution that has been shown to have a high sensitivity of 97.7% in the diagnosis of AK [16]. Furthermore, RCM can be used for noninvasive monitoring of lesions during treatment.

4.1.3 Histopathology

Histopathologically AKs are characterized by an epidermal proliferation of atypical keratinocytes. The dysplastic keratinocytes that are present in AK may not be distinguished from those cells found in invasive squamous cell carcinoma. According to the extent of epidermal dysplasia, three subtypes may be differentiated. Cockrell et al. classified AK in a similar way to the classification of cervical intraepithelial neoplasia in KIN I–III (Keratinocyte intraepithelial neoplasia). However, this classification does not define AK as a carcinoma in situ, and therefore it has recently been proposed by Roewert-Huber et al. to classify AK into early in situ SCC type AK I (mild), early in situ SCC type AK II (moderate), and in situ SCC type AK III (severe). This classification describes the disease continuum from AK to SCC [17].

For a more detailed description with regard to the histopathologic features of AK, please refer to Chap. 2.

4.1.4 Treatment

The natural course of AK is not predictable, and on clinical grounds, it is not possible to determine which AK will progress into invasive squamous cell carcinoma. Histopathologically, Type III AK with full thickness atypia will more likely progress into invasive SCC. However, progression cannot reliably be determined and time of invasion cannot be foreseen. Invasive squamous cell carcinoma shows destructive growth with metastatic potential. Therefore, it is recommended that all AKs should be treated.

A variety of treatment modalities can be used in the management of patients with AKs. The decision regarding which treatment form should be used is depending on different factors. The age and performance status of the patient should be considered as well as the location and extent of disease, mental status, compliance, and the individual risk of the patient (especially immunosuppression).

With regard to AK occurring in the context of field cancerization, two major treatment categories can be distinguished, the treatment of single lesions and the treatment of a whole area (“field treatment”) that includes treatment of subclinical lesions. The different modalities used in AK management are described below.
4.1.4.1 Surgical Excision, Curettage

Complete excision of AK is not used as a first-line treatment of AK and is usually performed if the lesion is highly suspicious for invasive squamous cell carcinoma. Shave biopsy or curettage can be performed in single lesions. With this technique, sutures are not necessary and histologic diagnosis can be obtained [18]. Curettage may be combined with electrodissection [19]. These surgical techniques require local anaesthesia and have potential to leave a scar.

4.1.4.2 Cryotherapy

Cryotherapy is the most common treatment for AKs, especially for the management of multiple AKs [19–21]. Cryotherapy is available in techniques using liquid nitrogen spray or contact-cryotherapy. However, only single lesions are treated and the surrounding of field cancerization remains untreated [22].

A method to overcome this problem is to use cryopeeling. However, cryopeeling is a relatively invasive method that is not widely performed. The frequency, duration, intensity, and definitive specification of temperature in the frozen tissue have not been standardized.

As a nonspecific technique, cryotherapy destroys atypical, but also normal cells by disruption and separation of the epidermis from the dermis. Pain, redness, edema, and blistering can occur during and after treatment. Scarring and hypopigmentation are commonly observed.

Although cryotherapy is often used, controlled studies are missing. Complete responses differ from 75 to 98% [23]; the recurrence rates of AKs have been estimated from 1.2 to 12% within a 1-year follow-up period [22, 24].

4.1.4.3 Chemical Peeling

Trichloroacetic acid, alpha-hydroxy acids, zinc-chloride, or phenolic acid are used as chemical peeling through unspecific destruction of tissue. Chemical peeling can be a useful alternative for treatment of extensive facial AK [25]. The efficacy of chemical peelings depends on the agent used and is quoted to be round about 75%; recurrence rates are from 25 to 35% within 1 year after therapy. Side effects of chemical peelings include pain, inflammation, pigmentary alterations, and the risk of scarring [26–28].

4.1.4.4 Laser

Near infrared laser systems including carbon dioxide (CO₂) or Erbium-YAG lasers can be used for the treatment of AK and actinic cheilitis. As both systems are ablative, they can be used for single lesions as well as full face resurfacing. Full face laser resurfacing has been shown to provide effective, long-term prophylaxis against AK and may reduce the development of SCC from AK [29]. Side effects include pain inflammation, pigmentary changes, and scarring as well as delayed healing and postinflammatory erythema. Complete remission rates range from 90 to 91%. However, recurrence rates for single lesions range from 10 to 15% within 3–6 months [30, 31]. Disappointing results reported in earlier literature may be related to technical aspects, as the outcomes of full face resurfacing are strongly user-dependent [32].

4.1.4.5 Radiation

The treatment of AKs with X-rays is considered obsolete as X-rays themselves have a cocarcinogenic effect.

4.1.4.6 Photodynamic Therapy

Photodynamic therapy (PDT) is a combination therapy that combines a photosensitizer and high intensity red light. The photosensitizer, either 5-aminolevulinic acid (ALA) or methyl aminolevulinate (MAL), is applied 3h prior to irradiation under occlusion and selectively accumulates in tumor cells. Irradiation with high intensity infrared light leads to formation of reactive oxygen species and results in destruction of atypical keratinocytes. The penetration depth of PDT is 3–4 mm.

In Europe, the European Medical Evaluation Agency (EMEA) labeled MAL as indication for AK. The clinical experience in AK patients receiving MAL-PDT shows complete response rate of 70–78% after a single treatment session, and 90% after two treatment sessions 1 week apart. Side effects of PDT include local pain, risk of photosensitivity (mainly for ALA), and time delay between application of cream and treatment. PDT in
comparison to cryotherapy shows significantly better
cosmetic results [23, 33–35]. Advantages of PDT include
the selective absorption and treatment of subclinical
lesions, and the fluorescence of the photosensitizer can
be visualized using Wood’s light before the initiation of
therapy [36]. On the other hand, the costs of treatment
are considerably higher compared to cryotherapy.

4.1.4.7 Imiquimod

Imiquimod 5% cream is a topical treatment and belongs
to the novel class of immune response modifiers (IRMs).
Imiquimod is toll-like receptor (TLR) 7-agonist and
stimulates the immune response by induction, synthe-
sis, and release of cytokines. Through the induction of
cytokines like TNFα, INFα, and IL-12, Imiquimod has
an indirect antiviral and antitumoral potency [37, 38].
Topically applied imiquimod causes a local skin reac-
tion, including erythema, itching, and burning, that is
generally mild to moderate in intensity. In areas of field
cancerization, imiquimod is able to highlight subclini-
cal lesions by induction of an inflammatory response.
Normal skin, on the other hand, does not show any reac-
tion to the application of Imiquimod cream. Treating
AK with Imiquimod has been shown to be effective
and safe and response rates show complete remission
in 84%; a recurrence rate of 10% within 1-year follow
up and 20% within 2-years follow up [39, 40]. A ran-
domized, double-blind, placebo-controlled study in
436 patients with AKs showed a complete resolution
of all lesions in 45.1% (vs. 3.2% placebo) and a partial
reduction of AKs in 59.1% (vs. 11.8% placebo) after a
treatment period of 16 weeks (twice per week) [41].
Imiquimod is labeled for the indication of superfi-
cial basal cell carcinoma, AKs, and genital warts in the
USA, Australia, and Europe. In the States, Imiquimod
is FDA approved as treatment for AK with an applica-
tion twice a week for 16 weeks. For Europe, the EMEA
approved Imiquimod for AK with an application three
times a week for 4 weeks. After 4 weeks, a re-evalua-
tion is performed and a second cycle of 4 weeks treat-
ment is performed if residual disease is present.

4.1.4.8 Topical 5-Fluorouracil

5-fluorouracil (5-FU) is a topical chemotherapeutic
agent that destroys tumor cells via interference with
DNA and RNA by blocking the methylation reaction
deoxyuridylic acid to thymidylic acid.

5-FU can be used for the treatment of multiple
lesions and is applied twice daily for 2–4 weeks.
Topical 5-FU can result in severe dermatitis with
wound infections, pruritus, pain and ulceration with
scarring, and the application is of limited help in the
therapy of extensive AKs. For localized disease, clearance
rates of approximately 50% and recurrence rates
up to 55% have been reported with 5-FU [42–44].
Meanwhile, new formulations with different concentra-
tions and galenics of 5-FU are under clinical inves-
tigations, but have not yet been approved for their use
in Europe [44–46].

4.1.4.9 Retinoids

Retinaldehyde is a natural derivative of vitamin A; it
has effects similar to retinoic acid. Besides counteract-
ing the UV-induced vitamin A deficiency of the epi-
dermis, topical retinaldehyde may have an antioxidant
effect [47, 48] and decreases the number of sunburn
cells. A placebo-controlled randomized study docu-
tments that systemic administered etretinate reduces
AKs in 85% [49]. Some publications show that the
epidemiological characteristics of AKs were not modi-
fi ed by the application of retinaldehyde and that
retinaldehyde has no prophylastic effects on the devel-
opment of AKs. Side effects of topically applied retino-
oids are increased sensitivity to sunlight, erythema,
erosions, pruritus, and pain.

Retinoids can also be administered orally, espe-
cially in patients who develop large numbers of skin
cancers. Systemic therapy can be considered for high-
risk patients. such as patients with inherited disorders
such as xeroderma pigmentosum (abnormal repair of
UV-induced DNA damage), nevoid basal cell carcino-
ma syndrome (tumor suppressor gene abnormality)
or in organ-transplant recipients with chronic immuno-
suppression [50, 51].

4.1.4.10 Diclofenac in Hyaluronic Acid Gel

In the past decade, the antineoplastic properties of
selective inhibitors of cyclo-oxygenase 2 (COX-2)
have been investigated. The therapeutic effect of
COX-2 inhibitors is due to the suppression of
immune-regulatory lymphocytes, T-and B-cell proliferation, and the cytotoxic activity of natural killer cells via inhibition of Prostaglandin E2 synthesis (PGE2). Furthermore, COX-2 inhibitors have anti-angiogenetic effect by up-regulation of vascular endothelial growth factor (VEGF) [52]. Apart from its affinity to the inducible COX-2, NSAIDs have been demonstrated to activate peroxisome proliferator-activated-receptor-gamma (PPAR-gamma), which decreases cancer cell proliferation. Topical diclofenac is applied in hyaluronic acid (HA), which is necessary for the bioavailability of diclofenac in the epidermis. Several randomized, double-blind, HA gel vehicle-controlled clinical studies have evaluated the efficacy of topical diclofenac HA gel in patients with AK. The 30-day interval between the end of treatment and the evaluation of efficacy was due to earlier findings stating a significant advantage for diclofenac HA gel over placebo, when efficacy was evaluated 4 weeks after the end of treatment. The product significantly reduced lesions when applied for 60 or 90 days. A double-blind, randomized, placebo-controlled multicenter study showed response rates of 79 (verum group) vs. 45% in the placebo group; a complete healing was seen in 50 (verum group) vs. 20% in the control group ($p < 0.001\%$) [53]. Other controlled studies showed similar effects [54, 55]. Adverse effects were skin-related and mild to moderate in severity (pruritus, erythema, dry skin, hyp- and paraesthesia). Systemic bioavailability of diclofenac was demonstrated to be considerably lower after topical application than after systemic administration and the drug demonstrated a good safety profile.

### 4.1.5 Prevention

Prevention of AKs is an important part in AK-management [56, 57]. Education of patients (UV-protection, self-examination, and detection of early lesions) is particularly important. AK is an ongoing disease that requires frequent follow-up and long-term management. A recent study evaluating a liposomal highly effective sunscreen (Daylong actinica®) in 120 organ transplant recipients showed a decrease in AK and no new SCC with daily application of this sunscreen for 24 months [58].

### 4.2 Bowen’s Disease

#### 4.2.1 Epidemiology and Etiopathogenesis

Bowen’s disease (BD) is defined as an intraepidermal (in situ) squamous cell carcinoma of the skin and has first been described in 1912 [59]. In contrast to AK, Bowen’s disease shows different clinical and histopathological findings. Without treatment, BD persists and may progress to invasive squamous cell carcinoma (Bowen carcinoma).

Known risk factors include UV exposure, arsenic, immunosuppression, advanced age (>60 years), and ionizing radiation. Human papilloma virus 16 has been detected in up to 30% of anogenital lesions of BD. The risk of progression into invasive squamous cell carcinoma is about 3–4, but increases to 10% in genital and anal lesions [60].

Association of BD with internal malignancies has been reported in retrospective analysis, but larger studies and a metaanalysis of the literature did not confirm these findings [61].

#### 4.2.2 Clinic and Diagnosis

Clinically, BD represents a slowly growing, well demarcated erythematous plaque with an undulating border. Superficial scaling or crusting, ulceration, and pigmentation may occur. In contrast to AKs, Bowen’s disease manifests as solitary lesion in the majority of cases.

In the genital area, lesions with histological findings of Bowens’s disease are referred to as Erythroplasia Queyrat (EQ). EQ is most common in uncircumcised men on the glans penis, but may also occur on the shaft or on the vulva in female individuals.

The diagnosis of BD is often made clinically. However, it may resemble chronic eczema, psoriasis plaques, Paget’s disease, or AK, and histologic examination may be required for differential diagnosis. Furthermore, invasion can be excluded through histopathological exam. Histopathologically, BD shows characteristic features with full thickness epidermal dysplasia and individual cell dyskeratosis.
4.2.3 Treatment

4.2.3.1 Excision

Simple excision is a good option for the treatment of BD. Recurrence rates vary from 4.5–19% after simple excision. If performed in the genital region, Moh’s micrographic surgery should be considered in order to spare tissue and avoid mutilation [60].

4.2.3.2 Curettage and Electrodissecation

Curettage and electrodissecation have been shown to be effective in the treatment of BD. A large study reported a 20% recurrence rate [62].

4.2.3.3 Photodynamic Therapy

PDT has recently been introduced for the management of BD. Complete response rates of 90–100% and recurrence rates of 0–11% have been reported [60].

4.2.3.4 Cryotherapy

BD may be treated also by cryotherapy. However, the lack of standardization with regard to intensity and duration of freezing leads to different response rates in the literature. Recurrence rates are usually less than 10%. However, healing time may be prolonged, especially in lesions on the lower leg.

4.2.3.5 5-Fluorouracil

Smaller case series and open studies have evaluated 5-FU for Bowen’s disease. The commercially available 5% cream is most commonly used and cure rates range from 87 to 92%. In order to reach lower recurrence rates, prolonged therapy regimens (≥8 weeks) have been recommended [63]. However, the use of 5-FU is limited due to its irritant potential, especially in the genital area.

4.2.3.6 Imiquimod

Besides its use in superficial basal cell carcinoma and AKs, Imiquimod 5% cream has also been applied for Bowen’s disease. A large case series reported a complete response rate of 86% during a median follow-up of 18 months. Lesions of the genital area had been included (11% of all lesions) [64]. Imiquimod can be recommended for the treatment of BD, especially in circumstances where excision is difficult or may cause mutilation. However, larger prospective trials are needed to further assess the efficacy of Imiquimod in BD.

References


46. Loven K, Stein L, Furst K, Levy S (2002) Evaluation of the efficacy and tolerability of 0.5% fluorouracil cream and 5% fluorouracil cream applied to each side of the face in patients with actinic keratoses. Clin Ther 24:990–1000


52. Jung YJ, Isaacs JS, Lee S, Trepel J, Neckers L (2003) IL-1β-mediated up-regulation of HIF-1α via an NFκB/COX-2 pathway identifies HIF-1 as a critical link between inflammation and oncogenesis. FASEB J 17:2115–2117


5.1 Epidemiology and Etiopathogenesis

SCC accounts for 20% of all nonmelanoma skin cancer (NMSC), and as such, is the second most common skin cancer worldwide. It is the most common skin cancer in skin of color, notably among African and African–American patients. Because SCC is not a reportable disease, its exact incidence is unknown, but estimates place...
the number of new cases in the United States around 100–150 per 100,000 people annually [1]. The incidence is highest in Australia, where 499 per 100,000 men and 291 per 100,000 women are diagnosed with SCC annually [2]. In nontanning, lightly-complected people, the number is even higher (611 per 100,000 Australians) [3], Canada (34 per 100,000) [4], Germany (17.4 per 100,000) [5], Finland (7.2 per 100,000) [6], and China (0.8 per 100,000) [7]. The annual incidence is on the rise worldwide and is expected to increase as the world’s population ages [8]. Because ultraviolet radiation is the primary risk factor associated with the development of SCC, the incidence doubles with every 8–10° decrement in latitude and is highest near the earth’s equator [1]. For unknown reasons, SCC occurs more commonly in men than in women. The estimated lifetime risk for White men is 9–14%, while the estimated risk for White women is 4–9% [9]. Some researchers theorize that men have more total lifetime sun exposure than women, but unknown biological factors have also been recently implicated in this gender discrepancy [10]. Other demographic factors linked to increased risk of SCC include advanced age, fair skin, Celtic ancestry, red or blond hair, and blue eyes [8]. In contrast to basal cell carcinoma (BCC), SCC has a well-known potential for metastasis, and therefore, accounts for the highest percentage of mortality caused by NMSC. Although the overall mortality from NMSC is decreasing despite rising incidence rates [11], more than 2,000 deaths per year are attributed to SCC in the United States alone [12]. Mortality rates have decreased greatly in Germany, with 0.56 disease-specific deaths per 100,000 patients with SCC in 1968 compared to just 0.24 deaths per 100,000 cases in 1999 [13].

### 5.1.2 Etiology

Of all known etiologic risk factors (Table 1) associated with the development of SCC, ultraviolet radiation (UV) is by far the predominant contributor [14]. In fact, 90% of all SCCs occur on sun-exposed skin [14]. The risk of developing SCC is related to the cumulative lifetime sun exposure, and excessive childhood exposure appears to be more important than exposure in later adulthood [15]. Specifically, a history of blistering sunburn during childhood significantly increases the risk of developing SCC [15].

UV-B radiation (290–320 nm) is the most damaging wavelength [12]. The mechanism of UV-B photocarcinogenesis is reviewed in more detail in Sect. 5.1.3.

The link between skin carcinoma and environmental carcinogens was first noted in 1775 by Percival Pott, a British physician who attributed scrotal carcinoma in young chimney sweeps to chronic soot exposure [16]. Polycyclic aromatic hydrocarbons have since been implicated in the carcinogenesis of SCC and are present in coal tar, pitch, soot, creosote oil, and petroleum fuels, among other chemical compounds [12]. Hydrocarbons in burnt tobacco smoke, particularly benzo[a]pyrene, are linked to the development of SCC of the lips and oral cavity [17]. Other carcinogens, namely nitrosamines, are found in smokeless tobacco and also lead to SCC of the oral cavity [17, 18]. Additionally, chronic exposure to arsenical compounds has been linked to the development of invasive SCC, which may be preceded by the so-called “arsenical keratoses” or Bowen’s disease. Arsenicism should be considered in patients who drink untreated well water or who have ingested medicinal Fowler’s solution, a 1% potassium arsenite solution historically used to treat a variety of ailments including malaria, rheumatic fever, and psoriasis. Arsenic exposure, and subsequent SCC development, is also an occupational hazard for a handful of industries. Specifically, exposure to arsenic occurs in patients working in insecticide or herbicide manufacturing plants and in plants where copper, lead, or zinc ore is smelted [19].

Many cases of invasive SCC arise from precursor lesions in the SCC spectrum, including actinic keratosis (AK) and Bowen’s disease. In AK, the epidermis is irregularly hyperplastic with cellular atypia in the basal layer [20]. In Bowen’s disease, there is hyperkeratosis and cellular atypia throughout the full thickness of the

<table>
<thead>
<tr>
<th>Etiologic risk factors for SCC</th>
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<tbody>
<tr>
<td>Ultraviolet radiation</td>
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<tr>
<td>Chemical carcinogens (arsenical compounds, polycyclic aromatic hydrocarbons)</td>
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<tr>
<td>Precursor lesions (actinic keratosis, Bowen’s disease)</td>
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<tr>
<td>Chronic inflammation or ulceration (osteomyelitis, hidradenitis suppurativa, discoid lupus erythematosus, lichen sclerosus et atrophicus, stasis ulcer)</td>
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<tr>
<td>Scar or burn injury</td>
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<tr>
<td>Ionizing radiation</td>
</tr>
<tr>
<td>Human papilloma virus infection (especially oncogenic subtypes)</td>
</tr>
<tr>
<td>Genetic disorders (xeroderma pigmentosum, oculocutaneous albinism, epidermodysplasia verruciformis)</td>
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</table>
Invasive Squamous Cell Carcinoma of the Skin

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When the basement membrane is disrupted by neoplastic keratinocytes, invasive SCC is deemed to be present. It is generally estimated that the overall risk of any single AK developing into invasive SCC is 0.1–0.24% annually [21]. However, the published risk of progression varies wildly from as low as 0.025% to as high as 16% [22]. Bowen’s disease progresses to invasive SCC in 3–5% of cases [14, 23, 24].

Although relatively few precursor lesions progress to SCC, a high proportion of SCC shows evidence of development from precursor lesions. More than 40% of metastatic SCC tumors show evidence of contiguous AK [20]. In another published series of invasive SCC, 97% of cases had evidence of contiguous Bowen’s disease at the periphery or within the confines of the SCC tumor [25]. The potential for precursor lesions to progress to frank invasion is thought to be related primarily to the duration of disease, patient age, and patient immune status [24]. Strategies for disease prevention through treatment of precursor lesions are discussed briefly in Sect. 5.4.1.

A subset of clinically aggressive SCC develops from preexisting lesions, including scars, thermal burns, and sites of chronic erosion or inflammation. Together, these tumors are referred to as secondary SCC. The most common chronic dermatoses in which secondary SCC has been documented include osteomyelitis, hidradenitis suppurativa, discoid lupus erythematosus, lichen sclerosus et atrophicus, dystrophic epidermolysis bullosa, lymphohgranuloma venereum, granuloma inguinale, erythema ab igne, acne conglobata, stasis ulcerations of long duration, and (rarely) chromoblastomycosis [12]. Congenital lesions with potential for secondary SCC include nevus sebaceous, branchial cleft cysts, and linear epidermal nevus [12].

Exposure to ionizing radiation increases the risk of developing SCC. In the 1940 and 1950s, radiation was used to treat a number of benign conditions of the face, including acne, hypertrichosis, and hemangiomas [12]. The risk of developing SCC is directly related to the total amount of cumulative radiation exposure.

Infection with the human papilloma virus (HPV), especially the beta-genus HPV types five and eight, increases the risk of developing SCC by up to 60% [26–28]. Furthermore, infection with multiple beta-HPV types increases this risk by 80% [26]. Tumor specimens of immunosuppressed patients with SCC demonstrate HPV infection in more than 90% of cases [26]. Alpha-HPV types, particularly HPV-16, are particularly associated with periungual SCC [29]. It is thought that HPV infection acts as a susceptibility cofactor, increasing the risk of infection in combination with other predisposing factors. Antibodies directed against the E6 oncogenic protein of HPV are associated with decreasing incidence of SCC [28]. This finding suggests that the E6 oncoprotein plays a role in the development of SCC, and that antibodies to this protein may protect against development of the disease.

Finally, certain genodermatoses increase the risk of SCC development. Patients with xeroderma pigmentosum typically develop skin cancer by the age of 8 because of a genetic defect in the repair of UV-induced damage to cellular DNA [12]. Patients with oculocutaneous albinism are also at increased risk of developing SCC due to increased susceptibility to the damaging effects of UV radiation. Patients with epidermodysplasia verruciformis develop multiple flat warts with HPV-5 and HPV-8 infection, characterized by a high rate of progression to SCC [26].

5.1.3 Pathogenesis

The process by which SCC develops has been explored primarily through studies of the photocarcinogenic properties of UV radiation. The process was elucidated in 1963 when Winklemann demonstrated that UV radiation led to SCC development in mice [30]. It has since been determined that mutations in the tumor suppressor protein p53 play a significant role in the pathogenesis of SCC [31]. In fact, p53 mutations are found in more than 90% of SCC tumor specimens [31] and in approximately one-third of cases of Bowen’s disease [23].

UV-B radiation leads to cyclobutane pyrimidine dimer mutations in keratinocyte DNA [31, 32]. Normal skin responds to UV-B radiation by upregulating p53 activity, ultimately leading to cell cycle suppression and/or apoptosis of damaged keratinocytes. When mutations occur in p53, damaged keratinocytes proliferate rather than regress. Mutations in the p53 gene are common and early events in the development of SCC and are thought to precede invasion in most cases [23]. Other genetic abnormalities frequently observed in SCC include mutations in p14, p16, Rb, and CDH1 (E-cadherin), which were present in 95% of tumors in one series [32]. Ultimately, the progression from the clinical lesion of actinic keratosis to frankly invasive SCC depends upon the continued accumulation of mutations in other genes, such as H-ras and p16; thus,
the development of invasive SCC can be thought of as a linear and evolutionary process [33].

5.2 Clinical Presentation and Morphologic Variants of SCC

5.2.1 Typical Cutaneous SCC Including the Keratoacanthoma Subtype

The spectrum of cutaneous SCC includes multiple variants of frankly invasive SCC. These variants are distinguished by clinical and histopathological characteristics. Most cutaneous SCC occur on the head and neck at sites of maximal sun exposure, but the trunk and extremities may also be involved [1].

The most common presentation of SCC is a hyperkeratotic and erythematous poorly-margined papule or nodule which tends to erode or ulcerate. (Fig. 5.1 and 5.2) Ulcerations may be hidden beneath serosanguinous crusts. Alternatively, the nodule may be smooth or develop a cutaneous horn. Palpation of SCC reveals induration, and the lesion may be fixed to underlying structures in later stages of progression. Typical SCC is characterized histologically by atypical keratinocytes invading into the dermis, as well as atypical cellular hyperchromasia, pleomorphic nuclei, and frequent mitotic figures [34]. Intercellular desmosomal bridges and keratin pearls may be seen in well-differentiated SCC [34].

A distinct subtype of typical cutaneous SCC is the keratoacanthoma (KA). Although some controversy persists as to the most accurate classification of KA, the lesion is generally considered to be a variant of SCC and is managed as such. KA classically presents as a rapidly expanding dome-shaped nodule on the face or extremity of the elderly [1]. Classically, the lesion demonstrates a central crater filled with hyperkeratotic debris. (Fig. 5.3) KA typically occurs as a solitary lesion. However, there are clinical settings where multiple KAs are noted. These clinical settings include multiple self-healing KAs seen in the autosomal dominant Ferguson-Smith syndrome, eruptive KAs of the Gryzbowski type, and KAs in association with...
sebaceous tumors in Muir-Torre syndrome [35]. Although KA has been observed to regress spontaneously, the potential for local destruction is high and warrants inclusion of KA in the spectrum of frankly invasive SCC.

### 5.2.2 Secondary SCC

Cutaneous SCC may arise de novo or in preexisting lesions. A subset of SCC, called secondary SCC, arises in existing scar tissue or at sites of chronic ulceration and inflammation. SCC arising from scar tissue (classically related to thermal burn injury) is termed Marjolin’s ulcer in honor of the French surgeon Jean Nicolas Marjolin who first described the lesion in the early nineteenth century [36]. The states of chronic inflammation in which secondary SCC has been observed are listed in Sect. 5.1.2.

Secondary SCC usually develops after many years of chronic inflammation or continued erosion of scar tissue. Marjolin’s ulcer arising in burn scars does not typically appear until 20–40 years after the initial injury [37]. Patients with secondary SCC provide a history of a nonhealing wound within a site of chronic inflammation, ulceration, or scar. Clinical suspicion for secondary SCC must be high, especially when patients report the development of a new mass, persistent bleeding, or a change in the character of the inflammatory drainage [37]. (Fig. 5.4) Secondary SCC displays an aggressive clinical behavior and is characterized histologically by marked atypia [37].

### 5.2.3 Anogenital SCC

Although the topic of anogenital SCC is covered in detail elsewhere in this textbook, the disease warrants a brief discussion herein as a subset of SCC. Invasive SCC of the anogenital region generally develops from precursor lesions including squamous cell carcinoma in-situ (SCCIS) and, less commonly, lichen sclerosus. SCCIS of the vulva and penis is characterized by velvety erythematous plaques with or without superficial erosion. On the glans penis, this lesion is historically termed erythroplasia of Queyrat [34]. Ten percent of cases of anogenital SCCIS progress to frankly invasive disease, and progression may be influenced by host immunosuppression and duration of disease [24]. The progression to invasive SCC is marked clinically by increased nodularity, acute ulceration, and/or notable friability of the lesion. (Fig. 5.5) Histopathology reveals atypical keratinocytes invading past the basement membrane into the deep dermis. Remarkably, pain is usually minimal compared to the dramatic appearance.

### 5.2.4 Verrucous Carcinoma

Another distinct morphological variant of SCC is verrucous carcinoma (VC). This subset is further divided into several clinical entities, all of which are characterized by slowly growing exophytic nodules capable of extensive local destruction, but with less pronounced potential for metastasis [34].
The Ackerman’s tumor, or oral florid papillomatosis, is a VC of the intra-oral mucosa (buccal or labial) and accounts for up to 9% of all oral cavity tumors [34]. The tumor occurs in elderly patients, and risk factors include chewing tobacco or betel nuts [34]. Beginning as a white patch on an erythematous base, the tumor progresses slowly to form white-gray warty and papillomatous plaques or nodules [14, 34]. (Fig. 5.6) Advance tumors have a cauliflower-like appearance. The Ackerman’s tumor is characterized histologically by well-differentiated SCC with a papillomatous growth pattern and numerous broad rete pegs [34].

The Buschke-Löwenstein tumor, or giant condyloma, occurs on the anogenital mucosa (classically the uncircumcised glans penis) and presents as a large, cauliflower-like exophytic lesion [14]. Ulceration of the tumor or fistula formation is common [34]. The tumor is associated with HPV types 6 and 11 and accounts for 5–16% of all penile cancers [14, 34]. Histopathology of the Buschke-Löwenstein tumor is characterized by minimal atypia, coupled with extensive verrucous acanthosis, and koilocytosis [34].

A third variant of VC is the epithelioma cuniculatum, a slow-growing bulky and warty polypoid mass occurring on the skin overlying the metatarsal heads, particularly the first metatarsal head [34]. (Fig. 5.7) Because this tumor tends to occur in this anatomic location, it is also known as plantar carcinoma. Sinus-like openings in the tumor communicate with the skin’s surface and drain a foul-smelling keratinous debris. Like other variants of VC, epithelioma cuniculatum is capable of extensive local tissue destruction, but displays limited metastatic potential.

5.3 Diagnosis

5.3.1 History and Physical Examination

The diagnosis of SCC begins with the identification of clinically suspicious lesions based on a thorough history and physical examination. Clinicians should ask patients about risk factors for SCC, including degree of UV exposure and documentation of exposure to chemical carcinogens. Patients with chronic inflammatory dermatoses or nonhealing scars should be asked about changes in the appearance and drainage of the wound. Physical examination should be focused on inspection and palpation of the lesion, noting the presence of ulceration, bleeding, induration, and surrounding scar tissue or inflammation. Specific attention should be directed to establishing the clinical borders of the lesion. Importantly, the lymph node basin draining the suspicious lesion should be carefully palpated. Any associated lymphadenopathy warrants further evaluation. The
5.3.2 Tissue Biopsy

Although clinically suspicious lesions are identified by history and examination, the diagnosis of SCC is always made histopathologically. All suspected tumors should be biopsied and examined microscopically. Biopsy specimens must be sufficiently deep to characterize the tumor depth and evaluate the extent of invasion. The shave technique may be acceptable for small, clinically superficial tumors. Larger or deep tumors should be biopsied by the dermal punch technique or by surgical incision (including wedge incision or total excision). These techniques provide enough tissue to determine the presence and extent of tumor invasion. In order to direct subsequent management and provide prognostic indicators, the histopathologist should specifically report on the following parameters: cell morphology, degree of differentiation (classically reported as Broder’s grade, Table 2), tumor depth (in millimeters), level of dermal invasion when present, and the presence or absence of perineural, vascular, or lymphatic involvement [38]. The prognostic value of these parameters and their influence on subsequent management is addressed in detail in Sect. 5.4.

Table 2  Broder’s Classification System

<table>
<thead>
<tr>
<th>Grade</th>
<th>Percentage undifferentiated cells</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Less than 25</td>
<td>Keratinization,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intercellular bridges</td>
</tr>
<tr>
<td>2</td>
<td>Less than 50</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Less than 75</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Greater than 75</td>
<td>Anaplasia</td>
</tr>
</tbody>
</table>

5.3.3 Differential Diagnosis

The differential diagnosis of invasive SCC based on clinical morphology is extensive. Benign considerations in hyperkeratotic lesions include verruca, seborrheic keratoses, and melanocytic nevi. Malignant lesions in the differential diagnosis of SCC include other epidermal carcinomas such as BCC, Merkel cell carcinoma, and atypical fibroxanthoma. Additionally, melanoma should be considered. Because of the broad differential diagnosis for SCC, the diagnosis requires tissue biopsy and histopathologic assessment.

5.4 Management

The management of invasive SCC requires clinicians to make informed decisions regarding available diagnostic studies and treatment modalities. For example, diagnostic imaging or sentinel lymph node biopsy may be appropriate for some patients, but unnecessary for others. There is a paucity of head-to-head clinical studies to aid clinicians in selecting the optimal treatment modality, and large scale randomized trials are few. Nevertheless, a careful review of the readily available literature can guide clinicians and assist in making evidence-based decisions when managing patients with invasive SCC. The following recommendations for the management of SCC are based on committee-generated guidelines, retrospective reviews, clinical trials, and the published experience of experts in the field. These recommendations are summarized visually in a management algorithm (Fig. 5.8).

5.4.1 Primary Disease Prevention

The management of SCC within a population begins with primary prevention of the disease. Importantly, clinicians should counsel patients regarding risk factor avoidance. Because UV-B radiation is ubiquitous and constitutes the major risk factor for developing garden variety SCC, all patients should be counseled about sun protection and avoidance. The daily use of sunscreen with a protection factor of at least 16 has been shown to reduce the incidence of SCC by 40% over an 8-year follow-up period in a study involving fairly-complected Australians [39]. Additionally, at-risk patients should be made aware of the link between SCC and arsenic, nitrosamines, and polycyclic aromatic hydrocarbons.

Primary prevention of invasive disease can also be achieved by screening for and treating early precursor lesions such as AK and SCCIS. Options for the treatment of AK include liquid nitrogen cryotherapy, topical 5-fluorouracil cream, and topical 5% imiquimod cream. Bowen’s disease has been successfully treated with cryosurgery, curettage, carbon dioxide laser ablation, topical chemotherapy, micrographic surgery, photodynamic therapy (PDT), and topical 5% imiquimod cream [24].
Additionally, ongoing research has indicated a potential role for both topical and oral nonsteroidal antiinflammatory drugs in the chemoprevention of skin cancer [40].

There are two subsets of patients who may benefit from specific measures taken to primarily prevent SCC: psoriasis patients treated with psoralen-UV A phototherapy (PUVA) and immunosuppressed organ transplant recipients (OTR). The development of skin cancer is now a well-known adverse event accompanying prolonged PUVA therapy. The incidence of SCC has been estimated to be as high as 2% per year for patients receiving high dose PUVA therapy (greater than 200 treatments or greater than 2,000 J/cm² total exposure) [41]. There is a strong dose-response relationship between PUVA and SCC development: patients receiving more than 500 PUVA treatments are 20 times more likely to develop SCC than patients receiving fewer than 200 treatments [42]. Oral retinoid use has been demonstrated to have a protective effect against the development of SCC in PUVA patients. Retinoids reduce SCC development through antiproliferative properties [43], inducing the apoptosis of tumor cells and promoting normal cellular differentiation. One published series observed a reduction in the annual incidence of SCC by 20–30% in PUVA patients who take more than 25 mg daily of either etretinate or acitretin [42].

OTR represent another important group of patients in which specific measures should be taken to prevent invasive SCC. The annual incidence of SCC in OTR is estimated to be up to 250 times that of the general population, and most skin cancers begin to arise 3–5 years after transplantation [43, 44]. OTR patients with high number of keratotic skin lesions are at highest risk for developing subsequent SCC [45]. Skin cancer is a major adverse effect of the immunosuppression associated with orthotopic organ transplantation, with fully 5% of recipients dying from skin cancer [44]. Two-thirds of these deaths are attributed to SCC [44].

A significant reduction in the incidence of SCC can be achieved by oral retinoid therapy. OTR patients
taking 0.2–0.4 mg/kg of acitretin daily have been observed to develop 50% fewer SCC than untreated OTR patients [45]. Unfortunately, the chemopreventative effects of oral retinoids do not persist beyond the treatment period [45]. Furthermore, it is also noted that patients who inadvertently discontinued oral retinoid chemoprevention experienced an abrupt rebound increase in the number of SCCs developed [45]. It is for these reasons that patients should be advised that beginning retinoid chemoprophylaxis is likely a lifelong commitment [45].

Guidelines for oral retinoid chemoprevention have been published [46]. Candidates for the treatment include PUVA patients and OTR, among other chronically immunocompromised patients [46]. These guidelines recommend a gradual dose escalation titrated to clinical response and acceptability of adverse effect profiles. Specifically, patients should begin treatment with 10 mg of acitretin every other day for 2 weeks and then every day for 2 more weeks. After 1 month, patients should increase the dose of acitretin to 20 mg daily [46]. Patients should be monitored closely for side effects, including mucosal xerosis, alopecia, musculoskeletal pain, abnormal liver enzymes, and elevated triglycerides and hypercholesterolemia [45, 46]. Adverse effects may require additional pharmacotherapy (e.g., atorvastatin or gemfibrozil for dyslipidemia) or discontinuation of the retinoid therapy.

Because of the significant adverse effect profile associated with oral retinoid chemoprophylaxis, alternative prophylactic treatments have been sought. Both topical imiquimod cream [47] and PDT [48] have emerged as potential alternatives. In a small pilot trial, OTR patients were evaluated after applying 5% imiquimod cream 3 times weekly to 60 cm² of skin for 16 consecutive weeks [47]. The treatment achieved a moderate 36% decrease in the number of AK and a 50% decrease in “skin atypia” as perceived by experienced clinicians [47]. PDT has also been recently shown to reduce the number of precursor lesions (AK and SCCIS) in OTR patients [48]. Patients treated with two cycles of methyl-aminolevulinate PDT achieved clinical and histological resolution of all precursor lesions in almost 90% of lesional areas receiving treatment [48]. Although long-term follow-up is currently lacking, imiquimod and PDT may prove to be useful alternatives to oral retinoids for SCC chemoprevention.

5.4.2 Identification of “High Risk” Tumors and Further Disease Stratification

Unlike BCC, invasive SCC has a well-known potential for metastasis. Overall, less than 10% of SCC metastasize [14], but this risk increases based on specific tumor parameters. Clinicians should stratify patients based on their risk for tumor recurrence and metastasis in order to make optimal management decisions. Several comprehensive reviews, including a seminal review by Rowe et al. [49], have identified specific parameters which increase a patient’s individual risk of local tumor recurrence or metastasis. The prognostic implications of these different parameters are reviewed in detail in Sect. 5.4.7.

In order to optimize management, clinicians should identify patients with “high risk” tumors. Factors known to increase the risk of recurrence or metastasis are summarized in Table 3 and include tumor diameter greater than 2 cm, tumor depth greater than 4 mm, poor cellular differentiation, perineural invasion, host immunosuppression, prior tumor treatment (i.e., recurrent tumor), and anatomic site [34, 49]. High-risk anatomic sites, in decreasing order of relative risk, are secondary SCC (scar tissue or chronic inflammatory states), non-sun exposed sites, the external ear, and the lip [38].

The identification of high-risk tumors constitutes the first major branch point in the management algorithm. The highest-risk patients are those with clinical

<table>
<thead>
<tr>
<th>Table 3 Characteristics of Squamous Cell Carcinoma at High Risk for Local Recurrence or Metastasis</th>
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<tr>
<td><strong>Clinical parameters:</strong></td>
</tr>
<tr>
<td>• Tumor diameter greater than 2 cm (1cm on lip)</td>
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<tr>
<td>• Ill-defined clinical borders</td>
</tr>
<tr>
<td>• Immunocompromised patient</td>
</tr>
<tr>
<td>• Locally recurrent tumor</td>
</tr>
<tr>
<td>• Rapidly growing tumor</td>
</tr>
<tr>
<td>• Secondary tumor (arising at site of thermal injury, scar, ionizing radiation, or chronic inflammation)</td>
</tr>
<tr>
<td>• Primary tumor of the lip or ear</td>
</tr>
<tr>
<td><strong>Histopathologic parameters:</strong></td>
</tr>
<tr>
<td>• Tumor depth greater than 4 mm or Clark’s level IV or V</td>
</tr>
<tr>
<td>• Poor keratinocyte differentiation (Broder’s grade 3 or 4)</td>
</tr>
<tr>
<td>• Acantholytic pattern</td>
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<tr>
<td>• Presence of perineural invasion</td>
</tr>
<tr>
<td>• Perivascular encroachment</td>
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<tr>
<td>• Invasion to muscle, bone, or other subcutaneous tissue</td>
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evidence suggestive of metastasis. If palpable regional lymphadenopathy is detected, an evaluation for metastatic disease is warranted. Palpable nodes should be evaluated by either fine needle aspiration or excisional biopsy. The management of patients found to have metastatic SCC is addressed in Sect. 5.4.5.

In patients without palpable lymphadenopathy, the use of diagnostic studies to identify occult metastases is controversial. Some of the techniques used to identify occult metastatic disease include sentinel lymph node biopsy, elective lymph node dissection, Doppler ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) scanning. In general, these studies are reserved for patients with very high-risk tumors. Unfortunately, there is scant reliable data to inform clinicians as to the actual utility of these relatively expensive tests.

In one reported series, sentinel node biopsy yielded evidence of occult metastases in 24% of patients with anogenital SCC and 21% of nonanogenital SCC [50]. Although complications from sentinel node biopsy are rare, the procedure has not been incorporated into standard practice because its prognostic significance, even in the management of high-risk SCC patients, is unproven. However, persuasive evidence exists to suggest that elective neck dissection has no utility in the evaluation of patients with cutaneous SCC of the head and neck in the absence of palpable lymphadenopathy [51]. Based on the available data, neither sentinel node biopsy nor elective neck dissection is recommended as part of the initial evaluation of patients with SCC in the absence of enlarged lymph nodes.

Diagnostic imaging studies have also been used to evaluate high-risk patients and are reported to be 50–85% sensitive in identifying occult nodal metastases [51]. Doppler ultrasonography detects abnormal blood flow and characterizes nodal architecture. This technique may actually be superior to CT scanning for identifying occult metastases in lymph nodes [52]. However, ultrasonographic examination takes at least 30 min to complete, when compared with 3 min for the completion of a CT scan of the neck. This discrepancy limits the practical use of ultrasonography. Because both CT and ultrasonography are relatively safe, either may be employed as part of the routine evaluation of patients with cutaneous SCC at high risk for metastasis. Because there is no data to specifically support their inclusion in the evaluation of these patients, the use of such imaging modalities remains at the discretion of the managing clinician.

PET scanning with $^{18}$F-fluorodeoxyglucose is used in clinical oncology for whole body mapping in the staging and posttreatment evaluation of multiple cancers including colon cancer, melanoma, lung cancer, and lymphoma [53]. The technique relies on increased uptake of radiolabeled glucose by neoplastic cells in a hypermetabolic state and can identify primary tumors as well as nodal and distant metastases. The PET scanning technique has been recently employed in evaluating cutaneous SCC and has demonstrated some promising results [53]. Occult nodal metastases were identified in 25% of patients overall and in 100% of patients with high-risk tumor characteristics [53]. Although not yet part of the routine evaluation of high-risk patients, PET scanning may represent the future of diagnostic evaluation of invasive SCC.

MRI is another imaging technique which has been used to evaluate high-risk patients for hidden metastases. The technique is especially useful for identifying perineural involvement of the tumor [54]. MRI is specifically indicated for patients with clinical evidence of neuropathy and SCC located in the distribution of a peripheral nerve [54]. The technique is also indicated for patients with histopathologic evidence of perineural invasion and a tumor located within the typical distribution of a cranial nerve (commonly cranial nerves V and VII) [54]. The identification of gross perineural invasion on MRI has both prognostic and therapeutic implications: patients have only a 50% survival rate at 5 years and should undergo radiotherapy of the involved nerve pathway [54].

5.4.3 Treatment Techniques Without Margin Control

The identification of high-risk tumors is an important first step in the management algorithm for SCC. Once patients are stratified based on inherent tumor parameters, the appropriate treatment can be chosen from a multitude of options. Definitive treatment of invasive SCC should aim for complete removal or destruction of the primary tumor. Some treatment modalities, namely wide local excision (WLE) and Mohs micrographic surgery (MMS), confer the ability to control tumor margins and ensure complete resection. The
other treatment modalities do not provide the opportunity for tumor margin control. Nevertheless, some of these techniques are valid treatment options and can provide excellent cure rates when employed in appropriately selected patients. In general, treatment modalities without margin control should be reserved for patients with tumor diameters less than 1 cm and no characteristics of high-risk tumors [49]. These modalities include liquid nitrogen cryosurgery, electrodesiccation and curettage, primary radiation therapy (XRT), PDT, and topical imiquimod cream.

Liquid nitrogen cryotherapy destroys tumor cells by subjecting them to intense freeze-thaw cycles. Local anesthesia may be necessary for patient comfort, and tumors should be debulked by curettage before treatment [55]. Tumors should be treated with cryogen for 40–90 s, and the goal is to achieve tissue temperatures of −50°C [55]. Treatment should also include 3–5 mm margins of normal skin surrounding the tumor. Thermocouple needles are necessary to verify optimal tissue temperature in deeper tumors. This treatment modality, when applied to small tumors with clinically well-defined margins, is capable of achieving short-term and long-term cure rates in excess of 97% [49, 55]. Rowe et al. determined the 5-year recurrence rate after cryotherapy to be 3.2% [49].

Electrodesiccation and curettage (ED and C) is an alternative treatment option for small, well-defined SCCs. Prior to treatment, local anesthesia is achieved and the tumor is debulked by curettage. Because tumor tissue is more friable and creates a looser stroma than normal skin, the tumor tissue debulks readily. A needle-tipped electrosurgical device is used to pass an electrical current through the remaining tumor and surrounding stroma, leading to tissue destruction. This process of curettage and electrodesiccation is repeated at least 2 times. The wound heals over the course of 2–6 weeks and usually leaves a hypopigmented and possibly depressed scar. ED and C can potentially lead to poorer cosmetic outcomes than other modalities, and thus, should be used with caution on the face or other cosmetically sensitive areas. Furthermore, extreme caution should be used when applying electrosurgery to patients with implanted cardiac pacemakers, as the electrical current may disrupt the pacing activity. When applied to small tumors, ED and C achieves excellent cure rates [38]. Five-year recurrence rates are estimated to be only 1.3%, and long-term recurrence rates estimated at only 3.7% of patients [49].

XRT is a suitable alternative treatment for SCC when cosmesis is of primary concern or when various surgical techniques might be difficult due to such factors as anticoagulation, a debilitated patient state, tumor proximity to an orifice, and friable skin. The technique is especially useful for treating tumors of the nose, ear, and periorbital regions. Additionally, XRT may be used for primary treatment of very advanced tumors [38]. For small tumors with diameters less than 1 cm and well-defined margins, XRT can achieve good cure rates, although less than cryosurgery or ED and C [49]. Rowe et al. estimate the 5-year recurrence after XRT to be 6.7%, while approximately 10% of patients have local recurrence after long-term follow up [49]. Small tumors should be irradiated with orthovoltage radiography (75–125 kV) or electron beam radiation, although the latter modality requires more complex adjustments and dosing schedules [56]. A margin of normal skin, typically 0.5–1 cm, should also be irradiated. Small tumors with diameters less than 1 cm should be irradiated with a total of 40 Gy in 8 fractions [56]. Mid-range tumors with diameters between 1 and 2 cm require total radiation of at least 50 Gy in 15–20 fractions [56]. Finally, larger tumors or infiltrating tumors require 64–66 Gy in 30 or more fractions [56]. The role of XRT as an adjuvant therapy in the treatment of metastatic SCC is addressed in Sect. 5.4.5.

PDT has emerged as a treatment option for AK, Bowen’s disease, and some superficial NMSC [57]. The treatment begins with the topical application of photosensitizing agents, including 5-aminolevulinic acid or methyl-aminolevulinate, to tumors. The neoplastic cells convert these agents into photoactive porphyrins. After an incubation period of 3–14 h, the tumor area is then exposed to a calibrated light source, generating cytotoxic reactive oxygen species from activated porphyrins [57]. Early reports from small trials of PDT in the treatment of superficial invasive SCC have yielded complete resolution rates ranging from 54 to 100% [57]. While these results are promising, recurrence rates are high. Only 40% of tumor remained recurrence-free after 1–3 years [57]. Because of the high rate of recurrence after PDT and the metastatic potential of SCC, PDT is not currently recommended for the treatment of invasive SCC [57].

The topical application of 5% imiquimod cream has also emerged as a new treatment option for invasive SCC. Imiquimod acts as a toll like receptor seven agonist, inducing the production of interferons alpha and
beta, interleukins six and eight, and tumor necrosis factor alpha. The elaboration of these cytokines ultimately leads to apoptosis of tumor cells. While imiquimod has an established role in the treatment of precursor lesions of SCC, its utility for treating invasive SCC is yet unproven. Reports of successful treatment of SCC with imiquimod appear in the literature [58, 59] and have sparked interest in further investigation. In one small trial, 71% of invasive SCC tumors showed complete clinical and histopathologic regression after 16 weeks of topical treatment with imiquimod 5 times weekly without pretreatment debulking [60]. These reports suggest that imiquimod may be useful for patients with small tumors who are unwilling or unable to undergo surgical treatment. However, recurrence rates after imiquimod treatment are unknown and long-term follow up is lacking. At this time, the role of imiquimod in the treatment of invasive SCC is uncertain. While it may prove to be an appropriate option in selected patients, topical imiquimod cannot currently be recommended for the treatment of invasive SCC.

### 5.4.4 Treatment Techniques with Margin Control

Surgical resection with postoperative or intraoperative margin assessment is considered the standard of care in the treatment of tumors at high risk for local recurrence or metastasis [38, 49, 61]. These techniques include WLE and MMS.

The goal of treating skin cancer via WLE is to completely resect the tumor along with a surrounding rim of normal tissue. The clinical boundaries of the tumor may be determined visually and by palpation. The surgical specimen is fixed in formalin, embedded in paraffin, and the margins are examined histopathologically. Tumor cells extending beyond the surgical margins indicate incomplete resection of the tumor and warrant additional treatment. Recurrence rates following WLE are 5.7% after 5 years and 8.1% during long-term follow-up [49]. An extensive review has yielded recommendations for appropriate surgical margins in the treatment of invasive SCC with WLE [62]. Margins of 4 mm achieve complete clearance in 95% of cases and are appropriate for low-risk tumors arising from suitable anatomic sites (i.e., not arising from the scalp, eyelid, nose, ear, or lip) [62]. If WLE is used to treat high-risk tumors, surgical margins of 6 mm are required [62]. In general, WLE is an appropriate treatment option for any invasive SCC tumor less than 2 cm in diameter and at low risk for recurrence or metastasis.

Larger, high-risk tumors are best treated with MMS [38, 49, 61, 63]. This surgical technique, innovated by Frederic Mohs in the 1930s, involves the resection of tumors without predetermined margins of clinically normal skin. The resected specimens are precisely mapped, and the surgical margins are examined microscopically after intraoperative, frozen section preparation. When involved margins are found, another layer of tissue is removed in the distribution of the involved margin. This technique affords precise control of tumor margins and maximizes sparing of normal skin. When all tumors and all treatment modalities are considered, the best cure rates are achieved with MMS [49]. Long-term follow-up reveals recurrence rates of 3.1% after MMS and an average of 7.9% after all other “non-Mohs” modalities [49].

The indications for MMS in the treatment of SCC are multiple, and guidelines have been established [61]. In general, MMS is indicated for all SCC tumors at high risk for local recurrence or metastasis (Table 3). Furthermore, because MMS facilitates preservation of normal tissue, the technique is indicated in areas where wide surgical margins are technically difficult to achieve without disfigurement or functional impairment [38]. These areas include the nasal tip, nasal ala, lip, eyelid, external ear, genitalia, and periungual tissues. (Figs. 5.9 and 5.10) Additional and somewhat more discretionary indications for MMS include rapidly growing or clinically aggressive tumors and tumors...
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of long-standing duration [61]. In sum, WLE is appropriate for low-risk tumors while MMS is indicated for all high-risk and anatomically difficult tumors.

The science of intraoperative margin control is advancing rapidly, and two new techniques appear to be at the forefront. Both fluorescent stereomicroscopy (FSM) and confocal laser microscopy (CLM) have emerged as novel methods to detect tumor margins during surgical resection of tumors.

FSM is a technique whereby fluorophores are conjugated to antibodies which bind preferentially to tumor cells. Tumor specimens are then examined microscopically to determine tumor boundaries as revealed by the distribution of fluorescence. Epidermal growth factor receptor (EGFR) is overexpressed in SCC tumors, and anti-EGFR antibodies (cetuximab) conjugated to fluorophores have been used in mouse models to delineate tumor boundaries [63]. This technique is capable of identifying nests of residual tumor less than 1 mm in size [63]. Further research and clinical trials are necessary to determine its role in the routine management of SCC.

CLM allows for the rapid imaging of fresh tissue specimens and the identification of neoplastic cells based on nuclear morphology. This technique requires no conventional histochemical preparation procedures. Rather, fresh specimens are washed in 5% acetic acid and viewed under a confocal laser microscope. The time required to prepare tissue samples for CLM evaluation is less than 5 min [64]. The technique has been demonstrated to be 95% sensitive and 96% specific for the identification of SCC tumor boundaries based on criteria for nuclear atypia [64]. CLM could potentially save significant amounts of time in the intraoperative assessment of tumor margins. Although both CLM and FSM are early in the stages of research and development, these techniques may represent the future of margin-controlled surgical treatment of SCC.

5.4.5 Therapy of Metastatic Cutaneous SCC

As is true of most carcinomas, SCC tends to spread via lymphatic tissues. When metastases of SCC develop, regional lymph nodes are involved first in 85% of cases [51]. It is, therefore, crucial that clinicians palpate regional nodes in patients with suspected SCC and biopsy potentially metastatic nodes [38].

Once the diagnosis of metastatic SCC has been made, treatment goals must encompass not only management of the primary tumor, but also management of metastases. A multidisciplinary team, including dermatologists, surgeons, medical oncologists, and radiation oncologists, is usually necessary when managing metastatic SCC. Although no standardized guidelines or indications have been formulated, clinicians should consider diagnostic imaging in patients with lymph node metastases in order to clinically stage the disease by identifying distant metastases.

Current recommendations for treating metastatic SCC include both surgical treatment and adjuvant XRT. Patients who are physically able to tolerate surgery and have technically suitable tumors should undergo resection of the primary tumor followed by adjuvant radiotherapy to regional lymph nodes [65, 66]. Combined surgery and adjuvant XRT achieves a 5-year disease-specific survival rate of 75% compared to 52% for XRT alone and just 18% for surgery alone [66]. Despite combined treatment, up to 15% of patients develop locoregional recurrence after surgery and adjuvant XRT [66].

Chemotherapy has no demonstrated role in the management of metastatic cutaneous SCC either as primary treatment or adjuvant therapy [67]. Despite initially promising results, phase III trials of adjuvant 13-cis-retinoic acid and interferon-alpha have shown no benefit in the treatment of metastatic cutaneous SCC [68]. Although chemotherapy is commonly used for both definitive treatment and palliation in the management of SCC of the head and neck (nasopharyngeal and laryngeal origin), its utility in treating cutaneous...
SCC has not been established. Surgery and adjuvant XRT remain the optimal treatment.

5.4.6 Therapeutic Alternatives for Distinct SCC Subtypes

While the general principles of managing SCC may also be applied when treating the distinct subtypes of SCC, certain alternatives can be considered. Specifically, treatment options for KA, anogenital SCC, and VC differ slightly from standard therapy of SCC and warrant special consideration.

Although KA has a well-known tendency toward spontaneous resolution, the tumor is treated aggressively due to its potential for local tissue destruction and recurrence. Surgical excision, via WLE or MMS, offers the benefit of margin-controlled tumor resection and is the mainstay of the treatment of KA. However, many alternative treatment options have been employed with excellent responses reported in the dermatologic literature. These options for managing KA include intralesional injection of 5-fluorouracil, intralesional injection of methotrexate (MTX), application of topical imiquimod, and administration of oral retinoids [69].

The intralesional injection of 5-fluorouracil (5-FU), an antimetabolite used in the chemotherapy of many diverse solid tumors, has been used to successfully treat KA for many decades [70–72]. The technique may be used in patients who cannot tolerate or do not desire surgery, and in patients for whom posttreatment cosmesis is of primary concern [70]. Because of the pain and discomfort associated with intralesional injection of 5-FU, local anesthesia should be achieved with 1% lidocaine prior to treatment. Undiluted 5-FU (50 mg/mL solution) is then injected intralesionally, generously infiltrating the tumor base and periphery [70, 72]. Injections are repeated every 1–4 weeks according to the clinical response of the tumor. Each injection requires 0.5–1 mL of undiluted 5-FU solution, and reported case series suggest that anywhere from 2 to 12 injections may be required for complete regression [70, 72]. No recurrence has been reported after achieving clinical regression with intralesional 5-FU.

Successful intralesional treatment of KA has also been reported with MTX [69, 73, 74]. An antimetabolite and inhibitor of dihydrofolate reductase, MTX has also been used extensively in treating solid and hematologic malignancies. Solutions of MTX may be prepared with either 12.5 mg or 25 mg/mL, and both have been successfully used to treat KA [69]. The solution is injected intralesionally, blanching the tumor rim and central core [69, 74]. Central necrosis occurs 5–8 days after the injection [74]. The patient is reexamined 2 weeks later, and a repeat injection may be performed if complete clinical regression has not been achieved. Four or more injections at 2-week intervals may ultimately be necessary [69]. According to a recent review of this topic, complete clinical regression occurs in 92% of cases of KA treated with intralesional MTX [69]. Intralesional MTX may be superior to 5-FU in several regards. First, intralesional MTX requires no local anesthesia. Second, fewer injections are required, thereby making MTX more economical than 5-FU [74].

XRT is also a valid treatment option for KA. The technique is especially useful in poor surgical candidates, locally recurrent tumors, and cosmetically-sensitive patients [75, 76]. Historically, KA of the nose does not respond well to radiotherapy. When treating KA with XRT, 3 to 5 fractionated treatments of 3.5 to 5 Gy each should be delivered weekly [76]. A total dose of 40–60 Gy is required to achieve clinical regression [76]. Nearly all KA regress within 3 months of XRT [75], and one author reports no recurrence after more than 20 years of follow-up [76].

Topical 5% imiquimod cream has recently been explored as a treatment option for KA. Reports have been published indicating that monotherapy with topical imiquimod 3–5 times weekly results in complete clinical regression of the tumor in 8–12 weeks [77, 78]. In one report, tumor resolution was confirmed histologically [77]. While initial case reports suggest that imiquimod may be used successfully in managing KA, its role has not yet been clearly defined [77, 78].

Finally, oral retinoids have also been used to successfully treat KA and are most useful for patients with residual or recurrent tumors [79, 80]. In one series, patients with recurrent or residual KA were treated with oral isotretinoin (0.5–1 mg/kg daily) for an average of 6.3 weeks [79]. Most, but not all, patients responded to therapy with complete regression and excellent cosmetic results [79].

Anogenital SCC is primarily treated by surgical means, although nonsurgical ablative techniques may be used in some cases. Small tumors of the penis limited to the foreskin may be treated via circumcision,
while superficially invasive SCC of the glans penis may be treated by either carbon dioxide or Nd:YAG laser ablation as a skin-sparing technique [81, 82]. Tumors less than 2 cm in diameter are generally amenable to MMS, while larger or deeply-infiltrating tumors require partial or total penectomy [81, 82]. Surgical treatment is the standard of care for nearly all vulvar SCC, including early stages [83]. For early stages of vulvar SCC, treatment via WLE with 2 cm margins is advised and should be followed by either sentinel lymph node biopsy or inguinofemoral lymph node dissection [83]. Advanced stages of vulvar SCC require initial chemoradiation followed by surgery [83]. In contrast to penile and vulvar SCC, surgery does not constitute first-line therapy in most cases of anal SCC [84]. Rather, combination therapy with external beam radiation followed by chemotheraapy with 5-FU and either mitomycin-C or cisplatin is the initial treatment of choice [84]. Chemoradiation offers the advantage of preserved anal sphincter function and has been shown to achieve equal survival rates compared to abdominoperineal tumor resection [84]. Surgery is now used in the management of anal SCC as salvage therapy for patients with recurrent disease following chemoradiation [84].

Special considerations are also necessary when managing VC. Although successful treatment has been reported with intrallesional chemotherapy, cryotherapy, laser ablation, PDT, and oral retinoid therapy [85, 86], surgical excision remains the treatment of choice. Both MMS and WLE are acceptable forms of treatment, but MMS offers the advantage of maximal tissue sparing, an especially important consideration when treating VC of the oral or genital mucosa. Of note, radiotherapy should not be used in the management of VC [86, 87]. Irradiated VC initially regresses, but more than 10% of tumors recur and undergo anaplastic transformation [86]. For this reason, radiation is contraindicated in the management of VC.

5.4.7 Prognostic Indicators

The importance of stratifying patients based on risk factors for recurrence and metastasis cannot be overstated. In addition to informing treatment decisions, these parameters have significant prognostic implications. Distant metastases confer the worse prognosis, with less than half of patients surviving 5 years [49] and less than 10% of patients achieving 10-year survival [1]. Regional lymph node metastases are also grave prognostic indicators, with less than 30% of patients surviving beyond 5 years [88] and less than 20% surviving past 10 years [1].

The absence of distant or regional lymph node metastases is associated with a much better prognosis. However, individual tumor parameters become extremely important in determining specific prognoses at this point. Overall, 3-year disease specific survival is 100% in treated patients with no high-risk tumor characteristics [89]. In contrast, the presence of any high-risk tumor parameter is associated with a 70% disease specific survival at 3 years after treatment [89].

Within the group of high-risk parameters, prognostic implications vary significantly. Metastatic rates of low-risk tumors are 5.2% at 5 years [49]. Tumors greater than 2 cm in diameter are 3 times as likely to metastasize [38]. The same is true of poorly differentiated tumors (Broder’s grades 3 or 4) [38]. Anatomic site also influences prognosis. Tumors arising from sun-exposed sites have 5-year metastatic rates of 5.2%, compared to 13.7% for tumors of the lip, and 37.9% for tumors arising from scar tissue or from nonsun-exposed sites [49]. The presence of perineural invasion, with an estimated incidence of 3.7%, is particularly ominous [49]. Metastases of tumors with perineural invasion occur after MMS in 8.3% of cases and after WLE in 47.3% of cases [49]. Radiographic evidence of perineural invasion is also prognostic. The 5-year survival in patients with radiographic evidence of perineural invasion is just 50%, compared to 86% in patients without such radiographic findings [54].

5.4.8 Recommendation for Patient Follow-Up

A careful analysis of demographic trends and prognostic indicators can inform clinicians regarding appropriate follow-up for patients with invasive SCC. Patients diagnosed with SCC have a 6% incidence of developing another SCC within 3 years, a rate 30–40 times that of the general population [8]. Furthermore, greater than 95% of local recurrences and metastases appear within the first 5 years after treatment [49]. These trends reveal that the first 3–5 years after initial diagnosis are a critical time for patient surveillance.
Clinicians should follow patients biannually or annually during this time, depending on initial patient risk factors. A thorough history and physical examination should be performed, looking for evidence of local recurrence, metastasis, or additional primary tumors.

References

Cutaneous malignant melanoma (melanoma) is less common than the familiar basal and squamous cell tumors of the skin, but accounts for the vast majority of the skin cancer deaths. It mainly affects White Caucasians, although melanomas also occur in ethnic groups characterized by a more pigmented skin.
According to the most recent global estimates for 2002, there were an estimated 160,000 new cases of melanoma, the 16th and 15th most commonly diagnosed cancer in males and females, respectively, although in predominantly White populations it was much more common: Australia and New Zealand (4th males, 3rd females), North-America (6th males, 5th females), and Europe (16th males, 8th females) [1]. Approximately 79,000 males and 81,000 females were diagnosed with melanoma worldwide in 2002, of which about 80% occurred in the predominantly White populations of Northern America, Australia, New Zealand, and Europe. Worldwide, around 22,000 males and 19,000 females died of their disease [1].

Melanoma had a poor prognosis in the 1950s and 1960s, but from the mid 1970s, mortality rates have been stabilizing in many high-risk populations, and recently, incidence also seems to be leveling off, mainly among younger women [2–4]. Survival has improved substantially, mainly in countries with high incidence rates [5, 6]. This is mainly due to early detection of melanomas as a result of an increasing awareness of the disease, probably partly owing to the success of primary and secondary prevention campaigns.

6.1.1.1 Time Trends

Since the 1970s, there have been reports of alarming increases in melanoma, initially in terms of mortality [7] and then in incidence [8]. These reports observed a doubling in rates every one or two decades (mean annual increments of between 3 and 7%) per annum in populations of European origin for both genders [9]. The incidence rates increased markedly for intermittently exposed body sites (trunk, legs, etc.), whereas increases in the face and neck were moderate. In males, the largest increases were found on the trunk, and in females on the legs and arms [10–18]. In an analysis of the SEER data, it was found that melanomas of all stages increased from 1988 to 1997, but that localized and in situ lesions increased the most [19]; during the period 1996–2003, the percentage of localized melanomas among men was 80%, and among women it was 85% [20].

A recent plateau in melanoma mortality rates (in some cases followed by incidence rates) are reported in high-incidence countries, such as Australia, USA, Sweden, Norway, and Germany [2, 9, 12, 17, 21]. Only the mortality rates leveled off initially, starting in the late 1970s, with increasing incidence rates. These plateaus in mortality were due to improving survival [16, 17, 22] as a result of earlier detection, as there were no major advances in systemic treatment for advanced disease. In high-incidence countries, melanoma incidence rates have been reported to be leveling off, or even decreasing in younger age groups, starting in the 1980s [2, 3]. Furthermore, the mean and median stage or thickness at diagnosis is decreasing [16, 22–25], with an increasing registration of thin, superficial spreading melanomas. In contrast, in Southern and Eastern Europe and in Latin America, rates are increasing [2, 21, 26–28]. Incidence rates in Asia have been rather stable [29, 30]. There is insufficient data at present to report on time trends in melanoma incidence among African populations.

6.1.2 Geographical Differences

The levels of both melanoma occurrence (incidence) and mortality vary considerably worldwide (Figs. 6.1 and 6.2). Rates are high in predominantly White populations, especially those living close to the equator, and low in countries where inhabitants are of mainly Asian or African origin.

6.1.2.1 Melanoma in Caucasians

As the most important environmental risk factor in Caucasians is the exposure to ultraviolet radiation, incidence within White populations generally increases with increasing proximity to the equator. The highest rates are observed in Australia, where many inhabitants are of Northern European descent and live in a climate with substantially more sunshine than the norm in Northern Europe.

In Western Europe, a diverging pattern is observed: incidence rates are higher in Northern Europe (more distant from the equator) than in the South, reflecting a combination of lighter skin type and higher wealth, allowing for holidays in the (sub)tropics, in the North of Europe (Figs. 6.1–6.2). Of interest, survival rates of melanoma are generally higher in areas with high incidence, probably due to more awareness, better early detection, and adequate initial treatments.
6.1.2.2 Migrant studies

Groups of migrants from regions of low melanoma incidence to high incidence regions acquire higher rates of melanoma than in their home country, but lower than those in the host country, in both sexes [31]. Incidence and mortality rates of native Australians and New Zealanders, largely of British origin, are roughly twice those of recent British immigrants to these countries [32, 33]. Likewise, native Israelis experience a twofold increased risk of incidence compared to immigrants to Israel from Europe; this risk pertains at least 30 years following immigration [34]. The risk of immigrants has been shown to approach that of the native populations in both Australia and Israel with increasing duration of residence in the host country [31–34].
Among Northern European migrants to Australia, the incidence rates of melanoma have been observed to increase with duration of residence, but decrease with later age of arrival (after puberty), suggesting that sun exposure at young ages is an important risk factor [32]. The lowest risk in immigrants to Australia has been found to be for Southern European and Eastern Asian migrants, reflecting the protective effect of a higher degree of skin pigmentation [32]. Differences in skin color are also assumed to be the reason underlying the higher incidence of melanoma in White immigrants to Hawaii from the United States mainland [35].

### 6.1.2.3 Melanoma in NonCaucasians

U.S. Whites (age-standardized rates per 100,000 person-years for the period 2000–2004 (US standard population): 27.2 males and 17.6 females) have much higher rates than U.S. Blacks (1.1 males and 0.9 females) (Table 6.1) [36], and a similar contrast in risk has been observed in the White and Black populations of South Africa and Zimbabwe [37]. Melanoma is also uncommon among Asians [29, 38] and Middle- and South-American populations (Table 6.1) [39], probably due to a better protection afforded by a larger amount of pigment in the skin and possibly different (“wiser”) sun-exposure patterns. In the region of Cali,
Colombia, however, incidence and mortality rates of melanoma are on the increase [40].

Melanomas appear more often on the nonpigmented areas of the skin in non-Caucasians [41], are often of the acral lentiginous melanoma type, and appear at the palms of hands, soles of the feet, and under the nails [39, 42]. A common problem in these populations is that pigmented lesions in the skin are often more difficult to notice, and are, therefore, often detected at relatively late stages, which, at least in part, explain the high case-fatality rates [39, 42]. In many African and Asian societies, it is considered beautiful to have a light skin and people try to avoid sun-exposure and even try to bleach their skin [43, 44].

6.2 Risk Factors

6.2.1 Established Risk Factors

Both familial and environmental factors are established risk factors for the development of cutaneous melanoma. The familial/genetic components include skin type, number of naevi, having clinical atypical naevi, and having a family history of skin cancer. They are the most important predictors of melanoma risk. Intermittent exposure to UVR is the major environmental risk factor for melanoma, especially in combination with endogenous factors, and exposure during childhood and adolescence (skin types I and II, immune deficient status, genetic predisposition) [45]. The association between UVR and melanoma is ambiguous, with differences in risks associated with the dose, the way it is delivered (intermittent vs. chronic exposures), and critical time periods (childhood vs. cumulative exposure during life). The relative risk of UV exposure for the development of melanoma is around two, but when skin characteristics are taken into account, the relative risks increase markedly for those with a sun-sensitive skin. As sunbeds also emit UV-radiation, they most likely also confer a risk for the development of melanoma, as was confirmed in a large prospective study [46].

Melanoma is more common among people with a higher socioeconomic status, probably due to a higher excessive intermittent exposure to UV-radiation (outdoor sports, winter sports, sunbathing, getting a tan) in this group.

6.2.2 Genetics

People with parents or siblings who were diagnosed with a malignant cutaneous melanoma have a 2–3-fold increased risk of developing a melanoma compared to persons without a family history of melanoma [47]. Clustering of melanoma in families is, however, not frequent and the genes implicated in large melanoma families only play a small role in population-based melanomas. Two genes have been discovered in melanoma families: CDKN2A (p16) on chromosome 9p21, and CDK4 on chromosome 12. Mutations in the CDKN2A gene have been found in up to 25% of melanoma families worldwide and in nearly 75% of melanoma cell lines, whereas CDK4 has only been observed in a few rare families. The CDKN2A gene acts as a tumor suppressor gene and plays a crucial role in cell cycle regulation and senescence. The p16 protein is a cyclin-dependent kinase inhibitor which works by binding to CDK4. The p16 gene tends to be transmitted in an autosomal dominant fashion. Its penetrance varies with population incidence rates, indicating that the same factors that affect population incidence of melanoma may also mediate CDKN2A penetrance [48].

Other genes, such as MC1R (Melanocortin 1 Receptor) and DNA repair genes, are likely to be more important in determining susceptibility for melanoma in the general population. The MC1R gene is also involved in skin and hair pigmentation and in senescence and immunity [49–51], and coinheritance of MC1R variants increases the penetrance of CDKN2A in melanoma families. Naevus genes also seem to be low-penetrance susceptibility genes, which is in line with the observation that the presence of multiple naevi increases melanoma risk [48]. Patients with genetic abnormalities in the DNA repair system, like Xeroderma Pigmentosum patients, are at a 1000-fold increased risk [52].

6.2.3 Nonestablished Risk Factors

UV exposure among young people is the only established environmental risk factor for melanoma, although many other factors might be related to the occurrence and/or prognosis of melanoma.

An international group of experts convening at the International Agency for Research on Cancer concluded
that the use of protective cream could indeed prevent erythema and squamous cell carcinoma after *nonintentional* sun-exposure (i.e., exposure to the sun without the objective of getting exposed, for example, work-related exposure). Its protective effect for basal cell carcinoma and melanoma, however, is not yet determined, as it is difficult to study due to a long latency period.

Paradoxically, there is inconsistent evidence that the use of sunscreens may increase the risk of melanoma development by increasing sunbathing-time. Of fifteen case-control studies examined by an expert panel, only three showed a significantly reduced risk of melanoma, with relative risks between 0.2 and 0.6, the others observing no significant effect (four studies) or an increased risk (eight studies, RR between 1.7 and 3.5)[53].

Vaccination during childhood against tuberculosis with the Bacille Calmette–Guérin (BCG) vaccine or against smallpox with the vaccinia vaccine, or having experienced one or more infectious diseases may decrease the risk of developing melanomas (odds ratios between 0.29 and 0.44) [54–58]. If this protective effect of vaccinations is real, part of the increases in melanoma incidence could be due to the abolishment of this type of vaccination in many developed countries.

Recently, there are indications that certain dietary factors might be related to melanoma risk, such as circulating adiponectin levels, which have been found to have a protective effect [59]. Also, the use of statin has been postulated to be involved in melanoma incidence and progression [60]. Certain work-related exposures may increase cutaneous melanoma risk, such as polychlorinated polycyclic aromatic hydrocarbons (PAHs), benzene, polychlorinated biphenils (PCBs), and ionizing radiation [61].

Recently, polymorphisms in the vitamin D receptor gene have been shown to be related to melanoma susceptibility and prognosis, indicating that vitamin D deficiencies might confer an increased risk of melanoma [48].

### 6.3 Types of Melanoma

The four main clinical types of melanoma are:

- **Lentigo maligna melanoma** (Fig. 6.3): This type of melanoma develops when an invasive tumor arises in a lentigo maligna. It is most common in the head and neck region and in elderly people, and has a relatively favorable prognosis.

- **Superficial spreading melanoma** (Fig. 6.4): This type of melanoma grows laterally before vertical invasion develops. Increasingly, this is the most common type of melanoma in Caucasians, and has a relatively favorable prognosis being frequently observed in young patients and on body sites that are intermittently exposed to sunlight. They generally have a better prognosis compared with other histological subtypes, because they usually have a thin Breslow thickness [62].

- **Nodular melanoma** (Fig. 6.5) usually presents as a rapidly growing pigmented nodule (amelanotic nodular melanomas are rarely observed), which bleeds or ulcerates. This is the most aggressive type of melanoma. It often presents on body sites that are intermittently exposed to sunlight.

- **Acral lentiginous melanomas** (Fig. 6.6) are pigmented lesions, which arise on the palm of the hand, sole of the foot, or under the nails (See also Chap. 9). They often present late and represent the most common type of melanoma in heavily pigmented people.
Fig. 6.4 (a) Superficial spreading melanoma. The lesion appeared a year before the diagnosis on the leg of a 37-year-old woman. (b) Dermatoscopic image of the same lesion. Courtesy of Dr. V. del Marmol, Belgium

Fig. 6.5 (a) Nodular melanoma on the chest of a young female patient. Courtesy of Dr. A. Patsatsi. (b) Nodular, amelanotic melanoma on the leg of an old male patient. Courtesy of Dr. V. del Marmol

Fig. 6.6 Acral lentiginous melanoma. (a) Melanoma on 5th toe with Breslow 2.7 mm, Clark IV. Courtesy of Dr. P. Souvatidis, Greece. (b) Melanoma on the nail of the 1st toe evolving more than 2 years. The patient had her nail taken out twice for “mycosis.” Notice the melanocytic lesion adjacent to the distal nail border; histology of both this lesion and the nail bed showed malignant melanoma
6.4 Clinical Diagnosis

Early recognition of melanoma presents the best opportunity for cure [63]. The objective of clinical diagnosis is, therefore, to identify melanomas as early in their evolution as possible (with a Breslow < 1 mm or even better melanomas in situ) because excision of these lesions has an excellent prognosis. Clinical diagnosis of melanoma is difficult and its accuracy may vary according to a clinician’s level of experience with reports of considerable variation in sensitivity from 50 to 86% and an inverse relationship between sensitivity and experience [64–66].

Melanoma may arise from a preexisting nevus (Fig. 6.7) or in unblemished skin. The proportion of melanomas arising in normal skin has been estimated to be from 30 to 70% [67]. Identification of a lesion suspicious for melanoma is performed by clinical examination of the patient’s skin. Skin examination should be performed in a well lit room and should include the whole of the patient’s mucocutaneous surface (including scalp, genital area, intertriginous areas, palms of hands, soles of feet, and the areas between fingers and toes and nail beds). This is best done with the patient completely undressed or with him wearing only a hospital robe. The elements to consider during the examination are the number, form and size of melanocytic lesions, their appearance, their topography, and their distribution. Every skin lesion suspicious for melanoma and every skin lesion susceptible to evolve into a melanoma can be, thus, identified.

6.4.1 Key Steps to Diagnosis of Melanoma

Step one: Taking a careful history and addressing risk factors of the patient associated with:

- Personal or family history of melanoma in a first degree relative (parent, sibling, or child)
- Personal history of another type of skin cancer
- Immunosuppression
- Presence of giant congenital nevus (diameter >20cm)
- Presence of many moles (>25 moderately increased risk, >100 greatly increased risk)
- Presence of >2 atypical naevi

Fig. 6.7 Melanoma arising on a preexisting naevus on a 34-year-old patient with many dysplastic naevi who was followed up regularly both clinically and dermatoscopically with the use of photographs. The melanoma developed in a 6-month period. (a) Previous examination. Notice slight increase of pigment on the border of dysplastic lesion numbered 4. (b) Examination 6 months after: the color on the border of lesion 4 has evolved, the histology showed an early melanoma, Breslow 0.65 mm, Clark II developing on a preexisting naevus. (c) Dermatoscopic image of lesion. Courtesy of Dr. V. del Marmol
Lifestyle and/or profession (people who have received frequently intense and intermittent sun exposure for professional or recreational reasons in countries with a lot of sunshine such as tropical or subtropical countries. For LMM also, people that work or have worked for many years outdoors such as farmers, fishermen, construction workers, etc.)

Sun sensitivity and inability to tan (phototypes I and II) and numerous previous sunburns at any age, especially in childhood

Red or blond hair, very fair skin, blue or green eyes

Presence of numerous freckles

Other elements to consider are the age of the patient and the reason that prompted this consultation such as the appearance of a new lesion in a patient over 40-years-old or a recent change in a preexisting lesion that has been observed over a period of some months. ‘Months’ is the key word to look for when a patient reports a change in a lesion. A very recent-occurring change over a period of few days or a couple of weeks is most probably due to something of an infectious or irritative nature that has caused inflammation such as a pyogenic granuloma or mechanic trauma of a mole. A change observed over years is also reassuring because it advocates for a benign lesion, especially when it is noted on a growing period such as the period of adolescence.

Step two: Physical examination, analysis of the patient’s melanocytic lesions, and factors influencing the decision to biopsy:

1. Different clinical approaches to the analysis of melanocytic lesions
   - The ABCDE rule

The ABCD rule was first described by Friedman et al. [68] in 1985 and latter modified to include E by Thomas et al. [69] in 1998. This list of features, easy to memorize and use, stands for A = asymmetry, B = borders, C = color, D = diameter, and E = evolution. The vast majority of early melanomas can be identified using this rule. Studies have found that the sensitivity of ABCD rule ranges from 90 to 100%, but the specificity is much lower [70]

So, most of melanomas (Figs. 6.8 and 6.9) have:

Asymmetry of pattern and asymmetry of shape.

Lesions cannot be divided in half and have one half mirror the other. This is clinically apparent with bright light and magnification; however, it is easier to assess using dermatoscopy.

Fig. 6.8 Early melanomas <1 mm. These lesions all presented with the ABCD criteria both clinically and dermatoscopically, with a history of Evolution. Courtesy of Dr. P. Souvatzidis, Greece

Border irregularity, notched borders, and borders resembling a “coastline” [67]. Borders can be often sharply demarcated which is a characteristic that differentiates melanoma from atypical naevi where
the border is typically ill-defined fading into the adjacent skin.

Color variability and irregularity. Most early melanomas have at least two different colors ranging from subtle nuances of browns to areas of black and sometimes red, grayish, or white areas (regression) to bluish areas (deeper pigment).

However, for Color, one has to bear in mind two points: (1) small nodular melanoma may be uniform of color and may have a shiny/glossy surface that the patient often describes as looking like a blood blister (Fig. 6.10) [67], (2) most amelanotic melanomas will present as the same color as normal skin or will be red or pink colored, and it will be the element of a recently growing lesion that will alert the physician (once again the timing to keep in mind is weeks to months – if it is days to weeks, it points to inflammatory lesions, and if it is years, it is most
probably benign). Sometimes an amelanotic melanoma may have some subtle pigmentation within the lesion, which helps the observer in making a diagnosis [71].

Maximum Diameter >6 mm: This is the least helpful of all the criteria as many benign lesions, including atypical naevi, will have a diameter more than 6 mm [67]. Furthermore, some studies have shown that a significant proportion of melanomas may be smaller than 6 mm. An Australian paper showed that 30% of melanomas in their study at diagnosis were <6 mm in size [72]. Another retrospective study examined the pathology reports of 383 melanomas [73]. In their series, a total of 38.21% of melanomas were less than or equal to 6 mm in diameter after processing. Melanomas greater than 6 mm in diameter occurred in significantly older patients and at a greater Breslow’s thickness than smaller melanomas. The ABCD criteria are not absolute; melanomas have many different appearances and start as small lesions, so it is important that even small skin lesions with atypical appearance be considered for biopsy.

Furthermore, as mentioned above, nodular melanomas could be overlooked using the ABCD rule as most of these lesions tend to be evenly colored, have smooth borders, and at their early stage, may be smaller than 6 mm; therefore, the added E criterion is a key point for melanoma diagnosis.

Evolution that emphasizes changes in color, shape, size, elevation, skin surface, and symptoms such as itching or bleeding of a lesion is a hallmark sign of malignancy. The health care professional should be attentive to any change in a lesion reported by the patient or his family as well as to the appearance of any new lesion on previously normal looking skin in a patient over 40-years old.

- The seven point checklist

This checklist is recommended for use for both patient and general practitioner education by the U.K. guidelines for the management of cutaneous melanoma [74]. It was described by MacKie in 1989 [75] and it emphasizes a history of change in size, shape, and color of a preexisting pigmented lesion (E point in ABCDE rule).

So, according to this list, major features are:

- Change in size
- Irregular shape
- Irregular color

and minor features are:

- Largest diameter 7 mm or more
- Inflammation
- Oozing/bleeding/crusting
- Change in sensation
- Lesions with any of the major features or three minor ones are suspicious of melanoma [75].

- Cognitive and Comparative procedure

Experienced practitioners use frequently this method of clinical diagnosis based on two complementary procedures: a sense of the overall pattern of a lesion and the so-called ugly-duckling sign. The ugly-duckling principle is based on the hypothesis that each person’s moles have a homogenous clinical aspect; therefore, in a patient any nevus that appears markedly different from the others should be considered suspicious for melanoma.

A prospective study done in France [76] was the first to survey 135 dermatologists concerning the criteria and the recognition process they use when examining a skin lesion and deciding upon its excision. More specifically, this study looked into how dermatologists identified which lesions were melanomas among a total of 4,036 melanocytic lesions. Interestingly the results of this work pointed out that dermatologists relied rather on the cognitive and comparative procedure than on the ABCDE algorithm.

2. Use of dermatoscopy in the detection of melanoma (See also Chap. 2)

Any clinician who deals with patients with pigmented skin lesions should consider acquiring a dermatoscope and training to use it. In most studies the diagnostic accuracy of melanoma has been shown to increase by the use of dermatoscopy [77]. Morphologic features of lesions that are otherwise not visible to the naked eye are observed with the use of this technique (see for more details Chap. 2). However, dermatoscopy improves the diagnostic accuracy for melanoma in comparison with naked eye inspection only for experienced examiners [78]. There is a study that even demonstrates that for nonexperienced users, dermatoscopy actually decreases the diagnostic accuracy [79]. In order to facilitate the diagnosis of melanoma, different diagnostic algorithms using dermatoscopic findings have been developed: pattern analysis, the ABCD rule of dermatoscopy, Menzies’ 11-point scoring method, and the 7-point checklist.
Experts during the Second Consensus Meeting on Dermoscopy compared these four different algorithms and concluded that they were all valid ways to evaluate pigmented lesions [80]

3. Differential diagnosis

The differential diagnosis of melanoma can be done either on the basis of clinical features alone or with the aid of dermatoscopy to improve the accuracy of diagnosis. The clinician has to be familiar with the aspect of common benign melanocytic lesions such as simple lentigos, junctional, compound nevus, and intradermal nevus. These lesions are generally uniformly pigmented and usually appear before the age of 40.

Common pigmented lesions that are relatively easy to differentiate from melanomas are seborrhoeic keratoses, hemangiomas, and dermatofibromas.

Seborrhoeic keratoses (Fig. 6.11) are very common lesions and should be easy to diagnose in the majority of cases. They have a superficial “stuck on” appearance and a slightly greasy feel to their surface. They usually have a dull or warty surface due to excessive keratinization and keratin pearls or horn cysts that can be viewed with the aid of a hand lens or a dermatoscope. Lesions that are resistant to cryotherapy should be examined attentively to rule out a possible melanoma.

The diagnosis of hemangioma is also usually not difficult. Their color is more often red to violet; they are well demarcated and have a smooth surface. Using a glass slide to apply pressure on these lesions, the blood is forced out of them and they blanch, with color returning back immediately once the pressure is removed. In cases of doubt, the diagnosis can be facilitated using a dermatoscope.

Dermatofibromas are common, asymptomatic to slightly itchy lesions appearing usually on the legs of women. They can be easily diagnosed by pinching the margins of the lesion between two fingers and seeing a depression or dimpling of the center of the lesion and feeling a palpable nodule (Fig. 6.12). As dermatofibromas may represent a fibrous reaction to trauma, a viral infection, or insect bite, there is often a history of an insect bite or a red itchy lesion that the patient has scratched for some time before it became hard and palpable.

Lesions that are more difficult to differentiate from melanoma are dysplastic naevi, Spitz naevi, pigmented basal cell carcinoma, blue naevi, and some rare adnexal tumors. The amelanotic melanoma differential diagnosis includes basal cell carcinoma and other spindle cell tumors.

History of these lesions and the expert use of dermatoscopy can facilitate diagnosis. Distinguishing clinically a dysplastic naevus from a melanoma can sometimes be impossible and even experts in dermatoscopy may occasionally be unable to make a diagnosis. Therefore, histologic evaluation is often required to make the distinction.

**Step three: Excision of suspicious lesions and histological examination**

A definitive diagnosis or an exclusion of melanoma requires an appropriate biopsy and experienced pathological analysis. Since a correlation exists between the prognosis of a patient with melanoma and the vertical
depth of the lesion (Breslow), an adequate specimen depth must be achieved regardless of biopsy technique; transecting a potential melanoma could result in the loss of important prognostic information. The optimal specimen for histological evaluation of a suspected melanoma is a complete excision with a 1–3 mm surrounding normal skin and extension to the subcutaneous fat. If the lesion is confirmed to be a melanoma, additional surgery can be performed to obtain surgical margins and, if indicated, it can be followed by sentinel lymph node biopsy.

Cutting out wider margins with the initial excision provides no advantage. On the contrary, wider margins (1 cm) may disrupt cutaneous lymphatic flow and affect the ability to identify the sentinel lymph node [81]. Also, some data show a decreased recurrence rate in patients who had surgical margins taken out with a second excision [82]. Nonexcisional biopsy as mentioned above may lead to inadequate histology. If, however, an incisional biopsy cannot be avoided either because the suspicious lesion is very large or because it is located in an anatomically sensitive area, it can be performed as it has been demonstrated that its use will have no effect on prognosis [83, 84].

The pathology requisition form should be filled in meticulously and contain adequate information on the specimen in order to obtain an optimal histologic diagnosis with good clinicopathologic correlation. A good mnemonic to use for filling in pathology forms is the essential 6 Ds [85, 86]: (1) demographics of patient (name, age, sex, race), (2) diseases and drugs of patient, (3) description of lesion (biopsy site, color and shape of lesion, symptoms, other areas of involvement, previous therapy, or previous biopsy on lesion site), (4) diameter of lesion, (5) duration of condition, and (6) differential diagnosis.

Criteria for the histological diagnosis of melanoma are based on architectural and cytologic features and need to be interpreted in the context of the clinical situation [87] (for more details on melanoma histology please see Chap. 3).

### 6.5 Staging

The TNM (tumor, node, metastasis) system is used for clinical staging of melanoma as designated by the American Joint Committee on Cancer (AJCC) staging system. The classification system was updated in 2002 by the AJCC [88].

This version (Tables 6.2 and 6.3) retains the anatomic compartmentalization, consistent with staging for other cancers, which categorizes patients with localized melanoma (i.e., without any evidence of metastases) to stages I and II, those with regional metastases to stage III, and those with distant metastases to stage IV.

The primary criteria for the T classification are tumor thickness measured in millimeters (Breslow classification) and the presence or absence of ulceration (determined histopathologically). These are also the most powerful predictors of survival, while the level of invasion (Clark classification) has a significant impact only within the subgroup of thin T1 (< or = 1 mm) melanomas [89].

Melanoma ulceration heralds such a high risk for metastases that its presence upstages the prognosis of all patients with ulcerated melanomas compared with patients who have melanomas of equivalent thickness without ulceration. The N category uses as criteria the number of metastatic lymph nodes rather than their gross dimensions and the delineation of clinically occult (i.e., microscopic) vs. clinically apparent (i.e., macroscopic) nodal metastases, while the site of distant metastases and the presence of elevated serum lactic dehydrogenase are used in the M category. A merging of satellite metastases around a primary melanoma and in-transit metastases into a single staging entity that is grouped into stage III disease is also introduced in this version. Finally, a new convention for defining clinical and pathologic staging has been introduced so as to take into account the staging information gained from intraoperative lymphatic mapping and sentinel node biopsy.

### 6.6 Prognosis

Melanoma thickness, body site, histological type of the melanoma, gender of the patient, stage at diagnosis, and ulceration are important indicators of patient prognosis (Table 6.4) [90]. By far the most important prognostic indicator of melanoma survival is stage at diagnosis, followed by thickness and ulceration. Females have a superior survival compared to males, regardless of their stage at diagnosis or Breslow thickness [5, 91]. Reports on prognosis usually come from specialized centers.
92 M. Trakatelli et al. resulting in the estimates for survival being lower than those estimated on the basis of population-based cancer registry data [5, 6, 92], possibly because mainly the patients with less favorable prognostic factors are the ones being referred to the specialized centers.

Table 6.2 TNM classification of melanoma

<table>
<thead>
<tr>
<th>T classification</th>
<th>Breslow thickness</th>
<th>Ulceration status</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>≤1.0 mm</td>
<td>a: no ulceration and level II or III</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: ulceration and level IV or V</td>
</tr>
<tr>
<td>T2</td>
<td>1.01–2.0 mm</td>
<td>a: no ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: ulceration</td>
</tr>
<tr>
<td>T3</td>
<td>2.01–4 mm</td>
<td>a: no ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: ulceration</td>
</tr>
<tr>
<td>T4</td>
<td>≥4 mm</td>
<td>a: no ulceration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b: ulceration</td>
</tr>
</tbody>
</table>

N classification

<table>
<thead>
<tr>
<th>No of metastatic nodes</th>
<th>Nodal Metastatic Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>1 node</td>
</tr>
<tr>
<td></td>
<td>a: micrometastasis^</td>
</tr>
<tr>
<td></td>
<td>b: macrometastasis^</td>
</tr>
<tr>
<td>N2</td>
<td>2–3 nodes</td>
</tr>
<tr>
<td></td>
<td>a: micrometastasis^</td>
</tr>
<tr>
<td></td>
<td>b: macrometastasis^</td>
</tr>
<tr>
<td></td>
<td>c: in-transit metastases or satellite lesions without metastatic lymph nodes</td>
</tr>
<tr>
<td>N3</td>
<td>Four or more metastatic nodes, or matted nodes, or in-transit combination of in-transit metastases/satellites or ulcerated melanoma and metastatic lymph nodes</td>
</tr>
</tbody>
</table>

M classification

<table>
<thead>
<tr>
<th>Site</th>
<th>Lactate dehydrogenase (LDH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal metastases</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Pulmonary metastases</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastases</td>
</tr>
<tr>
<td></td>
<td>Raised</td>
</tr>
</tbody>
</table>

^Micrometastasis are diagnosed after elective or sentinel lymphadenectomy
^Macrometastasis are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension

Table 6.3 Staging for cutaneous melanoma

<table>
<thead>
<tr>
<th>Clinical staging*</th>
<th>Pathologic staging^</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAGE</td>
<td>T</td>
</tr>
<tr>
<td>0</td>
<td>Tis</td>
</tr>
<tr>
<td>I</td>
<td>T1a</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
</tr>
<tr>
<td></td>
<td>T2a</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b</td>
</tr>
<tr>
<td></td>
<td>T3a</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3b</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
</tr>
<tr>
<td>IIIC</td>
<td>T4b</td>
</tr>
<tr>
<td>III</td>
<td>Any T</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>T1 – 4a</td>
</tr>
<tr>
<td>IIIB</td>
<td>T1 – 4b</td>
</tr>
<tr>
<td></td>
<td>T1 – 4a</td>
</tr>
<tr>
<td></td>
<td>T1 – 4a/b</td>
</tr>
<tr>
<td>IIIC</td>
<td>T1 – 4B</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
</tr>
</tbody>
</table>

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases
^Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic stage 0 or stage 1A patients are the exception; they do not require pathologic evaluation of their lymph nodes
^There are no stage III subgroups for clinical staging

Table 6.4 Prognostic indicators for melanoma

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Most favorable when:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breslow thickness</td>
<td>Thin (&lt;1.51 mm)</td>
</tr>
<tr>
<td>Histology</td>
<td>Superficial spreading melanoma</td>
</tr>
<tr>
<td>Age</td>
<td>Young</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
</tr>
<tr>
<td>Body site</td>
<td>Not on the trunk</td>
</tr>
<tr>
<td>Ulceration</td>
<td>Absent</td>
</tr>
<tr>
<td>Mitotic Activity Index</td>
<td>Low</td>
</tr>
</tbody>
</table>

[90], resulting in the estimates for survival being lower than those estimated on the basis of population-based cancer registry data [5, 6, 92], possibly because mainly the patients with less favorable prognostic factors are the ones being referred to the specialized centers.
Survival from melanoma is related to stage at diagnosis. The stage distribution is generally more favorable in high-resource settings, and thus, countries with high incidence rates tend to also have better survival than lower incidence (and lower resource) countries [16, 17, 22, 93].

In high incidence countries, most melanomas are discovered at localized stages (cases diagnosed in the U.S. SEER program 1996–2003, 82% had localized disease, 11% regional disease, 3% distant disease, and 3% were unstaged), and the proportion of localized melanomas continues to increase with time [20].

Young patients and women are often diagnosed with melanomas that have a thinner Breslow thickness than older patients and men [20]. Because of the shift in the stage distribution of melanomas toward thinner lesions, together with a disproportionate increase in incidence relative to mortality, some have questioned whether some of these thin lesions that were removed would have ever progressed to metastatic disease [94, 95].

6.7 Management of Melanoma

6.7.1 Surgical Excision of Primary Melanoma

Proper surgical excision of an early stage primary melanoma is the best case scenario in the treatment of this aggressive cancer. Indeed, surgery plays a major role in the treatment of melanoma and the proper surgical treatment of this tumor was a major topic of discussion for many years.

In the early 1970s, the prevailing view on the appropriate treatment of cutaneous melanoma was the wide (5 cm) excision of the primary lesion. This attitude was established in an era when evidence-based medicine had not evolved and it was only a matter of time that this “dogma” of the 5 cm margin would be revised based on well-designed randomized trials. A number of randomized trials have since been performed that have investigated the relevance of width of excision. Four trials involved patients with thin/intermediate melanomas (<2 mm) and compared margins of 1 vs. 3 cm (WHO-ten Trial [96, 97]) and 2 vs. 5 cm (French [98] and Swedish [99] Melanoma Study Group trials). A US Intergroup Trial [100, 101] randomized patients with 1–4 mm melanomas to undergo an excision of 2 or 4 cm. The results from all these trials were consistent in that local recurrence rates, disease-free survival (DFS), and overall survival (OS) were virtually identical irrespective of the width of excision.

The lack of impact of width of excision on efficacy also applies to thick melanomas. A large nonrandomized study suggested that a 2 cm excision margin was safe in patients with primaries thicker than 4 mm [102] and this has now been confirmed by the results of a large randomized trial from Scandinavia [103]. The study involved 936 patients with melanomas thicker than 2, and 2 cm vs. 4 cm margins of excision were compared. There were no significant differences in locoregional recurrences, DFS, or OS between the treatment arms.

There is one large randomized trial that has given slightly discordant results. The UK Melanoma Study Group [104] compared excision margins of 1 vs. 3 cm in 900 patients with melanomas >2 mm thick. Outcome was inferior in the 1 cm arm with significantly more locoregional metastases (local, in transit, regional lymph nodes; Hazard Ratio, HR = 1.26, p = 0.05) and a trend for worse DFS (HR = 1.21, p = 0.06). However, no differences in OS were observed (HR 1.07, p = 0.6). The Scandinavian trial results avoid the argument to go to 3 cm margins, since it demonstrates that 2 cm margins are as good as 4 cm margins.

As a result of these well-designed trials, it can be concluded that a 1 cm margin is adequate for melanomas <2 mm thick and a 2 cm margin is safe for those with primary melanomas thicker than 2 mm. Indeed this attitude is the proposed surgical treatment in modern surgical practice as it is adapted by most published melanoma guidelines and consensus comities.

6.7.2 Surgery Beyond the Primary Lesion

6.7.2.1 Elective Lymph Node Dissection

Melanoma metastasizes by hematogenous and lymphatic spread and these two mechanisms of metastasis often take affect simultaneously. This observation leads many surgeons to “sample” lymph nodes in order to assess whether the primary lesion had already spread
via the lymphatic channels, offering a more accurate staging for the patient. Lymph node harvest by means of elective lymph node dissection was used as a “sampling” surgical staging technique. However, when this attitude went under the study of evidence-based medicine, no proof of clear benefit was demonstrated.

Four randomized trials have evaluated the role of elective (immediate) regional lymph node dissection (ELND) in relation to survival [105–108]. None of these four trials demonstrated a survival benefit for ELND, and as a result, ELND was largely abandoned. However, in one of these trials (WHO-14), a subset analysis suggested that in patients with thick truncal melanomas and micrometastases in the dissected ELND specimen, there was a survival advantage for ELND compared to delayed dissection following clinically diagnosed relapse in the regional lymph nodes [108]. These data supported the concept of sentinel lymph node biopsy as a sampling method that would detect lymphatic spread and allow surgeons to select the patient subpopulation that presented with proven lymphatic spread and would clearly benefit from an elective lymph node dissection.

### 6.7.2.2 Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy is a surgical staging technique based on the hypothesis that lymphatic spread of a primary melanoma will occur in an orderly “anatomical” fashion and that neoplastic cells will be trapped in the first relative lymph node draining the area of the primary lesion, celling the sentinel lymph node. However, the fact that malignant melanoma may metastasize simultaneously by hematogenous spread renders the sentinel lymph node biopsy technique a staging technique rather than a curative one, which helps establish a more accurate prognosis for the patient and evaluate the necessity for adjuvant surgical or medical treatment. There is good evidence to support the orderly progression of metastases at the regional lymph node basin level, and sentinel node (SN) status is the most powerful prognostic factor in melanoma patients. Studies have demonstrated 5-year survival rates of 93–89% for SN-negative patients and 67–64% for those with evidence of melanoma their SN biopsy specimen [109–112]. Despite this evidence, it is still a matter of controversy whether sentinel lymph node biopsy by itself has an impact on survival. Even though it appears that sentinel node biopsy does not seem to increase survival, more reliable bibliographic evidence is needed in order to clearly and unequivocally answer this question.

Sentinel node biopsy-positive patients represent a heterogeneous group with a range of outcomes ranging from relatively good to very bad and this observation provoked the curiosity of researchers: Is there a detectable criterion within the positive lymph node that can help us determine prognosis? Van Akkooi and colleagues recently published a series of patients from the ErasmusMC-Daniel den Hoed Cancer Center SN biopsy database [113]. They grouped SN biopsy-positive patients according to the diameter of the clusters of tumor cells within the infiltrated lymph node (< 0.1, 0.1–1, >1 mm). At a median follow-up of >3 years, SN biopsy-positive patients had the following distant metastatic event rates according to this scoring system: <0.1 mm, 6%; 0.1–1 mm, 37%; >1 mm, 71%; p <0.002. This translated into statistically significant difference in estimated 5-year survival of 94, 73, and 59%, respectively (p < 0.04). The 6% distant metastatic event rate in the group with a minimal tumor burden was lower than that seen in the SN biopsy-negative patient population in the Rotterdam SN-data base and the survival of these two groups reflects this; patients in the minimal tumor burden had a better 5-year survival than the SN biopsy-negative patients, although this was not statistically significant. It is also of interest to note that not a single patient in the minimal tumor burden group had additional positive nodes identified in their complete lymph node dissection (CLND), in contrast to a 30% positivity rate in the CLND specimens from patients with 0.1–1 mm or >1 mm diameter micrometastases. Therefore, not only is there an identifiable group of SN biopsy-positive patients who have an excellent prognosis, but they probably should be spared a CLND. These findings have now been confirmed by reclassifying all positive sentinel nodes in the large data sets of Rotterdam, Berlin, and Warsaw [114]. These results question the claim of the MLST-1 report that a survival benefit for SN biopsy-positive patients exists, when one realizes that 22% of SN biopsy-positive patients in the Rotterdam database are in the minimal tumor burden (very good prognosis) group. How many patients belonged to this category in the MLST-1 study? The Rotterdam database shows further that SN biopsy-positive patients and total lymph node
dissection-treated patients in the Rotterdam databases have very similar overall survival rates [115].

Recently, advanced ultrasound techniques showed an impressive capability of positive sentinel node detection. This technique, combined by fine needle aspiration biopsy, may be a useful alternative to surgery as it could reduce the rates of unnecessary operations for sentinel lymph node removal, preserving at the same time the capability of early detection of a positive lymph node.

### 6.7.2.3 Therapeutic Isolated Limb Perfusion

Therapeutic isolated limb perfusion is a technique used in many specialized centers for the treatment of multiple in-transit metastases with encouraging results. When the combination of Melphalan and TNF- alpha is used, complete remission rates of up to 70% of patients are reported. In contrast to the therapeutic isolated limb perfusion, prophylactic isolated lymph perfusion for the treatment of melanoma as an adjunct to the surgical management of patients at high risk of relapse is now considered obsolete and has no place in the treatment of melanoma.

### 6.7.3 Systemic Adjuvant Therapies

The risk of recurrence of melanoma is increased in thick primary melanomas and when there is lymph node involvement at diagnosis. Therefore, there is a need for these high-risk patients of an additional therapy that would eradicate possible clinically undetectable micrometastases present at the time of primary surgical excision.

#### 6.7.3.1 Chemotherapy, Nonspecific Immune Stimulants, and Vaccines

The lack of effective drugs in stage IV disease is reflected by a lack of effective adjuvant therapies in stage II–III melanoma; since up to now, chemotherapy, immunostimulants, and vaccines have all failed to produce the desired impact.

At least 25 randomized trials have been conducted in Stage II–III melanoma patients evaluating chemotherapy, nonspecific immune stimulants such as BCG (Bacillus Calmette–Guerin), C. parvum (Corynebacterium parvum), levamisole, or combinations of these agents with dacarbazine. These trials were almost invariably underpowered and yielded negative results with the exception of the occasional incidental nonrepeatable positive finding in trials involving small numbers of patients [116].

Not one among seven large randomized trials studying allogeneic melanoma cell-based vaccines has demonstrated a significant impact on survival. The only trial that came close to demonstrating a benefit for treatment was an Australian one investigating an allogeneic tumor cell-based oncolysate [117]. A trial of the Melacine vaccine conducted in the USA in Stage II patients showed no benefit for the total study population [118], but there appeared to be some activity in patients with particular HLA-types [119]. Unfortunately there was no consequent prospective study using this vaccine in patients with the relevant HLA-types. The two large randomized trials of an allogeneic tumor cell-based vaccine “Canvaxin” in patients with Stage III and resected Stage IV disease had negative results. Patients in the vaccine arms of these trials had worse outcomes than those in the control arms [120].

An EORTC large phase III adjuvant trial of ganglioside GM2 in patients with Stage II disease (18,961) including 1,318 patients of whom approximately 50% were staged by SN biopsy showed at the second interim analysis in 2007 that there was a detrimental outcome in the vaccine arm for survival and this led to early stopping of the trial.

#### 6.7.3.2 Interferon

Interferon (IFN) is presently the only agent to consider for adjuvant therapy as it has a consistent effect on relapse-free survival without, however, a significant overall survival (OS) benefit. Its impact is judged by many too small to be considered standard of care. This is also reflected in clinical practice in Europe where there are clear regional differences in the adjuvant use of IFN. In northwest Europe, IFN is hardly prescribed. In central and southern Europe, low dose IFN therapy is commonly prescribed for both Stage II and III melanoma. High dose IFN therapy, though approved by both the USA FDA and the European EMEA for
patients with high-risk melanoma (Stage IIB–III) and used in the USA, is used only in a few European centers because there is doubt on its impacts on OS to justify the toxicity and costs [116, 121]. High dose regimens are sparsely used in Europe, but only in stage III patients.

Results of Different Treatment Regimens with IFN in Adjuvant Setting

The only adjuvant therapy for high-risk melanoma currently approved by the USA FDA is IFN alfa 2b given at high dose (20 million U/m² for 5 days) for 1 month, followed by a lower dose (10 million U/m² three times weekly) for 11 months. Of interest is the communication by Gogas and colleagues, who demonstrated that 4 weeks of high dose IFN iv is as good as this classical ECOG1684 1 year schedule and much better tolerated [122]. Intermediate doses of IFN were tested in the largest phase III trial to date that involved patients with Stage IIB–III disease (EORTC18952). The results demonstrated a nonstatistically significant 7.2 % increase in distant metastasis-free interval and a 5.4% increase in OS at 4.65 years of follow up. However, this benefit was only in patients treated for 25 months with 5MU; there was no effect in patients treated for 13 months at a dose of 10MU [123]. The results suggested that the duration of therapy may be more important than the dose.

The question of treatment duration was addressed in the next EORTC trial (18,991) in which patients were randomized to 5 years of Pegylated IFN α-2b (PEG-IFN) or observation. In this trial the dosing schedule was comparable to the high-dose IFN. The PEG-IFN were tested in the largest phase III trial to date that involved patients with Stage IIB–III disease (EORTC18952). The results demonstrated a nonstatistically significant 7.2 % increase in distant metastasis-free interval and a 5.4% increase in OS at 4.65 years of follow up. However, this benefit was only in patients treated for 25 months with 5MU; there was no effect in patients treated for 13 months at a dose of 10MU [123]. The results suggested that the duration of therapy may be more important than the dose.

A systematic review of all trials [125], a metaanalysis of all trials [126] and a pooled data analysis of all high dose IFN trials [127], demonstrated a consistent DFS improvement, but no statistically significant impact on OS. Of interest is an individual patient data-based metaanalysis [128] that confirms the consistently reported statistically significant benefit on DFS and also shows for the first time, a definite, statistically significant impact on OS. However, not only this impact is a small 3% absolute improvement, but also it is partly due to the inclusion of trials that have the ganglioside GM2 vaccine as comparator arm. (The validity of inclusion of ganglioside trials in the analysis has become very doubtful since the EORTC 18961 GM2 study as mentioned above was stopped because of a detrimental effect in the vaccination arm). Another interesting point of this individual patient data-based metaanalysis is that the benefits of IFN are observed across a wide range of IFN doses, and thus, are not clearly dose related.

In stage II, low dose IFN therapy has been particularly successful; a consistent and significant effect on DFS was observed in the French [129], Austrian [130], and Scottish [131] studies with even a borderline significant effect on survival in the French trial. Low-dose IFN therapy was approved as an adjuvant therapy for Stage II patients by the EMEA in Europe, while being rejected for this indication by the FDA in the USA. Metaanalysis confirms an impact on DFS, but no significant impact on OS for low-dose IFN. The quite significant impact of IFN in stage II patient trials at the time when these patients were not SN-staged corresponds very well with the observations in the EORTC18952 and 18991 trials where the best benefit was observed in patients with positive sentinel nodes.
Biomarkers as Predictors of Response to IFN Therapy

The population of patients that can benefit from IFN needs to be identified in order to optimally use this treatment option. The development of markers that might predict who will mount a host immune response could, therefore, be extremely important. Such markers could be used to define which patients to treat with IFN and for how long.

The observation that autoimmunity is associated with clinical benefits such as higher response rates and longer DFS and OS has been made since many years. This association was not only observed in patients treated with immunotherapy, but also in those given chemotherapy and sometimes in patients that did not receive any treatment at all.

One study has reported that patients who developed autoantibodies against thyroglobulin, antinuclear factors, or cardiolipin when treated with adjuvant IFN had a significantly better outcome than patients that did not develop these signs of autoimmunity [132]. An evaluation of the presence or emergence of autoantibodies in patients who participated in the EORTC adjuvant IFN intermediate dose trial (18952) did not confirm these observations [133]. Also a study in the ECOG2696 could not confirm autoantibodies as a strong independent prognostic factor [134], nor did antibodies have any prognostic value in the EORTC1899 pegylated IFN trial in stage III melanoma [135].

In contrast, the serial determination of serum S100 levels was demonstrated to be a very powerful prognostic factor in an analysis of the EORTC18952 trial on intermediate doses of IFN in stage IIB–III patients, and its prognostic value was even superior to the number of positive regional lymph nodes [136].

6.7.3.3 Emerging Therapies in the Adjuvant Setting

Novel targeted agents, antiangiogenics, and immune modulators are actively being investigated in the Stage IV setting and some, such as bevacizumab and anti-CTLA4, are already being considered as potential adjuvant therapies. Adjuvant trials of bevacizumab and anti-CTLA4 (EORTC18071) will commence in 2007/2008 and results will not be known before 2011. Pegylated IFN will also be explored by EORTC (EORTC18081) in high-risk stage II patients.

6.8 Metastatic Melanoma

Metastatic melanoma is one of the most dreaded human diseases. Patients with stage IV melanoma have a median survival of 6–9 months and a 5-year survival of only 1–2% [137]. Many of these patients are young (median age ~50 years) and otherwise healthy. Melanoma ranks in the United States second among solid tumors in terms of years of productive life lost, even though it is only the ninth most common cancer.

The aggressiveness of melanoma is associated with its propensity to metastasize many organs and body parts and with its relative resistance to traditional therapies such as chemotherapy and radiation therapy. Autopsy findings show that melanoma tends to metastasize to many major organ systems simultaneously. The most common sites of metastasis are the lung, liver, brain, and lymph nodes. However, essentially every visceral site may be involved, including the gastrointestinal and genitourinary tracts, bones, heart, pleura, adrenal glands, spleen, pancreas, thyroid, ovaries, and prostate. Ocular melanoma tends to metastasize specifically to the liver first. The site of metastasis is an important prognostic factor. Patients with subcutaneous and lymph node metastases have the best median survival that approaches 11 months, patients with pulmonary metastases have a median survival of 8–10 months, and patients with central nervous system (CNS) and hepatic involvement have a median survival of 2–4 months.

Symptoms associated with metastatic melanoma depend on the sites of involvement. They may include mental status changes, focal neurologic deficits or seizures from CNS metastases, pain from local masses, gastrointestinal bleeding from small bowel involvement, or generalized symptoms such as weight loss and anorexia. Melanosis is a diffuse slate-gray coloring of the skin that may develop in patients with metastatic melanoma. It is thought to result from the uptake of melanin by dermal macrophages. In conclusion, any new symptom in a patient with a history of cutaneous melanoma should be thoroughly worked up given the variable presentation of metastatic melanoma.

Staging for metastatic melanoma should always include the head. Therefore, a brain MRI is recommended in addition to a CT scan of the chest, abdomen, and pelvis. Further staging should be based upon patients’ symptoms such as a bone scan in the case of
bone pain or a small bowel follow-through in the case of gastrointestinal bleeding. Positron emission tomography (PET) scanning using fluorine-18 deoxyglucose has shown very promising results in the detection of melanoma metastases [138] and may in the near future replace CT scanning in this setting. For the time being it should be used as a complementary tool to CT scanning, especially in cases where the detection of occult metastases is of clinical importance such as in the evaluation of a patient with limited disease for surgical resection.

Metastatic melanoma is not considered curable even though long-term responses to immunotherapy and spontaneous regressions have been observed. Progression of disease may be rapid or remain relatively stable for a prolonged period. Treatment also depends on the sites of involvement and the patient’s performance status. Therapies include surgical excision, radiation therapy, chemotherapy, immunotherapy, and experimental approaches. Therefore, a multimodality approach should be undertaken in patients with metastatic melanoma. A treatment algorithm is presented in Table 6.5.

### 6.8.1 Brain Metastases

Brain metastases are unfortunately frequent in melanoma. They are the cause of death in 20–54% of patients with stage IV melanoma [139] and can affect their expected survival and quality of remaining life more than any other site of metastasis. Therefore, treatment of brain metastases should take priority over treatment of any other metastatic disease.

Most patients present with symptoms of increased intracranial pressure (such as headache or nausea and vomiting), mental status changes, focal neurologic symptoms, or seizures. Melanoma brain metastases tend to frequently bleed.

The prognosis for patients with melanoma brain metastases is typically poor with a reported median survival of about 4 months [140]. There is, however, a subgroup of patients who can survive much longer with aggressive treatment. These patients usually have a good performance status, no extracranial disease, and a single brain metastasis.

Surgical resection is the preferred mode of action in patients with a single or a limited number of surgically accessible lesions, no or small extracranial disease, and a good performance status [141–143].

Recently stereotactic radiosurgery (SRS) has emerged as an alternative to surgery [144–146]. SRS uses multiple convergent radiation beams in order to deliver high radiation doses to a small volume. It can be used in patients with a single or a small number (up to six) of cerebral metastases. Its efficacy has not been compared to surgery in a randomized setting, but its advantages are that it is noninvasive and can provide easier access to lesions in anatomically difficult areas.

### Table 6.5 Treatment algorithm for the initial management of metastatic melanoma

<table>
<thead>
<tr>
<th>Staging</th>
<th>Brain mets? (Yes)</th>
<th>Limited subcutaneous or nodal disease (No)</th>
<th>Young patient with good performance status (Yes)</th>
<th>Chemotherapy with Temozolamide</th>
<th>Neurosurgery or SRS and / or WBI</th>
<th>consideration for surgical excision</th>
<th>consideration for high dose IL-2</th>
</tr>
</thead>
</table>
Whole brain irradiation is used in the adjuvant setting after the removal of the metastases by surgery or SRS in order to eliminate any residual microscopic disease [147]. It is also used as the primary treatment in patients with multiple metastases or a poor performance status. The most commonly used regimen is a total dose of 30 Gy in 10 daily fractions of 3 Gy [148]. Patients with more favorable prognosis may be treated with prolonged fractionation in order to decrease the likelihood of late CNS toxicity and receive a higher total dose in smaller fractions.

### 6.8.2 Surgery

Most patients with metastatic melanoma have widespread metastases [149]. There is, however, a subset of patients for whom surgical resection of a metastatic site should be considered. Even after proper patient selection with detailed staging, excision of metastatic disease is very rarely curative, but can prevent morbidity from local tumor growth and may extend the survival.

The patients most likely to benefit from a surgical approach are the ones with a solitary metastasis in the skin or subcutaneous tissue or in distal lymph nodes. Careful surgical excision with negative margins in such patients results in 5-year survival up to 33% [150]. Patients with visceral metastases generally have a poorer prognosis and are not as amenable to surgical treatment. There is a subset of patients, however, with a single visceral metastasis (e.g., in the lung, liver, or gastrointestinal tract) and a good performance status for whom surgical resection should be considered.

### 6.8.3 Radiation Therapy

Early clinical studies and in vitro observations suggested that melanoma was a radioresistant disease. Newer studies have challenged this concept and external beam radiation has become an important therapeutic component in the treatment of metastatic melanoma, especially in patients with brain and bone metastases.

The best mode of delivery of radiation therapy in patients with metastatic melanoma has not been defined yet. Some studies suggest that doses above 4 Gy should be used and that these larger than conventional fraction sizes are associated with a higher likelihood of response [151]. These data have been challenged by other studies including a phase III prospective randomized trial [152]. It seems that the fraction size may be more important for visceral metastatic sites than for sites in the brain or bones, but definite data are lacking.

Nevertheless, radiation therapy can provide very effective palliation in up to 50% of patients with unresectable metastatic disease producing pain, hemorrhage, spinal cord compression, or neurologic compromise.

### 6.8.4 Immunotherapy

The immunogenicity of melanoma has been an observation for over a century now. Spontaneous regressions do occur and the presence of tumor infiltrating lymphocytes (TIL) in the primary tumor seems to protect patients from metastases [153]. These observations combined with the fact that metastatic melanoma is relatively resistant to chemotherapy have led investigators to try biologic immunomodulatory therapeutic approaches.

IFN alpha was the first recombinant cytokine that was tested in patients with metastatic melanoma. IFN alpha yields a response rate of about 16% with about one-third of those responses being complete [154]. The effective dose of IFN alpha in this setting ranges from 10 to 50 million units/m² three times a week. A pegylated form of IFN alpha may be administered once a week and has similar efficacy [155].

Interleukin (IL) 2 has produced the best results today of all biologic therapies. IL-2 was first isolated as a T cell growth factor. Recombinant IL-2 was shown to have potent immunostimulatory and antitumor effects in a number of murine tumor models in a dose-dependent fashion [156]. This led to the design of clinical studies utilizing high-dose IL-2 in metastatic melanoma. High-dose IL-2 is given at 600,000–720,000 IU/kg IV every 8 h on days 1–5 and 15–19 with a maximum of 28 doses per course. This regimen resulted in tumor responses in about 15–20% of patients with about 5% achieving a complete response [157, 158]. Even though the absolute number of responders is small, some patients may have a durable response. This observation has led the Food and Drug Administration in 1998 to approve IL-2 for the
treatment of patients with unresectable metastatic melanoma. Indeed a full analysis of 270 patients treated with high-dose IL-2 between 1985 and 1993 showed that the median duration of response for complete responders has not been reached yet [159]. In this series the responders were 16% (10 partial and 6% complete) with a median duration of response 9 months (4–106+ months), and most importantly, the disease did not progress in any patient responding for more than 30 months. These results suggest that a small minority of patients with metastatic melanoma may be cured with high-dose IL-2.

A major obstacle in the implementation of IL-2 has been its toxicity. High-dose IL-2 induces a sepsis-like syndrome. Severe hypotension, fever, chills, nausea, vomiting, diarrhea, and mental status changes are common. More serious side effects include the capillary leak syndrome, cardiac ischemia and arrhythmia, pulmonary edema, respiratory distress, shock, coma, and death. Central catheter-related and other infections also contribute to the toxicity of IL-2. Therefore, high-dose IL-2 should only be administered by experienced clinicians at centers with an intensive care unit. Efforts to reduce the toxicity of high-dose IL-2 by administering lower doses or a continuous infusion or a combination with other cytokines and/or chemotherapy have been made, but have not produced as good results as high-dose IL-2.

Recent studies have tried to explain why high-dose IL-2 is so effective in a small minority of patients but does not exert any effect in most patients. Advanced melanoma is associated with the presence of regulatory T cells that are thought to produce tumor immune tolerance [160]. In vivo survival of the CD4+CD25+ regulatory T cells seems to depend on signaling through the IL-2 receptor and promoted by the administration of IL-2. Therefore, high-dose IL-2 should only be administered by experienced clinicians at centers with an intensive care unit. Efforts to reduce the toxicity of high-dose IL-2 by administering lower doses or a continuous infusion or a combination with other cytokines and/or chemotherapy have been made, but have not produced as good results as high-dose IL-2.

Based on early animal studies, high doses of IL-2 were initially combined with IL-2 activated peripheral blood lymphocytes (LAK cells). This approach was abandoned when it was shown that the addition of LAK cells did not add anything to the effectiveness of high-dose IL-2 [161].

Animal studies of effector cells derived from TIL showed marked antitumor efficacy [162]. Some promising studies have combined high-dose IL-2 with TILs and nonmyeloablative chemotherapy to promote engraftment of tumor-reactive lymphocytes. In one study, 6 out of 13 patients responded to this approach [163]. In a larger study involving 35 patients with metastatic melanoma, all but one with disease refractory to treatment with high-dose IL-2 and many with progressive disease after chemotherapy, there were 18 responses (51%) including three ongoing complete responses [164]. These results are very promising, but wider use of this technique has been limited by its technical difficulty.

IL-2 has been tried in combination with IFN alpha based on preclinical data suggesting that IFN alpha upregulates histocompatibility and tumor-associated antigens on tumor cells, thereby increasing their susceptibility to IL-2 activated T cells. In clinical studies the combination, however, was not very effective [165]. More promising results were demonstrated in a study where a “decrescendo,” less toxic regimen of IL-2 was used [166], but a second study with the decrescendo schedule of IL-2 in combination with IFN alpha did not show a high degree of benefit [167].

Other cytokines that have been tested in metastatic melanoma with disappointing results include TNF alpha, IFN gamma, IL-4, and IL-6 [168, 169]. IL-12 and IL-21 have shown some activity in phase I trials, but more mature data are lacking [170, 171]. Studies of IL-15 and IL-21 are under way.

### 6.8.5 Single-Agent Chemotherapy

The alkylating agent dacarbazine (DTIC) is the only chemotherapy drug approved by the US Food and Drug Administration for the treatment of metastatic melanoma. Typical administration schedules for dacarbazine are 200 mg/m² daily for 5 days or 850 mg to 1000 mg/m² every 2–4 weeks. It is generally well tolerated causing modest bone marrow suppression and only minimal alopecia and fatigue. Nausea and vomiting are not very common with modern antiemetics. Dacarbazine is not as effective as we would like it to be. The response rate is around 16%, most of the responses are partial and last only 4–6 months, and only 2% of the responders are expected to be alive at 5 years [172, 173].

Temozolomide is an analog of dacarbazine. It is usually given orally at 200 mg/m² per day for 5 days
every 4 weeks. It can cause alopecia, fatigue, nausea, vomiting, and myelosuppression. In addition to its more convenient route of administration, it has the major advantage of being able to cross the blood–brain barrier. It could, therefore, in theory be more useful than dacarbazine in the treatment of patients with metastatic melanoma who frequently metastasize to the brain. Temozolomide was compared to dacarbazine in a phase III trial in patients with metastatic melanoma without brain metastases [174]. The response rate was 13.5 and 12.1% in the temozolomide and dacarbazine groups, respectively, and the median survival was slightly better in the temozolomide group, but the difference did not reach statistical significance (7.7 vs. 6.4 months). It is, therefore, fair to say that temozolomide has a similar efficacy and toxicity profile to DTIC and can be considered as an orally available alternative to DTIC in patients with metastatic melanoma.

The combination of temozolomide and thalidomide has been studied and seems to be feasible and active [175, 176], but phase III data regarding its activity compared to single-agent therapy are lacking. Temozolomide has also been studied in combination schedules with immunotherapy. Single-agent temozolomide was compared with temozolomide combined with INF gamma in a phase III trial [177]. The response rate was higher in the combination arm, but no differences in the overall survival were noted and there was greater hematologic toxicity with the combination.

Temozolomide has also been used in combination with radiation therapy as treatment for metastatic disease to the brain.

The platinum analogs cisplatin and carboplatin, the nitrosoureas carmustine (BCNU), lomustine (CCNU), semustine (methyl CCNU), fotemustine, the vinca alkaloids vinblastine and vindesine and the taxanes docetaxel, and paclitaxel are other chemotherapeutic agents that have shown single agent activity in metastatic melanoma with response rates ranging in the 10–20% range [178]. Nevertheless, these agents can be used in second-line treatment.

### 6.8.6 Combination Chemotherapy

A number of cytotoxic chemotherapy combination schemes have been used in metastatic melanoma such as the “Dartmouth regimen” (CDBT- cisplatin, dacarbazine, carmustine and tamoxifen) and CVD (cisplatin, vinblastine, and dacarbazine) [174, 179–182]. These combination schedules provoked great enthusiasm at first when in small phase II trials, response rates up to 50% were reported. No combination regimen, however, managed to produce an improved overall survival compared to single-agent dacarbazine in a randomized trial. In a multicenter phase III trial involving 240 patients with stage IV melanoma, there was no difference in survival time and only a small nonsignificant increase in tumor response for patients treated with the Dartmouth regimen compared to dacarbazine [183]. In addition, these combination schedules are very toxic. Therefore, treatment with single-agent dacarbazine or temozolomide should be preferred over combination chemotherapy unless in the setting of a clinical trial.

### 6.8.7 Hormonal Therapy

The presence of estrogen receptors in melanoma tumor cells and in benign naevi from melanoma patients suggested a pathogenic role for estrogen hormones in melanoma [184]. In addition, cases have been reported of melanoma regression following parturition or melanoma dissemination during pregnancy [185]. Tamoxifen has been studied as a single agent in metastatic melanoma, but it has limited if any activity [186]. It is not clear whether the inclusion of tamoxifen in the “Dartmouth regimen” [187] added anything to its effectiveness. One study suggested that dacarbazine plus tamoxifen is more effective than dacarbazine alone [187], but more recent phase III data failed to demonstrate any benefit from the addition of tamoxifen to cytotoxic chemotherapy [188]. Therefore, hormonal therapy is currently not routinely used in the treatment of metastatic melanoma.

### 6.8.8 Biochemotherapy

IFN alpha and IL-2 have been tested in combination with cytotoxic chemotherapy in patients with metastatic melanoma. In two large phase III trials, IFN did not increase overall survival when added to cytotoxic chemotherapy, but significantly increased toxicity [189, 190].
IL-2 has been tried in combination with dacarbazine, the most active cytotoxic agent in this disease [191, 192], but the response rate was only 13–33% albeit at significant toxicity. No benefit for biochemotherapy was shown in five published phase III trials: IFN and IL-2 with or without cisplatin [193], cisplatin, dacarbazine, and tamoxifen with or without IFN and IL-2 [194], cisplatin and dacarbazine with or without IFN and IL-2 [195], cisplatin, dacarbazine, and IFN with or without IL-2 [196], and cisplatin, vindesine, and dacarbazine with or without IL-2 and IFN [197]. The only marginally positive results were shown in a phase III study investigating cisplatin, vinblastine, and dacarbazine with or without IL-2 and IFN [198], but were not seen in the similarly designed Intergroup trial E3695 [199]. Taken together, these studies suggest that the combination of chemotherapy and immunotherapy results in greater toxicity, but no significant clinical benefit. Perhaps the use of chemotherapy limits the ability to give IL-2 at a high dose and the effect of IL-2 seems to be dose dependent.

6.8.9 Experimental Immunotherapy Approaches

Monoclonal antibodies targeting melanoma tumor antigens have been investigated. Most antibodies have targeted the gangliosides GD2 and GD3, which are upregulated upon malignant transformation [200]. Monoclonal antibodies have been given either alone or in combination with immunomodulatory cytokines or conjugated to cytokines, radionuclides, and immunotoxins [201]. So far no clinically meaningful benefit has been demonstrated with monoclonal antibodies, but further studies are ongoing.

The observation that patients with metastatic melanoma may harbor in their blood antibodies that recognize and bind to the malignant cells has led to the experimental development of vaccines. These vaccines are usually produced from whole melanoma cells or melanoma cell extracts [202]. Responses have been observed mainly in phase I trials, but not confirmed in larger numbers of patients, and recently a phase III trial evaluating the Canvaxin whole-cell vaccine in metastatic melanoma was halted because of a low likelihood of significant benefit [203].

Cytotoxic T cells (CTLs) seem to play a major role in antitumor immunity. CTLs recognize peptide fragments expressed on the surface of Antigen Presenting Cells (APCs) in the context of MHC (Major histocompatibility complex) presentation. T cell antigens have been identified in patients with melanoma and belong to three categories: cancer/testis-specific antigens (e.g., MAGE), melanocyte differentiation antigens (e.g., tyrosinase, MART-1, gp100), and mutated or aberrantly expressed antigens (e.g., MUM-1, CDK4, beta-catenin). Some of these antigens have been in use as components of various vaccines [204]. Vaccines have been constructed by pulsing dendritic cells with tumor antigens, using DNA fragments that encode a tumor antigen or combing tumor antigens with autologous heat shock protein. So far there are no solid phase III data supporting the use of vaccines in patients with metastatic melanoma, but early results [205] show this to be a very promising strategy that requires further investigation.

Gene therapy approaches have tried to enhance the immunoreactivity of melanoma cells by transfecting them with immunostimulatory genes such as the granulocyte-macrophage colony stimulating factor (GM-CSF), the T-cell costimulatory molecule B7-1, MAGE, or interleukin-6 (IL-6) [206]. Clinical trials showed promising early results with this strategy, but more definite data are lacking [207, 208].

6.8.10 Targeted Therapies

Oncology is experiencing the emergence of targeted therapies. Targeted therapies utilize small molecules specifically designed to counteract specific alterations in the molecular pathways of cancer cells. Major alterations in melanoma cells include the methylation of the APAF-1 gene, the sustained expression of the bcl-2 gene, and the presence of activating mutations in the BRAF gene. These result in resistance to apoptosis.

Sorafenib is novel small molecule that blocks BRAF and the VEGF and PDGF induced pathways. Sorafenib showed little activity as a single agent in metastatic melanoma [209]. It may potentate the effects of cytotoxic chemotherapy when added to it [210], although a recently presented phase III trial did not show any benefit of adding sorafenib to carboplatin and paclitaxel [211].
Oblimersen is an anti-Bcl-2 antisense oligonucleotide. A trial compared dacarbazine with and without oblimersen in 771 patients with previously untreated melanoma. Combined therapy was associated with a significantly higher objective response rate (14 vs. 8%), but there was only a trend toward longer overall survival (9.0 vs. 7.8 months, \( p = 0.08 \)). Based on these data, the Food and Drug Administration did not approve oblimersen for the treatment of metastatic melanoma.

### 6.9 Follow-Up of Patients

There are no internationally accepted guidelines for follow-up care of patients diagnosed with melanoma. Current practice in most countries is that all patients with an invasive melanoma have a period of follow-up and all patients with stage III disease have a prolonged follow-up, often for the rest of their life.

The purposes of follow-up apart from detecting recurrent disease or new primary melanomas are also to reassure the patient, provide him with adequate information on all aspects of his disease, support and give him psychological counseling, and teach him to perform self-examination in order to detect local or nodal disease.

The most important parameter that one has to bear in mind when following up a patient with melanoma is that this disease is too complicated, unpredictable, and deadly to be managed solely outside of a comprehensive center, and that it is better managed by a multidisciplinary team of expert physicians.

### References


103. Ringborg U, Mansson Brahme E, Drzewiecki K, Gullestad HP, Ninn M (2005) Randomized trial of a resection margin of 2 cm versus 4 cm for cutaneous malignant melanoma with a tumor thickness of more than 2 mm. Proceedings 6th world melanoma congress, Vancouver, September 6–10; Abstract 28


113. van Akkooi AC, de Wilt JH, Verhoef C, Schmitz PI, van Geel AN, Eggermont AM, Kliffin M (2006) Clinical relevance of melanoma micrometastases (<0.1 mm) in sentinel nodes: are these nodes to be considered negative? Ann Oncol 17(10):1578–1585


121. Eggermont AMM (2001) Role of interferon in melanoma remains to be determined. Eur J Cancer 2147–2153


Further Reading


7.1 Pathogenesis and Risk Factors

To date, the precise etiopathogenesis of MCC remains unclear. Tumor cells of MCC show morphological and immunohistochemical features of epidermal Merkel cells, which have therefore been proposed to be the cells of origin of this tumor. However, the predominant location of MCC is in the dermis, where usually only few (if any) Merkel cells are present. Therefore, the hypothesis exists that MCC may be derived from pluripotent epidermal stem cells or from dermal neuroendocrine cells.
Chronic UV exposure, older age, and immunosuppression represent well-established risk factors. The vast majority of MCC occurs in the Caucasian population of fair skin type and shows a slight male predominance. Most cases of MCC are located on sun-exposed areas of the head, neck, and extremities [1, 3], and data from the Seer database show regional differences correlated to UV indexes [4]. Furthermore, a 100-fold increase of MCC has been reported in psoriasis patients treated with UV-A and methoxalen [5]. However, the fact that MCC also occurs on sun-protected areas of the trunk, buttocks, and mucosae suggests that sunlight is not the only factor involved in the pathogenesis of this neoplasm. MCC mostly affects elderly patients above the age of 65 years, with only 5% of cases being diagnosed in patients under the age of 50 years. However, these observations do not apply to the immunocompromised population in which half of the cases occur in patients younger than 50 years [6, 7]. Due to the rarity of the disease, the precise incidence is not known, but has been estimated to be 0.13/1,000 person-years in renal transplant recipients [8]. Another observation supports the increased incidence of MCC in organ transplant patients [9]. In the normal population, melanoma is 65-fold more common than MCC, but following transplantation, this ratio is inverted, with MCC being sixfold more common than melanoma [6]. Other immunodeficiency conditions such as chronic lymphatic leukaemia or non-Hodgkin lymphoma are reportedly associated with an increased incidence of MCC. In patients with HIV infection, the relative risk of MCC is increased 13.4-fold compared to the normal population [10].

Despite the aging of the population and increase of outdoor activities with higher UV-exposure rates, the improved diagnostic ability of MCC is likely to contribute to the incidence increase. The development of special immunostains such as CK20 and TTF-1 enables the pathologist nowadays to differentiate MCC from other dermal small cell tumors such as metastatic small cell lung cancer, and have improved histological diagnosis.

Recently, a previously unknown virus was identified in MCC. The virus belongs to the polyomavirus family and has been referred to as Merkel cell polyomavirus (MCV or MCPyV). Feng et al. detected MCV in eight of ten samples by digital transcriptome substration technique and showed clonal integration of the MCV in the tumor genome in six cases [11]. A subsequent study by Kassem et al. investigated MCC specimens of 39 patients by PCR and found MCV in 30 cases (77%) [12]. These findings suggest the involvement of MCV in the pathogenesis of MCC, but further studies are warranted to prove the causal role of MCV in MCC.

7.2 Clinical Features and Diagnosis

The clinical appearance of MCC ranges from skin-colored to red-violaceous nodules or plaques. The overlying skin may show telangiectases, and ulceration is possible in larger tumors.

Macroscopically, MCC often shows rather nonspecific features, mimicking insect bites, cysts, or other benign or malignant tumors, a fact accounting for misdiagnosis or delayed diagnosis. However, rapidly growing lesions that are firm on palpation should raise suspicion for MCC and prompt a biopsy. Special awareness of this tumor is needed in the immunosuppressed population where MCC has an increased incidence and a worse prognosis (Please refer also to chapter 11.1). A total body examination with palpation of the draining region and lymph nodes should be performed in every patient in order to detect skin and nodal metastasis. For initial work-up, a chest X-ray and abdominal and lymph node ultrasound examination have been recommended [7, 13]. Other imaging techniques have been evaluated for staging of MCC such as CT, somatostatin receptor scintigraphy, and PET scans. Whereas imaging techniques may be of value for the detection of visceral localizations, a recent analysis has shown low sensitivity of CT scans for the detection of nodal metastasis.

Fig. 7.1 Primary Merkel cell carcinoma presenting as large erythematous plaque in a 89-year-old male
when compared with sentinel node biopsy [3]. Furthermore, organ metastases occur late in MCC and the lack of effective treatment in metastasized MCC questions the indication for scans as early diagnosis of metastasis may not improve survival (Fig. 7.1).

7.3 Pathology

The diagnosis of MCC is usually made by histologic examination as the clinical features are rather unspecific. Histopathologically, MCC represents a dermal tumor composed of round, small basophilic monomorphous cells with large nuclei, prominent nucleoli, and inconspicuous cytoplasm. Please refer to Chap. 2 for further details on MCC pathology.

7.4 Staging

Regarding tumor spread at the time of MCC diagnosis, three different stages have been defined (Table 7.1). Stage I disease includes tumors limited to the skin. If nodal involvement is present (either clinically or detected by sentinel lymph node biopsy (SLNP)), the tumor is defined as stage II. Stage III includes disease with distant organ (metastatic) spread. It has been suggested to further subdivide stage I MCC into Ia, with tumors less than 2 cm in diameter, and Ib with tumors over 2 cm in diameter. However, there have been controversial observations regarding the prognostic value of tumor size, since larger studies did not confirm any effect of tumor size on survival [1, 3].

The most common location of metastasis in MCC is the draining lymph node basin. At presentation, about one-third of patients have a positive sentinel node [3]. Other common sites of metastases are distant skin, followed by lung and central nervous system.

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7.5 Prognostic Factors

To date, the only consistent predictor for survival in MCC is the sentinel lymph node status. The prognostic value of SLNP has been evaluated in several studies. A large study reported a 75% disease-specific survival rate in patients clinically lymph node-negative, compared to 97% with a negative SLNP [1]. Another report showed that patients who were pathologically lymph node positive had a three times higher recurrence rate than those with negative SLNP (60 vs 20%).

While tumor size had been claimed to be a factor with impact on survival, recent studies with large cohorts failed to show this correlation. In melanoma the most important prognostic parameter is tumor thickness (Breslow index). Studies evaluating the value of tumor thickness in MCC did not show any effect on survival [14]. Furthermore, many other potential prognostic predictors (such as lymphocytic infiltration, mitotic activity, and immunohistochemical markers) have been suggested, but to date either inconclusive or controversial data have been reported [15]. Further studies are warranted in order to assess if any of these markers is relevant for pathologic staging of MCC.

MCC is an aggressive malignancy with a high mortality rate. In order to provide best patient care, a multidisciplinary approach is of special importance in these patients. As MCC is relatively rare, prospective, randomized trials and consensus guidelines are currently missing and the recommendations given are mostly based on retrospective data from the literature. The management of MCC will be discussed below according to the stage of disease.

7.6 Treatment of MCC

7.6.1 Primary MCC (Stage I)

7.6.1.1 Excision

Wide local excision with a margin of 2–3 cm is recommended for treatment of the primary lesions [7, 13, 16]. The excision should include the skin and subcutaneous tissue and the underlying fascia when the tumor comes close to it. In areas where such large margins are difficult to obtain (e.g., on the face), Moh’s micrographic
surgery can be used. A recent study comparing wide local excision and Moh’s surgery for primary MCC of the extremities did not show differences regarding local recurrence rates [17].

### 7.6.1.2 Sentinel Lymph Node Biopsy (SLNB)

Although SLNB is widely performed for melanoma (>1 mm), its applicability to MCC was evaluated only recently. Up to one-third of patients with MCC are sentinel lymph node positive at initial diagnosis, a rate about sixfold higher than in melanoma. An analysis of the largest cohort of patients with MCC who received SLNB showed that one-third of patients who were clinically staged as stage I were in fact stage II by SLNB. Furthermore, the prognosis varies significantly since SLNB negative patients have an 80% 3-year relapse-free survival rate compared with 20% in SLNB positive patients [3]. To date, SLNB seems to be the best predictor for disease outcome and influences the further management and adjuvant treatment of patients. Therefore, SLNB should be recommended in every patient with MCC and clinically negative lymph node status, provided there is no contraindication for performing this procedure. However, performing SLNB might be difficult or even fail, especially in the head and neck area and complications like facial nerve destruction might occur. Furthermore, the success of SLNB is dependent on the experience of the surgeon performing the procedure.

### 7.6.1.3 Radiation Therapy

MCC is a radiosensitive skin neoplasm. The role of adjuvant radiotherapy in the management of MCC has been evaluated and controversially discussed. However, a recent retrospective analysis of 1,254 patients demonstrated a lower loco-regional recurrence rate and prolonged overall survival in patients who underwent adjuvant radiation therapy after complete, margin-free excision. Local and regional 5-year relapse rates were about three times lower after adjuvant radiation treatment [18]. Two other studies have also shown that combined treatment with surgery and radiotherapy improves both loco-regional control and disease-free survival [19, 20], with patients at stage II deriving the greatest benefit from adjuvant radiotherapy [21]. Recent data from the SEER registry support these observations and show substantially longer overall survival rates after adjuvant radiation as compared to surgery alone [22]. Interestingly, the same study reported improved survival after adjuvant radiation, independent from the size of the lesion, although the benefit was prominent in tumors larger than 2 cm. Therefore, radiation therapy should especially be considered in tumors larger than 2 cm, but might also be performed in smaller tumors depending on the individual situation. Adjuvant radiation therapy should be strongly considered in patients with primary disease in whom wide surgical margins are unattainable, or in those found to have pathologically close or involved margins after optimal excision. The radiation field should include the primary site, the in-transit lymphatics, and the draining lymph node basin. 45–50 Gy with 2 Gy per fraction is recommended [7, 13, 16].

Although wide local excision is the first-line treatment for MCC, some patients may not be suitable for surgery, namely if they have significant comorbidities or very large tumors. In these cases, radiation might be considered as primary treatment.

### 7.6.1.4 Chemotherapy

The role of adjuvant chemotherapy has been controversially considered and regimens similar to those used in small cell lung cancer have been used. However, recent studies did not show a benefit for survival after adjuvant chemotherapy [22]. On the contrary, a study has reported a decrease in 4-year survival in node-positive patients from 60 to 42% if chemotherapy was administered [1]. This difference was not statistically significant, however, currently adjuvant chemotherapy should not be systematically recommended. The median age of patients with MCC is 69 years; therefore, these patients are likely to have comorbidities that may lead to increased morbidity and mortality associated with chemotherapy. Although the initial response rate of chemotherapy is relatively high, the tumor often develops resistance against the chemotherapy during treatment.

A small number of patients with MCC have been successfully treated with intratumor injections of TNF-alfa [23] or subcutaneous injections of interferon a2b [24]. Hyperthermic isolated limb perfusions with interferon gamma, TNF-alfa and melphalan, have also been applied for advanced MCC of the limbs [25]. However,
the number of patients treated with these modalities is limited, so that their efficiency needs to be evaluated by prospective studies in a larger number of cases.

### 7.6.2 Treatment of Metastatic Disease

#### 7.6.2.1 Stage II: Lymph Node Metastasis

For patients with positive lymph node status (either clinically or by SLNB), complete lymphadenectomy is recommended as primary treatment, and has been shown to improve disease-free survival [26]. It is still unclear if postoperative radiation of the lymph node basin improves survival. However, radiation therapy of the lymph node basin should be considered if complete lymphadenectomy is not feasible or if the lymph node involvement is extensive. Management of these patients has to take into consideration the individual situation and relevant comorbidities, age of the patient, and quality-of-life issues.

#### 7.6.2.2 Stage II: Local Recurrence

A curative approach should be attempted in case of local recurrence. Surgical treatment with clear margins remains the treatment of choice. Adjuvant radiotherapy should be considered in these patients. In situations where surgical clearance is unattainable, radiation therapy should be performed. Chemotherapy should be reserved for exceptional cases where surgery and/or radiation failed.

#### 7.6.2.3 Stage III: Distant Metastasis

The management of MCC patients with distant metastasis is difficult and remains palliative. Surgery, radiation, and chemotherapy or combination therapy may be used, depending upon the tumor location and the performance status of the patient. Regarding chemotherapy regimens, combinations are similar to those used in other neuroendocrine tumors (such as small cell lung cancer) and include among others doxorubicin (or epirubicin), cyclophosphamide, cisplatin (or carboplatin), 5-FU, dacarbazine, vindesin, and etoposide. Although initial response rates are high (up to 60–70%), the duration is relatively short. For second- and third-line chemotherapies, the response rates decrease significantly to 45 and 20%, respectively. So far, no impact on survival has been shown. Furthermore, chemotherapy may cause significant morbidity and this has to be considered given the advanced age of patients with MCC.

### 7.7 Occult MCC

Metastatic MCC in the absence of a known primary is found in about 12% of cases, mostly presenting as lymph node involvement. There have been reports of spontaneously regressive MCC [27], which support the hypothesis that primary nodal MCCs represent metastasis of originally cutaneous MCCs that have undergone complete regression. It has also been discussed whether the involved lymph nodes might in fact be the site of the primary MCC. Merkel cells are normally not present in lymph nodes, but derivation from pluripotent stem cells may be considered.

Management of these patients is difficult and the cause of disease might not be foreseeable. Complete lymphadenectomy should be performed as primary treatment. Subsequent radiation of the lymph node basin should be considered, but decision has to be made individually considering possible side effects of this treatment, e.g., lymphedema.

### References

previously recognized in a temperate climate. Transplantation 77:574–579
8.1 Epidemiology and Etiopathogenesis

8.1.1 Epidemiology, Cutaneous T-Cell Lymphomas

The skin is the second most common location for extranodal non-Hodgkin’s lymphoma [1], and the incidence...
of cutaneous T-cell lymphomas (CTCL) has increased by 2.9 cases per million each decade for the last 30 years [2]. Mycosis fungoides (MF) is the most common form of CTCL, accounting for up to 72% of CTCL reported and affecting up to 0.9 per 100,000 per year [3]. Sézary syndrome (SS), previously classified as a leukemic variant of MF, is comparatively rare, with only 2.5% [2]. MF patients are at higher risk for other hematological disorders, especially Hodgkin’s lymphoma [4, 5]. Other epidemiologic factors associated with an increased incidence include male sex (two times more likely than female), black race (50% more likely than white), and increasing age [2, 3].

8.1.2 Etiopathogenesis, Cutaneous T-Cell Lymphomas

The pathogenesis of MF/SS is poorly understood. One theory is that MF evolves as a consequence of chronic immune stimulation to an epidermal antigen [6, 7]. The chronic stimulation of skin-homing T cells in the epidermal compartment could lead to the acquisition of specific genetic defects that underlie the neoplastic transformation event. Specifically, alterations of NAV3, JUNB, or Fas/CD95 genes, as well as hypermethylation of mismatch repair genes have been demonstrated within a subset of CTCL cases [8–13]. Numerous causative infectious agents have been implicated, most commonly Staphylococcus aureus [86], but also Chlamydia spp [15], Epstein–Barr virus [120], cytomegalovirus [17], and human T-lymphotropic virus type I (HTLV-1) [56]. Indeed, HTLV-1 has been shown to be pathogenic for adult T-cell leukemia/lymphoma [19–21]. The Langerhans cell (LC) has also been postulated to be involved in the chronic antigenic stimulation of T cells that occurs in the skin of MF/SS, in view of the close apposition between neoplastic T cells and LCs in Pautrier microabscesses and ex vivo evidence of their providing growth enhancement of neoplastic T cells [22, 23]. It is also known that MF has a tendency toward Th2 cytokine production, with an increasing Th2 predominance as the disease progresses. Interleukin (IL)-4 and IL-5, both Th2 cytokines, have been shown to be overexpressed in MF lesions and may protect the malignant T-lymphocytes from apoptosis [24, 25]. Lastly, a familial occurrence has been reported in a few cases, indicating a possible genetic predisposition [26, 27].

8.1.3 Epidemiology, Cutaneous B-Cell Lymphomas

Primary cutaneous B-cell lymphomas (PCBCL) are less commonly encountered as compared to CTCL and account for only 4.5–25% of all cutaneous lymphomas [28–30]. No consistent difference has been identified between the incidence of PCBCL in females and males, but the more indolent subtypes of PCBCL are found at an increased frequency as compared to the more aggressive subtypes [31, 32]. The primary cutaneous follicle center lymphoma is the most common subset, accounting for up to 40% of all PCBCL [33]. Although PCBCL has a tendency to manifest in middle adulthood, with an average age of presentation in the sixth decade, it has been reported to present in the first through the tenth decade [33, 34].

8.1.4 Etiopathogenesis, Cutaneous B-Cell Lymphomas

The pathogenesis of PCBCL, although truly unknown, has been postulated to be secondary to infection with Borrelia species in some subtypes of PCBCL. Two European studies have identified Borrelia DNA sequences in 18–35% of PCBCL [35, 36]. Interestingly, similar results with Borrelia have not been demonstrated within North America [37–39]. Chronic antigenic stimulation leading to a proliferation of aberrant lymphocytes has also been proposed as a potential pathogenic factor. In addition to Borrelia, microorganisms have been evaluated for their potential role in antigenic stimulation and direct development of PCBCL, including Epstein–Barr virus [40–42], and human herpes virus 7 and 8 [40, 43], although none of these organisms have been convincingly linked to the pathogenesis of PCBCL. A variable presence of genetic and chromosomal defects has been shown in PCBCL with higher numbers in the more aggressive subtypes [44, 46]. To date however, no specific genetic alterations, such as translocation (14;18) in systemic follicular lymphoma, have been identified [47].
8.2 Clinical and Histologic Presentation of Cutaneous Lymphoma

8.2.1 Cutaneous T-Cell Lymphomas

8.2.1.1 Mycosis Fungoides

It is frequently encountered as pruritic, erythematous, scaly patches, with a predilection for sun-protected skin (e.g., buttocks, inner arms). The natural history of MF can be protracted over years, but classically will progress from patches to plaques, to bulky, erosive tumors, and may internalize with nodal and leukemic involvement. Histologically, small to medium-sized cerebriform atypical CD4+ T-lymphocytes are found within the upper dermis, with a noticeable epidermotropism of solitary lymphocytes aligned along the epidermal basal layer. In early lesions, small reactive lymphocytes predominate, hampering the diagnosis. Most commonly, there is reduced expression of CD8 as compared to CD4, and there can be loss of CD2, CD3, CD5, and CD7 [48, 49]. These aberrant lymphocytes may also cluster within the epidermis around LCs, forming the Pautrier microabscess (Figs. 8.1 and 8.2).

Folliculotropic Mycosis Fungoides

Folliculotropic MF is a variant of MF that is characterized by preferential follicular involvement, most commonly of the head and neck. Clinically, there are follicular-based papules and pustules, often associated with an alopecia. Histologically, the infiltrating atypical CD4+ lymphocytes are periadnexal and can be seen inside the follicular epithelium [29, 50]. There may also be mucin deposition in the degenerating follicles.

Pagetoid Reticulosis

Pagetoid reticulosis or unilesional MF is another variant of MF, and as the name implies, presents with a solitary lesion, usually an psoriasiform, erythematous, hyperkeratotic patch, or plaque on the extremity. The histology is similar to that of MF, but with markedly hyperplastic epidermis containing the vast majority of the malignant T-cells. The phenotype is either CD3+, CD4+, CD8− or CD3+, CD4−, CD8+[29].

Granulomatous Slack Skin

Granulomatous slack skin is a rare variant of MF (only 50+ case reports), characterized by loose, redundant appearing skin, often presenting in the groin and axillae [51]. Histology classically reveals granulomatous...
dermal infiltrates comprising predominately atypical T-cells (CD3+, CD4+, CD8−), macrophages, and multinucleated giants cells, which can be associated with elasto- and lymphophagocytosis [52].

8.2.1.2 Sézary Syndrome

Sézary Syndrome (SS) is historically characterized by a unique clinical presentation of erythroderma (>80% body surface area), lymphadenopathy, and elevated numbers of T-lymphocytes in the blood with hyper-convoluted or cerebriform nuclei (Sézary cells) [53]. For diagnosis, it is now recommended that there be (1) evidence of a circulating T-cell clone, (2) a CD4:CD8 ratio of >10, and (3) a Sézary count of at least 1,000 cells per μL [54]. Cutaneous histologic findings can be less robust in SS as compared to MF, with variable numbers of atypical cells in the epidermis. Phenotypically, abnormal cells found in the blood will often be CD3+, CD4+, CD8−, with loss of CD7 and/or CD26 [53].

8.2.1.3 Primary Cutaneous Anaplastic Large Cell Lymphoma

Primary cutaneous anaplastic large cell lymphoma (C-ALCL) is one of the CD30+ cutaneous lymphoproliferative disorders that comprise the second most common form of CTCL [29]. Clinically, C-ALCL most often presents as solitary or grouped papules to tumors, which may develop ulceration, and can appear anywhere on the skin. Similar to lymphomatoid papulosis, these lesions occasionally undergo spontaneous resolution. Histologically, there are sheets of large, atypical T-lymphocytes, of which the majority will stain positively for CD30. Most cases express a cytotoxic phenotype [55]. Unlike systemic CD30+ lymphomas, C-ALCL generally does not express anaplastic lymphoma kinase (ALK) or epithelial membrane antigen (EMA), but it does express cutaneous lymphocyte antigen (CLA) [56].

8.2.1.4 Lymphomatoid Papulosis

The other common CD30+ cutaneous lymphoproliferative disorder is lymphomatoid papulosis (LyP). LyP classically presents as a chronic, relapsing, self-healing disorder comprising erythematous to red–brown papulonodules that can have hemorrhage, central necrosis, and crusting, and there are commonly lesions in various stages of evolution. The individual lesions tend to resolve in 1–2 months (Fig. 8.3) with postinflammatory pigment changes or occasional atrophic scarring [29]. LyP type A lesions have the classic wedge-shaped lymphocytic (+/- neutrophils/eosinophils) infiltrate with scattered large, atypical CD30+ T-lymphocytes. LyP type B has histology more consistent with mycosis fungoides (MF) that consists of a band-like lymphocytic infiltrate with some evidence of epidermotropism, and a predominance of CD3+, CD4+, CD30− small, cerebriform lymphocytes. LyP Type C classically reveals dense sheets of large, atypical CD30+ lymphocytes, with little to no inflammatory cells. As LyP type C can be difficult to differentiate histologically with cutaneous anaplastic large cell lymphoma (C-ALCL), recent studies revealed that the more frequent presence

Fig. 8.2 Nodular type of MF on the face
of tumor necrosis factor receptor-associated factor 1 (TRAF1) or Multiple Myeloma Oncogene I (MUM1) was present in LyP compared to C-ALCL [57, 58]. Similarly to C-ALCL, most cases express cytotoxic markers [59].

8.2.1.5 Adult T-Cell Leukemia/Lymphoma

Adult T-cell leukemia/lymphoma (ATLL) is a malignancy known to be associated with HTLV-1 infection. Clinically, ATLL most often presents with leukemic, organ, and skin involvement (acute form), but there are cases where it will present with skin lesions alone that mimic MF (smouldering form) [60]. Histology of the affected skin reveals infiltrates of pleomorphic T-lymphocytes (commonly CD3+, CD4+, CD25+, and CD8−) with epidermotropism and again can be consistent with MF histology [60].

8.2.1.6 Extranodal NK/T-Cell Lymphoma, Nasal Type

Extranodal NK/T-cell lymphoma, nasal type (ENKL) is a malignancy of either cytotoxic T-cells or NK cells, often in association with EBV, which commonly presents in the nose/nasopharynx, with cutaneous manifestations on or around the nose (nasal type) and less often on the trunk and extremities [61, 62]. Clinically, there can be subcutaneous, erythematous to dark-purple nodules, often with ulceration [63]. Histology most often reveals CD2+, CD56+, TIA-1, granzyme-B, and perforin staining infiltrates in the dermis often with extension down to underlying structures, with extensive necrosis [64].

8.2.1.7 Subcutaneous Panniculitis-Like T-Cell Lymphoma

Subcutaneous panniculitic-like T-cell lymphoma (SPTL) is a malignancy of cytotoxic T-cells involving the subcutaneous fat, most commonly of the legs. There may be two different phenotypes, with 75% having a α/β T-cell phenotype (betaF-1+, CD8+) associated with a more benign, indolent course, and the remaining 25% having a γ/δ T-cell phenotype (betaF-1+, CD8−) associated with a more aggressive course, consistent with other γ/δ+ T-cell lymphomas [65–67]. Therefore, it is proposed that the term SPTL should further be used only for the α/β T-cell phenotype [29, 124]. Clinical presentation reveals subcutaneous plaques and/or nodules. Hemophagocytic syndrome may occur in about 17% of cases being associated with a more aggressive clinical course [124]. Histology is notable for subcutaneous infiltrates of normal and atypical lymphocytes (CD3+, CD8+, CD4−), with rimming of individual fat cells and necrosis and cytophagocytosis [66].

8.2.1.8 Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified

Primary cutaneous peripheral T-cell lymphoma, unspecified currently refers to all primary cutaneous T-cell lymphomas which otherwise do not fit into any of the aforementioned categories. Included in this grouping are cutaneous γ/δ T-cell lymphoma, and primary cutaneous aggressive epidermotropic CD8+ cytotoxic T-cell lymphoma.
8.2.2 Primary Cutaneous B-Cell Lymphomas

8.2.2.1 Primary Cutaneous Follicle Center Lymphoma

The primary cutaneous follicle center lymphoma (PCFCL) is composed of malignant, germinal center B-lymphocytes. Clinically, this cancer often presents as erythematous to purple papules, nodules, or tumors, and can be multiple or solitary, most often appearing on the head and neck, and less commonly on the trunk (back). Histologic examination reveals nodular to diffuse infiltrates of small to large lymphocytes, and a variable presentation of formed germinal centers. The pattern of growth can be follicular, diffuse, or mixed. Immunohistochemical staining reveals CD20/79a+(B-cell markers), Bcl-6+, commonly Bcl-2−, and multiple myeloma oncogene 1 (MUM1) [68, 69]. In contrast to reactive germinal centers, neoplastic follicles often show a reduced proliferation of less than 50% (Ki-67/MIB-1) [70].

8.2.2.2 Primary Cutaneous Marginal Zone B-cell Lymphoma

Primary cutaneous marginal zone B-cell lymphoma (PCMZL) is considered to be on the spectrum of the Mucosal-Associated Lymphoid Tissue (MALT) lymphomas. Clinically, PCMZL most commonly manifests as red–brown to violaceous papules and nodules on the extremities (arms > legs) and trunk, with rare ulceration. Histologically, there is a nodular to diffuse infiltrate of small lymphocytes, marginal zone B-cells, plasma cells, with frequent germinal centers surrounded by marginal zone B-cells (irregular nuclei, pale cytoplasm) [29]. Immunohistochemical staining reveals CD20/79a+ (B-cell markers), Bcl-2+, and most commonly Bcl-6− [71]. In most cases a monotypic expression of immunoglobulin light chains can be observed.

8.2.2.3 Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

Primary cutaneous diffuse large B-cell lymphoma, leg type (DLBCLLT) is a subtype of PCBCL which is composed of numerous large centroblasts and immunoblasts, and most commonly occurs on the legs. Clinically, DLBCLLT presents as red–brown to bluish nodules or tumors, often with ulceration, on the distal lower extremities. Despite the name, this malignancy can develop in site other than the lower extremities. Histologic examination reveals sheets of the large centroblasts and immunoblasts. Immunohistochemical staining is generally positive for CD20/79a (B-cell markers), Bcl-2, Bcl-6, and MUM1 [29, 72]. Expression of Bcl-2 and MUM1 is very helpful in differentiating PCFCL, diffuse type (Fig. 8.4).

Primary Cutaneous Diffuse Large B-Cell Lymphoma, Other

Primary cutaneous diffuse large B-cell lymphoma, other (PCLBCL, other) is the category for the large B-cell, skin-confined, lymphomas that do not fit within the DLBCTLL grouping. One better recognized entity within this group is the intravascular large B-cell
lymphoma (IVLBCL). Clinically, IVLBCL can have an extremely varied cutaneous presentation, ranging from no involvement to erythematous patches/plaques, telangectasia, and livedo [73, 74]. IVLBCL also predominately affects the central nervous system. Histologically, large atypical lymphocytes, staining for CD20/79a+, can be found within dermal and subcutaneous blood vessels.

8.3 Diagnosis

8.3.1 History, Physical Examination, and Skin Biopsy

For diagnosis, a thorough medical history and physical examination (including lymph node evaluation) are needed in conjunction with skin biopsy. Histopathologic evaluation should be performed with hematoxylin/eosin staining, followed by immunohistochemical markers (e.g., specific T- and/or B-cell markers) and polymerase chain reaction (PCR) of T- or B-cell receptor as indicated by the differential diagnoses. The clinical history and exam as well as the pathology, immunohistochemistry, and molecular pathology should all be factored into the rendering of a diagnosis.

8.3.2 Systemic Evaluation

After a diagnosis of cutaneous lymphoma is made based upon clinical evaluation and histology and immunohistochemistry of skin biopsy, it is prudent to follow up with a systemic evaluation to assess potential extracutaneous spread or a possible primary systemic malignancy. This would include a complete blood count, comprehensive metabolic panel, lactate dehydrogenase, flow cytometry, and B- or T-cell PCR of the peripheral blood to evaluate for phenotypically abnormal lymphocytes or a clonal lymphocyte population, respectively. Additionally, chest X-ray, ultrasound of abdomen and cervical, axillary inguinal lymph node basins, or imaging including computed tomography (CT) scan, or positron emission tomography (PET)/CT scan can be useful to evaluate for lymph node or other organ involvement. In case of PCBCL, a bone marrow biopsy to exclude systemic B-cell lymphoma is mandatory [75].

8.3.3 Staging

Staging of cutaneous lymphoma is based upon the tumor-node-metastasis (TMN) concept. The current revised staging system appears to be most applicable for MF and SS (Table 1a and Table 1b) (Olsen), and therefore, the

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8.4 Management and Prognosis

8.4.1 Cutaneous T-Cell Lymphomas

8.4.1.1 Mycosis Fungoides

The treatment for MF varies widely based upon the clinical staging of the disease. First-line therapies for stage IA, IB, and IIA are generally all skin-directed, and include photochemotherapy (PUVA), ultraviolet B (UVB), topical corticosteroids, topical nitrogen mustard, topical carmustine, localized radiotherapy, and total skin electron beam (TSEB). PUVA has been shown to produce an objective response (ORR) in 95%, with complete response (CR) in 65% in Stage IA and IB [81]. Given the more shallow depth of penetration, UVB is recommended for patch stage MF only, and has been reported to induce a complete response in up to 71% [82]. TSEB has also been associated with a high CR of 96% in stage IA, IB, and IIA [83]. Topical nitrogen mustard has been reported to produce an ORR of 83% with a complete response at 50% [84]. Second-line therapies for stage IA, IB, and IIA MF include interferon-alpha, bexarotene, denileukin diftitox (fusion protein of IL-2 and diphtheria toxin), methotrexate, and PUVA combination therapy with either interferon-alpha, or bexarotene [85].

First-line therapy of stage IIB MF includes combination therapies such as interferon-alpha with either PUVA (ORR 77% [86]) or retinoids. PUVA with retinoids and TSEB with superficial X-irradiation (CR 36% [87]) are also considered first-line. Bexarotene, single or multiagent chemotherapy, and denileukin diftitox are all second-line therapies for stage IIB MF [85]. Vorinostat, a histone deacetylase inhibitor, has recently been approved for the treatment of refractory CTCL. In a multicenter study with 82% of patients having stage IIB or greater CTCL, there was an ORR of 30% [88].

Stage III MF also has a number of first-line therapies, including PUVA + interferon-alpha, interferon alone, methotrexate (ORR 58% [89]), extracorporeal photopheresis (ORR 31–80% [90]), and TSEB with superficial X-irradiation. Second-line therapies include oral bexarotene and single or multiagent chemotherapy. Vorinostat may also be useful in this category.

The therapy for advanced Stage IV MF is considered palliative and this should be considered when weighing the potential clinical benefits and therapeutic side effects. Possible therapeutic agents include chemotherapies, methotrexate, interferon alpha, denileukin diftitox, bexarotene, alantuzumab (anti-CD52 antibody), and vorinostat [85, 88].

Prognosis associated with early stage IA MF is favorable, with studies reporting no alteration in lifespan compared to normal, healthy controls [84, 91, 92], but there is markedly increased morbidity and mortality associated with the more advanced MF. The expected 5-year survival decreases as the clinical stage increases: Stage IB 73–86%, Stage IIA 49–73%, Stage IIB 40–65%, Stage III 40–57%, Stage IVa 15–40%, and Stage IVb 0–15% [83].

Folliculotropic Mycosis Fungoides

Given the deeper, follicular location of the malignant cells, treatment for folliculotropvic MF usually involves...
skin-directed as well as systemic therapies. One recent study revealed limited response to ultraviolet therapy alone, with only one of 13 achieving a response [50]. Approximately half of the patients treated with a combination of either photochemotherapy (PUVA) and interferon alpha, or PUVA and oral retinoids had a PR or CR [50]. Radiotherapy has also been beneficial as a therapy. For those with more refractory disease (Stage ≥ IIB), chemotherapies such as CHOP or liposomal doxorubicin have not demonstrated much success [50].

The prognosis associated with folliculotropic MF is similar to that of tumor stage MF, with a 70–87% 5-year survival rate [50, 93, 94].

8.4.1.2 Sézary Syndrome

The first-line therapy for SS includes extracorporeal photopheresis alone, or in combination with other systemic therapies including interferon-alpha [85, 99]. ORRs have been reported to range from 46 to 75% [99–102]. Other first-line therapies include interferon alpha alone [103, 104], denileukin diftitox [105], and chlorambucil with prednisone [106]. Second-line treatment recommendations include bexarotene [107], methotrexate [108], alemtuzumab [109, 110], gemcitabine [111], and multiagent chemotherapy [112]. SS is associated with an elevated mortality, having a reported 30% survival at 5 years from diagnosis [113].
8.4.1.6 Extranodal NK/T-Cell Lymphoma, Nasal Type

Treatment for the extranodal NK/T-cell lymphoma requires systemic chemotherapy and despite treatment, the prognosis is generally poor with a 5-year survival of around 45% [120].

8.4.1.7 Subcutaneous Panniculitic-Like T-Cell Lymphoma

SPTL was most commonly treated with multiagent chemotherapy, such as cyclophosphamide, hydroxydaunomycin, Oncovin [vincristine], and prednisone (CHOP). However, since there is evidence of two subgroups (SPTL-α/β⁺ or SPTL-γ/δ⁺ phenotype) with the SPTL-α/β⁺ running an indolent clinical course, less aggressive therapies like cyclosporine and oral prednisone are the first choice of treatment [65, 123, 124]. Additionally, localized disease has been treated with surgical excision and radiotherapy [124]. The prognosis of the SPTL-α/β⁺ has an estimated 5-year survival at 82% [124], whereas the SPTL-γ/δ⁺ shows a 5-year survival of only 11%. Based on these data, SPTL-γ/δ⁺ is included in the category of cutaneous γ/δ⁺ lymphomas in the WHO-EORTC classification [29, 124].

8.4.1.8 Primary Cutaneous Peripheral T-Cell Lymphoma, Unspecified

Primary cutaneous peripheral T-cell lymphoma, unspecified is generally treated with multiagent chemotherapy, but despite treatment, the 5-year survival rate is less than 20% [32, 125, 128].

8.4.2 Primary Cutaneous B-Cell Lymphomas

8.4.2.1 Primary Cutaneous Follicle Center Lymphoma

Radiotherapy is generally first-line therapy for PCFCL, although surgical excision and oral antimicrobials (e.g., tetracyclines) have also been successful at achieving CR and PR [29]. Additionally, the anti-CD20 monoclonal antibody, rituximab, has been reported in case studies and series to be beneficial, especially when localized therapy is not an option [40, 126], although to date, there has not been a randomized, controlled trial evaluating this therapy. Intralesional rituximab has been reported for localized disease [127]. PCFCL tends to run a more indolent course, with an estimated 5-year survival at 97% [6]. Although local recurrence can occur in up to 50%, metastatic spread is exceedingly rare [33].

8.4.2.2 Primary Cutaneous Marginal Zone B-cell Lymphoma

The preferred therapy for localized PCMZL is surgical excision or radiotherapy. For those with multifocal disease, intralesional interferon alpha has been shown to induce CR in up to 50% of patients [129]. Additionally, topical corticosteroids, oral antimicrobials (especially in the setting of active Borrelia infection), topical Carmustine, and chlorambucil have all been utilized with varying success [79]. Lastly, systemic or intralesional rituximab has also been shown to be successful in the treatment of PCMZL [126, 130]. Like PCFCL, PCMZL also has a more indolent course, with studies reporting none or very rare incidence of metastatic spread [131].

8.4.2.3 Primary Cutaneous Diffuse Large B-Cell Lymphoma, Leg Type

Treatment of DLBCLLT generally requires an intravenous anthracycline-based chemotherapy and can be used in combination with rituximab with CHOP chemotherapy (R-CHOP) [25, 133], although some studies have shown response to radiotherapy [25]. The role of radioimmunotherapy has still to be evaluated [134]. The prognosis for DLBCLLT is less favorable with a reported 5-year survival of 50–55% [29, 132], although one study revealed that patients with solitary lesions had no mortality at 5 years [135].

8.4.2.4 Primary Cutaneous Diffuse Large B-Cell Lymphoma, Other

In the case of IVLBCL, the preferred therapy again includes an anthracycline-based chemotherapy (R-CHOP) [136]. The prognosis is poor for these patients, with a 3-year survival of 56% with skin-only involvement and 22% with systemic involvement [29, 41].
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Core Messages

Four main subtypes of Kaposi Sarcoma (KS) with different epidemiological profiles are recognized, all show a male predominance among affected patients. Its associated infectious agent is human herpes virus type 8.

Classic KS mainly affects older men of Mediterranean and Jewish lineage and generally follows an indolent clinical course with lesions that favor the skin of the lower extremities. The AIDS- associated KS almost exclusively afflicts homosexual or bisexual men and is currently considered to be a AIDS- defining disease in industrialized countries.

Organ transplant recipients are another group susceptible to develop KS.

African KS appears in children.

Important is the amelioration of immunosuppression, besides, different local and systemic therapies are available.

9.1 Introduction

Kaposi Sarcoma (KS) was first described as “idiopathic multiple pigmented sarcoma” in 1872 by Moritz Kaposi, a Hungarian dermatologist working as a faculty member at the University of Vienna. In 1994, an associated infectious agent, KS-associated herpes virus (KSHV), also known as human herpes virus type 8 (HHV8), was identified. It remains uncertain if KS represents an infectious process, a reactive hyperplasia, or a neoplasm. It seems most likely that HHV8 infection in concert with other factors initiates a dermocutaneous hyperplasia. With
time and additional immunosuppressive influences, this hyperplastic process gains features which allow its classification as a sarcoma [1].

9.2 Epidemiology

Four main subtypes with different epidemiological profiles are recognized, all with a male predominance among affected patients.

9.2.1 Classic KS (sporadic type)

Classic KS mainly affects older men of Mediterranean and Jewish lineage, with specific geographic foci located in Italy, Greece, Turkey, and Israel. In the Mediterranean, an up to tenfold higher incidence of KS has been reported compared to the rest of Europe and the United States. The male/female ratio of KS is approximately 10:1–15:1. A direct correlation between HHV8 prevalence and classic KS incidence has been documented [2]. Among Italian men, a variety of unusual factors have also been identified as increasing the risk of the development of KS: reduced frequency of bathing, asthma, and the presence of symptomatic cutaneous eczematous states.

Classic KS generally follows an indolent clinical course with lesions that favor the skin of the lower extremities. Immunosuppression and advanced age are strongly associated with a poorer prognosis among Classic KS patients [3]. However, the patients often die of other diseases unrelated to KS. Among patients with classic KS, a high prevalence (up to 30%) of secondary malignancies has been reported, particularly non-Hodgkin lymphoma [4].

9.2.2 AIDS-Associated KS (epidemic Type)

The AIDS-associated KS almost exclusively afflicts homosexual or bisexual males (>95% of all AIDS-related KS), and is currently considered to be an AIDS-defining disease in industrialized countries. In developing nations, particularly in Africa, AIDS-related KS is also encountered in heterosexual adults and, less commonly, in their offspring. In the beginning of the AIDS epidemic, about 15–25% of all HIV-infected homosexual men suffered from KS, and intravenous drug abuse was not associated with an increased risk of AIDS-related KS. In the era of HAART, the incidence among HIV-positive homosexual men is only 5–7%. Interestingly, cigarette smoking confers at least some reduced risk of KS development in those who are HIV-infected.

The AIDS-associated KS differs from the classic KS in clinical features. For example, the face, genitalia, trunk, and oral mucosa are much more likely to be involved, and the disease generally runs a more aggressive course. There is also more frequent involvement of inner organs (30%) and shorter life expectancy (1.5–2 years). The incidence of the tumor parallels the degree of immunodeficiency as measured by CD4 counts and viral load. In persons infected with HIV, HAART use may reduce excess risk of KS and non-Hodgkin lymphoma [5].

9.2.3 Iatrogenic KS

Another group susceptible to develop KS are patients receiving immunosuppressive medication, particularly (but not exclusively) following organ transplantation. Patients with an ethnographic background favorable for classic KS are at special risk for developing iatrogenic KS. The male to female ratio described in literature ranges from 1.5:1 to 4:1. The incidence of KS in transplant recipients is 500 times greater than that in the general population. KS occurs in approximately 2.5% of all transplant recipients, first appearing 1.5–3 years post transplantation. Iatrogenic KS varies from a chronic, relatively indolent disorder to rapid progression with involvement of lymph nodes, mucosa, and inner organs in about half of the patients. The progression of KS correlates with the level of immunosuppression and with the drugs utilized. For example, sirolimus is less frequently associated with iatrogenic KS than cyclosporine. The potential for regression of iatrogenic KS following reduction or removal of immunosuppressive medication provided early evidence for the reversibility of this disease [1, 6].

9.2.4 African KS (endemic type)

African KS was well described before the advent of HIV-AIDS. Twenty five percent of childhood cancers
and 10% of all cancers in HIV-negative central Africans are related to the endemic version of KS. The male to female ratio is near unity in childhood, but rises in puberty to 15:1. Different types of African KS have been described. The nodular type with multiple tumor masses is associated with a more benign course, whereas the infiltrative type is more aggressive with bony involvement which spreads readily along the extremities. The lymphadenopathic variety of endemic KS most often affects children and young adolescents; it is often limited to the lymph nodes and viscera, and is known for its fulminant course, with death occurring typically 3 years after diagnosis [1, 7].

9.3 Pathogenesis

The development and progression of KS depend on the individual immune status, but are more common in AIDS-related immunosuppressed patients than in iatrogenically immunosuppressed patients after organ transplantation. The vast majority of cases occur in males and an association with KS and homosexuality has been described.

As noted previously, HHV-8 was identified in 1994 in KS of HIV patients by Moore and Chang, and has also been referred to as Kaposi’s sarcoma-associated herpesvirus (KSHV) [8]. Infection with HHV8 is an inevitable step in the development of all KS subtypes. However, HHV8 infection alone is insufficient to induce KS. The virus is transmitted sexually, but may also be shed in saliva. HHV8-DNA can be found in 98% of all KS in patients regardless of HIV serostatus. HHV8 creates an inflammatory-angiogenic condition via multiple signal transduction pathways. In KS patients, HHV8 infected endothelial precursor cells circulate in blood and may possess the capacity to integrate into newly forming vasculature. Worldwide, HHV-8 seropositivity has been found to vastly exceed the incidence of KS. Several virally encoded genes, including bcl-2 and interleukin 6, facilitate cellular proliferation and survival. Development of KS is further stimulated by various proinflammatory cytokines and growth factors such as tumor necrosis factor alpha, basic fibroblast growth factor, and vascular endothelial growth factor [2, 9]. HHV8 is the most frequent cause of malignancy in patients with AIDS. It produces not only KS, but also, less commonly, non-Hodgkin lymphoma (effusion lymphoma) and Castleman’s disease.

Along with HHV8 infection, immune dysregulation is the other common thread which links all forms of KS described above. Diminished responsiveness of cytotoxic T-lymphocytes has been found in all varieties of KS. Restoration of cytototoxicity, such as following administration of HAART or removal of iatrogenic immunosuppression, is associated with KS regression.

Uncertainty still exists regarding whether KS should be classified as neoplasm or hyperplasia, or as multicentric or metastatic [1]. Furthermore, the strong androtropism and the role of lymphedema in the pathogenesis of KS still remain unclear.

9.4 Clinical Features

KS presents as a multicentric neoplasm which develops from macules to plaques, nodules, and dome-shaped tumors (Fig. 9.1a, b). Chronic lymphedema can be observed prior to KS and may predispose to tumor development. Conversely, lymphedema of the legs or face may follow development of KS, and likely represent lymphatic obstruction by infiltrating tumor. Post-traumatic irradiation may also predispose to the development of KS. This disease may be just limited to the skin or may simultaneously involve the oral cavity, lymph nodes, or viscera. To some extent, the subtype of KS influences the clinical manifestation(s) most likely to be encountered.

Classic KS usually shows uni- or bilateral red or black-brown macules on the lower extremities. The macules may develop to nodules and tumors, and ulceration is common. Spontaneous regression has also been described. The location and distribution of AIDS-KS differs and may present with lesions on the face (e.g., tip of the nose, ear, eyelid margins), genitalia, and upper torso. Multiple firm red nodules develop and tend to evolve swiftly. Visceral involvement, primarily of the lungs and gastrointestinal tract, may lead to morbidity and mortality. Oral KS, mostly appearing on the hard palate, tends toward ulceration and often accompanies visceral disease. Visceral lesions are far less frequent in classic KS.

Different classifications for this multicentric cutaneous disease have been postulated. The value of each system is limited. Mitsuyasu and Schwartz et al.
proposed different classifications of four stages including all types of KS [10, 11]. The AIDS Clinical Trials Group classification uses three categories (tumors, immune system, and systemic diseases) to stage AIDS-associated KS [12].

9.5 Diagnosis

The diagnosis of KS is established based upon clinical presentation and histologic confirmation from a biopsy specimen. Detection of HHV8-DNA in the tumor tissue is not routinely done, but may help in clinically and histologically atypical cases.

9.5.1 Histopathology

All forms of cutaneous KS have similar histopathologic features, including involvement of the reticular dermis. Early patch stage lesions show a proliferation of dermal vascular channels surrounding normal dermal vessels and adnexal structures accompanied by a variable, inflammatory lymphocytic infiltrate with a prominent plasma cell component. A slight proliferation of spindle cells is seen in the vessels of the lower dermis. Extravasated erythrocytes and focal hemosiderin deposition are often evident. Plaque stage lesions show histopathologically an increase of spindle cells and vascular channels throughout the entire dermis, sometimes extending into the subcutaneous fat. The inflammatory component, as well as erythrocyte extravasation and hemosiderin deposition, is more pronounced. Nodular KS demonstrates a well-circumscribed but unencapsulated proliferation of spindle cells with mild to moderate atypia and a wide network of vascular channels filled with erythrocytes. The undifferentiated spindle cells may be strongly positive for CD34. KS is thought to arise from lymphoid endothelial cells. However, so far it is not possible to differentiate the endothelial cell of lymphoid origin reliably from endothelial cells of blood or primary mesenchymal origin [2]. In fact, the vast array of positive immunohistochemical stains seen in KS specimens suggests that perhaps the cell of origin is a pluripotential mesenchymal line.

9.5.2 Differential Diagnoses

The differential diagnosis is broad, especially in atypical cases and includes: arteriovenous malformations (pseudo–KS), severe stasis dermatitis (pseudo-KS), bacillary angiomatosis, benign angiomatosis, angiosarcoma,
hemangioma, pyogenic granuloma, and various deep fungal diseases. The presence of lymphedema may also suggest such diagnoses as angioedema, venous obstruction, and rosacea.

9.6 Therapy

A functioning immune system provides the best basis for any therapeutic intervention. Thus, any possible amelioration of immunosuppression should be entertained, as this represents an important part of KS therapy. All therapies for KS must be individualized, and depend upon size, location and number of lesions; presence or absence of symptoms; overall state of health including comorbidities; and goals of therapy (palliation vs. cure).

Classic KS usually progresses slowly and does not always require systemic therapy. Different management modalities for localized disease exist, extending from deliberate nonintervention to laser ablation, cryosurgery (for small, superficial lesions), local immune upregulation (e.g., imiquimod application), and intraleveal chemotherapy (e.g., monthly with vinca alkaloids – 60–90% response rate). The topical retinoids, such as 0.1% alitretinoin, may be applied up to four times daily for 1–3 months; responses are seen in about half of all patients, though local irritation may be severe. Surgical excision frequently leads to local relapses, but may still be a viable therapeutic option when other modalities are inappropriate. Radiotherapy has been successful (80–90% response) in early-stage disease confined to skin and mucosa. Radiation may be delivered via orthovoltage or electron beam sources. With widespread cutaneous disease, extended field electron beam therapy is preferable to irradiation of many individual lesions.

For disseminated disease, intraleveal injection of IFN and systemic treatment with IFN-alpha and/or chemotherapy (liposomal doxorubicin and daunorubicin, vincristine, vinblastine, bleomycin, and etoposid) have been utilized. Liposomal drugs have increased response rates while lowering the risk of cardiac and myelotoxicity. Combination of IFN with chemotherapy is not significantly better than either of these modalities alone, and thus, they should be used (if need be) in sequence.

For AIDS-related KS, antiretroviral therapy in combination with chemo- or immunotherapy (e.g., pegylated liposomal doxorubicin or daunorubicin – response rate ~80%, paclitaxel – 50–70% response rate, interferons) is the mainstay. A direct Anti-HHV8 effect of HAART has been noted. If KS appears during HAART, the efficiency of the chosen antiretroviral therapy regimen must be revaluated. Interferon-alfa (2a or 2b) is the biomediator drugs most often used. In the HAART era, IFN is typically given only in low doses (1–10 U/m² administered 3–7 times weekly). Subcutaneous administration of interleukin-12 has shown a remarkable effect in a small series, but remains experimental at this time [13].

In iatrogenic KS, immunosuppressive medication should be reduced or discontinued, if possible. The observation of regressive KS lesions on discontinuation of cyclosporine therapy and recurrence after drug reintroduction has led to a dubious distinction of cyclosporine as a factor in posttransplant KS. As noted previously, switching to sirolimus or other mTOR-inhibitors has shown promising results in organ transplant recipients [14].

In the future, more controlled-trials for therapy of all forms of KS will hopefully lead to more evidence-based recommendations [15]. At present, trials involving potent anti-viral drugs, epidermal growth factor receptor inhibitors, and antiangiogenesis agents are underway.

References


Other Skin Cancers
Fibrohistiocytic Skin Cancers and Extramammary Paget’s Disease

Thomas Stasko and Sarah Grummer

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Core Messages

- Dermatofibrosarcoma protuberaus is a rare malignancy of intermediate aggressiveness which usually presents as an asymptomatic, slowly enlarging, indurated violaceous to flesh-colored plaque. Subclinical histologic extension consisting of tentacle-like projections between subcutaneous shelf-like tumor masses makes complete excision, even with wide margins, difficult. Mohs surgery appears to offer the best chance for complete excision. Inhibition of platelet-derived growth factor receptors with imatinib may reduce tumor size in metastatic or unresectable tumors.

- Atypical fibroxanthoma is a spindle cell tumor most commonly found on actinically damaged skin, primarily the head and neck, of elderly Caucasians with a small potential for metastasis. It is characterized by spindle cells, bizarre multinucleated giant cells, xanthomatous cells and atypical mitoses. Complete excision, often with Mohs surgery, is the usual treatment.

- Most tumors formerly diagnosed as malignant fibrous histiocytoma have now been reclassified as non-sarcomatous malignancies. The remaining tumors, which tend to have a very aggressive course, are now best termed undifferentiated pleomorphic sarcomas.

- Extramammary Paget’s Disease is a rare cutaneous adenocarcinoma occurring on apocrine glandbearing skin in which the initial diagnosis is often delayed because of its clinical resemblance chronic conditions such as intertrigo or contact dermatitis. Because of an association with internal malignancies, a thorough work-up for other cancers is necessary.
10.1 Fibrohistiocytic Skin Tumors

Included in the category of fibrohistiocytic skin tumors are dermatofibrosarcoma protuberans (DFSP), atypical fibroxanthoma (AFX), and malignant fibrous histiocytoma (MFH). These dermal spindle cell tumors are uncommon; therefore, the effectiveness of treatment modalities is challenging to assess. Nevertheless, as these tumors may have a locally aggressive behavior and the potential for metastasis, definitive treatment is important. The management of these three fibrohistiocytic tumors will be reviewed.

10.2 Dermatofibrosarcoma Protuberans

DFSP is a relatively unusual malignancy of intermediate aggressiveness which constitutes less than 0.1% of all malignancies. Reported incidence ranges from 0.8 cases per million persons per year to five cases per million persons per year. A large age range from birth to 80 years of age has been reported; however, the majority of cases are in early to middle adult life, between 20 and 50 years of age [1]. There is a largely equal sex distribution. Some large series document a slight male predominance. DFSP most commonly arises on the trunk (50–60%), predominately on the chest and shoulders. Other reported common sites of involvement include the proximal extremities (25%) and the head and neck (10–15%) [2]. Systemic metastasis is rare and usually occurs in the setting of recurrent lesions during the later stages of disease.

Clinical features which characterize DFSP are an asymptomatic, indurated, slowly enlarging plaque that may appear violaceous, red-brown, or flesh-colored (Fig. 10.1). Often the plaque evolves into a multinodular mass, reaching several centimeters in diameter. Initial presentation as an atrophic plaque has been noted in some cases [3, 4]. These nonspecific features

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**Fig. 10.1** DFSP. (a) Early DFSP. This photo was taken as part of photographic mapping after the removal of dysplastic nevi. The small scar-like lesion in the right inframammary area was assumed to be a scar from a previous biopsy. (b) DFSP 7 years later. There is a plate-like subcutaneous mass. (c) Defect after MMS
and the indolent behavior often lead to a delay in diagnosis (Table 10.1). The majority of patients have a long preoperative course, often on the scale of 10–20 years, most likely corresponding to the plaque stage of the disease. Rarely regional and/or distant metastases occur, most commonly to the lung. The risk of metastasis appears to increase with repeated incomplete excision and dedifferentiation toward a higher-grade fibrosarcoma [2].

The mainstay in therapy for DFSP is surgical resection (Table 10.2). DFSP has an infiltrative nature, growing slowly and contiguously with wide extension between adjacent collagen bundles, sometimes extending even into the underlying fascia and muscle [2]. Given the subclinical extension of DFSP, very wide surgical margins were initially felt necessary in order to remove the tumor entirely. A review of the literature revealed that as late as 1997, the recommended first-line therapy for DFSP was wide resection with 3–5 cm margins of normal tissue and deep resection [5]. Even with wide and deep margins, DFSP has a tendency to recur after excision. Histologic exam has demonstrated that peripheral portions of DFSP often exhibit tentacle-like projections of neoplastic cells that extend laterally between normal collagen bundles and deeply into fascia and muscle. Based on three-dimensional reconstructions of DFSP removed viaMohs Micrographic Surgery (MMS), a gross tumor structure with shelf-like tumor aggregates in multiple superficial and deep tissue planes joined by fingerlike projections and with fingerlike projections eccentrically from the periphery has been proposed [6] (Fig. 10.2). These extensions cannot be appreciated clinically and may be overlooked histologically by any technique that does not examine the entire undersurface and lateral margins of the specimen [1]. It has been proposed that failure to remove such projections is the reason for the high local recurrence rates after excision of DFSP.

Rates of recurrence after undefined or conservative surgical margins range from 25 to 60%, with a total rate of 44% during a follow-up period ranging from 1 to 34 years. In an attempt to improve on such rates, the recommendation for even wider surgical margins, such as 2 cm or more beyond the tumor border down to fascia, was introduced. However, even with margins of at least 2 cm, recurrence rates up to 60% have been reported, with an overall rate of 20% during follow-up varying from 1 month to 30 years [1]. Although the rates of recurrence are notably improved with wider margins, the recurrence rate is still excessive. A metaanalysis of the peripheral excision margins for DFSP, which reviewed 98 cases, showed a surgical margin of 3 cm would clear less than 90% of the lesions and even 4 cm would only clear 95% of small to moderate DFSPs [7].

| Table 10.1 | Differential diagnosis of DFSP |
| Clinical | Histologic |
| Morphea | Dermatofibroma |
| Dermatofibroma | Dermatomyofibroma |
| Scar | Neurofibroma |
| Keloid | Scar |
| Malignant fibrous histiocytoma | Fibrosarcoma |
| Fibrosarcoma | Malignant peripheral nerve sheath tumor |

| Table 10.2 | Treatment of DFSP |
| Treatment modality | Advantages | Disadvantages | Comments |
| Wide-local excision | Has been the accepted treatment modality | High recurrence rate even with wide margins | A multidisciplinary approach with MMS, permanent sections of final layers with or without IHC and involvement of surgical oncology or plastic surgery may be optimal for large tumors |
| MMS | Allows for analysis of tumor margins with permanent sections and IHC | Breadloaf sections may miss tumor extension | Not FDA approved for this indication |
| | Allows tracking of fingerlike tumor projections | Frozen section interpretation of DFSP may be difficult | Imatinib followed by MMS may allow for smaller surgical defects |
| | Allows removal of eccentric tumor growth without removal of excess normal tissue in noninvolved areas | Deep tumor may be difficult to remove under local anesthesia | |
| Imatinib | May shrink or resolve tumor without surgery | Response rates and tumor clearance rates have yet to be determined in trials | |
An advantage of MMS is the detection of these asymmetric projections, allowing the sparing of normal tissue in uninvolved directions. The efficacy of MMS in the treatment of DFSP has been well documented in the literature. The precise margin control allows the microscopic extensions to be detected and removed with accuracy as opposed to the random individual sections examined in an excisional specimen utilizing standard step vertical sections. These step sections may exclude fingerlike extensions present in the unexamined 2-4 mm of tissue between examined sections [1]. Over the past decade, MMS has become the accepted first-line treatment for DFSP with marginal recurrence rates ranging from 1 to 3%. Ratner et al. reported the results of a series of 50 patients with primary and recurrent DFSP treated with MMS. The mean follow-up period was 4.8 years during which only one patient had local recurrence [3]. In a review of the world literature in 1997, the cumulative recurrence rate with MMS was 2.4%. In 2002, a second review of the world literature by Nouri et al. reported a recurrence rate of 2.3% in 221 patients with DFSP treated with MMS. Park et al. emphasizing the ability of MMS to deal with the asymmetric growth patterns of DFSP, reported clearance of all tumors with a margin of 2.5 cm or less, with 80% cleared with only a 1.5 cm margin [9].

The histopathologic interpretation of DFSP in hematoxylin-eosin stained frozen sections during Mohs surgery can be difficult [10] (Fig. 10.3). These difficulties may be amplified at the margins of the

For some tumors, even a 10 cm margin of excision will not provide microscopic clearance [8]. In addition, the tendency of the tumor to occur in cosmetically sensitive areas makes wide excision and the subsequent extensive closures prohibitive [9].
tumor, and especially, in areas where scar tissue has formed secondary to previous excisions or biopsies. The use of CD34 staining for immunohistochemical margin control on MMS excisions proved successful for Jimenez and colleagues in delineating DFSP tissue from normal or scar tissue [11]. Although the sensitivity of CD34 staining of DFSP is not 100%, it may be a helpful tool to augment MMS frozen sections [10]. Sending an extra tissue layer (5 mm around the surgical defect) or the final stage of MMS for permanent section and CD34 immunostaining has been employed by others. This step helps reduce the possibility of remaining microinfiltrates due to the difficulty in distinguishing the spindle cells of DFSP from fibroblasts or scar tissue on H&E frozen sections at the time of MMS [5]. Finally, some authors recommend modified MMS on paraffin-embedded sections. This method utilizes routine histology techniques, including immunohistochemistry for CD34. This method allows for high quality slides, accuracy in discriminating fine tumor strands from normal skin, and a clear survey of the excised tumor [12, 13]. However, the procedure requires 24 h or more between MMS stages to allow for tissue processing.

Other treatment modalities for DFSP are also available. Adjuvant radiation therapy has been used for the management of microscopic residual disease in inadequately excised lesions or as a primary modality when complete resection would require severe cosmetic or functional loss. Close follow-up is mandatory as radiation therapy has the possibility of inducing a higher grade, more pleomorphic tumor [1]. Greater than 90% of DFSP cases are associated with a chromosomal translocation involving the COL1A1 gene on chromosome 17 and the platelet-derived growth factor B gene on chromosome 22 [14]. Recent data show that inhibiting platelet-derived growth factor receptors (PDGFR) with imatinib, an inhibitor of PDGFR and other tyrosine kinases, can induce high rates of clinical response in patients with unresectable or metastatic DFSP [14]. Treatment of DFSP with imatinib prior to MMS to reduce tumor size has recently been proposed [15].

Half of all DFSP recurrences are observed within the first year after treatment and 80% are seen within the first 3 years after surgery [3]. However, recurrences have been noted as long as 10 years after resection. Therefore, patients should be examined frequently, every 3–6 months, during the first 3 years after resection and annually thereafter for life [1].

10.3 Atypical Fibroxanthoma

AFX is an uncommon low-grade spindle cell tumor most commonly found on actinically damaged skin, primarily the head and neck, of elderly Caucasians. The tumor often begins as a pink to erythematous, small, firm nodule. It may grow rapidly and ulcerate. (Fig. 10.4) A second, smaller group of patients has localized lesions on normal appearing skin of sun-protected areas, specifically the trunk and extremities. The median age of this group is the fourth decade. Clinically, these lesions are often large, less well demarcated, and more nodular in appearance, with extension into the subcutaneous tissue [16]. Identified factors that may predispose an individual to AFX include sun exposure, local skin trauma, and previous radiation therapy [17]. Histologically, AFX reveals a dermal nodule with spindle cells, bizarre multinucleated giant cells, and xanthomatous cells. Many mitoses, often atypical, can be present [18] (Fig. 10.5) (Table 10.3). AFX has been termed a superficial variant of MFH. It has been proposed that the difference between AFX and MFH lies in mutations in ras oncogenes, which are present in MFH and not in AFX. The absence of these mutations may explain the less aggressive course of AFX [19]. With the reclassification of most of the tumors previously diagnosed as MFH, the relationship of AFX to MFH must also be reevaluated. Some current evidence suggests that AFX may derive from UV-damaged dermal fibroblasts [19–21]. On immunohistochemistry, AFX is usually positive for vimentin and often expresses alpha1-antitrypsin,
alpha1-antichymotrypsin. CD10 was recently found to be positive in 94% of AFXs [22].

Although AFX follows a relatively benign course, the literature has been peppered with reports of AFX complicated by local recurrence, in transit metastases, and nodal disease. The rates of local recurrence range from 2 to 20% and often occur after incomplete excision [23]. Further, regional metastasis, occurring in 1% of cases, is more likely to occur if the original tumor is large, deep, and necrotic; shows vascular invasion; is in an area of previous radiation exposure; or in an immunocompromised host [23–25]. When metastatic lesions do occur, they are usually preceded by one or more locally recurrent tumors [23].

Historically, AFX has been treated with wide local excision and narrow, or inadequate, surgical margins have been described as a potential cause of recurrence [23]. The average size of AFX is 15–20 mm with an average preoperative size of 17 mm [18]. Subclinical spread is estimated to average 10 mm [26]. The literature indicates that MMS requires an average of two stages to clear the tumor with a resultant defect of 29 mm [18]. Thus, MMS can be an important tool in tissue sparing and reducing recurrence on the cosmetically sensitive areas of the head and neck where AFX is prone to arise. Reviews comparing MMS to wide excision reveal a 0% recurrence rate at mean follow-up of 29.6 months with MMS and 16% recurrence rate at mean follow-up of 73.6 months, with conventional excision [23]. In another study, during a follow-up period of 3.3 years, the recurrence rate after MMS for AFX was found to be 6.9% [27]. The advantages of MMS are tissue conservation in important cosmetic areas and the assurance of tumor-free margins at the time of surgery [16].

### 10.4 Malignant Fibrous Histiocytoma

What has been termed in the past as MFH is the most aggressive of the fibrohistiocytic tumors and is associated with a poor prognosis secondary to the high local recurrence rate and a significant rate of metastasis. MFH came to be described as the most common of all soft tissue malignancies and usually developed late in adult life, between the fifth and seventh decades. MFH was more common in Whites than Asians or Blacks, and slightly more common in men than women. The primary sites of involvement were noted to be the extremities, especially the thigh, buttock, and limb skeletal muscles [16], and the retroperitoneum, although MFH has been described in almost any soft-tissue area of the body.

MFH was classified as superficial or deep, with the superficial variant confined to the subcutaneous tissue with or without attachment to the fascia [16]. The majority (90%) of MFH tumors described were deep and extended from the subcutaneous tissue through the fascia into the muscle, or were entirely located in the muscle [28]. MFH typically presented as a painless, solitary, enlarging nodule of several months duration (Fig. 10.6). Multinodular tumors have been documented and the size of the tumor at time of diagnosis has been reported to range from 5 to 10 cm.

In spite of MFH being considered the most common soft tissue malignancy, the 2002 World Health Organization (WHO) classification of soft tissue
tumors [29] reinforces an evolving opinion that most MFH should be more precisely categorized as types of pleomorphic sarcoma. Dei Tos [21] in 2006 detailed the progress in classification. In 1992, Fletcher proposed that the MFH did not represent a discrete diagnosis, but rather a morphologic pattern which could be observed in a number of poorly differentiated soft tissue malignancies [30]. Advances in histology, immunohistochemistry, electron microscopy and genetic profiling have allowed for the classification and subclassification of many tumors with the recognition that most were not compatible with a sarcoma of histiocytic origin. Although the WHO classification maintains the term MFH as a synonym for undifferentiated pleomorphic sarcoma, in the future the term will likely fall into disuse [21].

Five subtypes of MFH have been classically described: pleomorphic-storiform (most common), myxoid, giant cell, inflammatory, and angiomatoid. Many tumors once termed pleomorphic or storiform MFH are now being identified as nonsarcomas. These carcinomas, melanomas, and lymphomas with sarcomatoid, pleomorphic changes are now being better classified with resulting alterations in prognosis and treatment. The remaining undifferentiated pleomorphic sarcomas probably represent <5% of sarcomas. This category does clinically correspond to the clinical course of MFH above. The histology of these lesions is quite variable, but most show severe pleomorphic changes. The cellular atypia is similar to that of AFX with large, bizarre multinucleated giant cells, spindle cells, foamy histiocytes, and often prominent mitoses (Fig. 10.7). In most instances, the tumors are only consistently positive to immunohistochemical staining for vimentin [21].

The myxoid subtype of MFH has been synonymous with myxofibrosarcoma and that term is probably preferred. It is a common sarcoma in the elderly and usually presents on the extremities, but can occur on the trunk, head, or neck. Most are superficial, multinodular tumors. Histology extends from low-grade to high-grade with a corresponding range of prognosis [21]. Low-grade myxofibrosarcoma rarely metastasizes [31], while high-grade tumors may spread in up to 35% of cases [32].

What had been termed inflammatory MFH is now felt to represent a diverse group of unrelated tumors. Many of these lesions, which commonly occurred in the retroperitoneum, could be properly classified as lymphomas, leiomyosarcomas, or carcinomas [21]. One subset of inflammatory MFH has been described as dedifferentiated liposarcoma [33].

Giant cell MFH has also been found to include a number of more specific types of sarcoma including giant cell tumor of soft tissue, extra skeletal osteosarcoma, and leiomyosarcoma with osteoclastic giant cells [21].

Angiomatoid MFH is now felt to be a low-grade malignancy in which the cell of origin has not yet been identified. This tumor, which usually presents in younger patients, has a low metastatic rate (<2%) and those metastases are usually to the regional lymph nodes [21].
With reclassification of most MFH lesions (Table 10.4), treatment plans have required similar alterations. Most reported series probably represent treatment of a heterogeneous group of tumors. Surgical excision has been the primary mode of therapy for MFH. Historically, the recommendation has been aggressive wide and deep local excision, even for superficial tumors, given the usual spread of the tumor over a considerable distance beyond gross tumor margins [16]. The literature indicates a recurrence rate ranging from 44% after traditional wide excision to 71% after simple complete clinical excision [27]. Reported rates of recurrence after MMS range from 6 to 43%. Although some reported recurrence rates with MMS are similar to those with wide local excision, the major advantage of MMS remains the possibility of tissue conservation.

At first diagnosis, attempts should be made to further classify any lesions diagnosed as MFH or undifferentiated pleomorphic sarcoma. For tumors remaining in the category, the clinician should perform a complete lymph node exam and any suspicious enlargement should be biopsied. As the lung has been a primary site of metastatic disease, a chest radiographic evaluation should be performed as well [16]. Furthermore, given the high recurrence and metastatic rate of this tumor, adjuvant radiation therapy and/or chemotherapy for high risk tumors has been advocated. Consultation with medical and surgical oncologists should be obtained early to allow proper treatment planning in these patients [16].

10.5 Extramammary Paget’s Disease

Extramammary Paget’s Disease (EMPD) is a rare cutaneous adenocarcinoma occurring on apocrine gland-bearing skin. Caucasians between the fifth and eighth decades are most frequently affected, with a female predominance. The vulva is the most common site of involvement, although perineal, perianal, scrotal, and penile skin may also be affected [34] (Fig. 10.8). Perianal EMPD has frequently been reported in association with adenocarcinoma of the colon and occasionally may be due to direct extension of an adenocarcinoma of the gastrointestinal tract [35]. Ectopic EMPD has occurred in areas devoid of apocrine glands, but is rare [36].

The clinical appearance of EMPD is of a well-defined, moist, red or white, eroded plaque that may be accompanied by pruritus and discomfort [36, 37]. The nonspecific clinical presentation may lead to misdiagnosis as the lesions mimic chronic candidal intertrigo; contact, irritant, or seborrheic dermatitis; tinea cruris; inverse psoriasis; and Bowen’s disease [38]. (Table 10.5) On average, a full year may pass before biopsy of the lesion is performed [39]. EMPD may occur as a primary process, also known as cutaneous or primary EMPD [34, 40, 41]. This form, which is initially limited to the epithelium, may slowly progress to an invasive tumor, involving the dermis, blood, and lymphatic vessels. Lymph node or visceral involvement may occur in

![Fig. 10.8 EMPD presenting in the groin area of an elderly male. The erythematous, scaly plaque had been previously treated as tinea and psoriasis](image-url)
Other Skin Cancers

The precursor cell of origin is unknown; however, it may correspond to an undifferentiated pluripotent cell of the epidermis or its adnexa [34, 41]. The secondary form of EMPD is associated with epidermotropic spread of malignant cells from an underlying neoplasm in a dermal adnexal gland or a local internal organ with contiguous epithelium [34, 41].

EMPD can have a striking histologic appearance with a proliferation of large, intraepidermal atypical cells with abundant pale-staining cytoplasm and atypical nuclei. The atypical cells may extend down adnexal structures (Fig. 10.9). Often the basal cell layer is compressed, but otherwise spared. Although not completely specific, Cytokeratin 7 is a sensitive marker for EMPD [43, 44].

Given the association of underlying malignancy, the diagnosis of EMPD must trigger a work-up that is directed by the locality of the skin lesions. In addition to a full skin exam and palpation of all lymph nodes, the following exams may be indicated depending on location of skin lesions: rectal exam, sigmoidoscopy, cystoscopy, pelvic exam with Papanicolaou test, colposcopy, and breast exam. Imaging studies should be used to augment the physical and endoscopic examinations in assessing possible undetected internal malignancy. Patients with clinical evidence of nodal involvement may benefit from therapeutic regional lymph node dissection; however, there is no evidence that elective lymph node dissection, in the absence of palpable nodes, improves survival [45].

When possible, the treatment of choice for EMPD is surgical excision. However, EMPD represents a surgical challenge given its frequent large size and high local recurrence rates attributed to irregular margins, multicentricity, and propensity to microscopic extension [34, 35, 45]. The reported marginal recurrence of EMPD after wide local excision ranges from 30 to 60% at a mean of 54–96 months of follow-up, with invasive disease showing higher rates of local recurrence than in situ disease [35, 36, 45]. The reported marginal recurrence of EMPD after wide local excision ranges from 30 to 60% at a mean of 54–96 months of follow-up, with invasive disease showing higher rates of local recurrence than in situ disease [35, 36, 45]. The reported marginal recurrence of EMPD after wide local excision ranges from 30 to 60% at a mean of 54–96 months of follow-up, with invasive disease showing higher rates of local recurrence than in situ disease [35, 36, 45]. The reported marginal recurrence of EMPD after wide local excision ranges from 30 to 60% at a mean of 54–96 months of follow-up, with invasive disease showing higher rates of local recurrence than in situ disease [35, 36, 45]. The reported marginal recurrence of EMPD after wide local excision ranges from 30 to 60% at a mean of 54–96 months of follow-up, with invasive disease showing higher rates of local recurrence than in situ disease [35, 36, 45]. The reported marginal recurrence of EMPD after wide local excision ranges from 30 to 60% at a mean of 54–96 months of follow-up, with invasive disease showing higher rates of local recurrence than in situ disease [35, 36, 45].

Another comparison showed recurrence rates of 27 and 28% after MMS for vulval and perianal EMPD, respectively, compared to 43 and 50% for wide local excision [36]. A retrospective review of EMPD with 59 months of follow-up revealed a marginal recurrence

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**Fig. 10.9** Histopathology of EMPD. (a) “Pagetoid” proliferation of large, intraepidermal atypical cells with abundant pale-staining cytoplasm and atypical nuclei. (b) Cytokeratin 7 staining of the same cells
of 16% with MMS in primary cases and 50% in recurrent cases [45]. Thomas et al. reported no recurrences in ten cases of EMPD after MMS with a mean follow-up time of 34 months. The authors acknowledge that continued follow-up might reveal future recurrences [46]. It should be noted that a multidisciplinary approach that involves a colorectal surgeon, urologist, and gynecologist in the work-up is necessary as their expertise may be needed in following extensions of the disease, such as to the urethra or anus, and in repairing defects [37].

Some argue that MMS is not well suited for the treatment of EMPD given the multifocal, perhaps noncontiguous nature of the process. Studies have supported the use of perioperative tumor mapping. Such mapping can be achieved photodynamically with the topical application of delta aminolevulinic acid to help delineate the extent of the disease followed by scouting biopsies. Additionally, the use of topical fluorouracil, which results in inflammation and redness in the involved skin, has been made to delineate the tumor prior to excision [28]. It should be noted that PDT has also been used to reduce tumor size prior to surgery and to treat residual tumor after chemoradiotherapy [34].

Other treatment modalities for EMPD have been described. Laser excision is associated with high recurrences. A comparison of patients treated with wide local excision, laser alone, or limited surgery plus laser revealed recurrence rates at 1 year as follows: wide local excision 23, laser alone 67, and laser and surgery 33% [47]. It has been proposed that laser treatment may be more effective after visualization with delta-aminolevulinic acid. Radiotherapy has been indicated for patients medically unfit for surgery, recurrence following surgery, in patient’s wishing to preserve functional and structural integrity of the vulva, or as an adjuvant to surgery in patients with an underlying adenocarcinoma where there is a high risk of recurrence with surgery alone [34]. Systemic chemotherapy (e.g., docetaxel, 5-FU, vincristin, mitomycin-C, carboplatin, etoposide) has been used when surgery and radiotherapy are contraindicated [36, 41] or to reduce tumor bulk prior to surgery attempting to avoid extensive vulval resection and skin grafting [48].

Topical chemotherapy is another treatment modality that has been explored for the treatment of EMPD. Topical 5-fluorourcil (5-FU), bleomycin, and more recently imiquimod have all been employed. 5-FU has been used for symptomatic relief, preoperative delineation of disease extent, cytoreduction prior to surgery, and postoperative detection of early disease recurrence [34]; however, it is not usually considered curative due to the limited depth of penetration of only 1–2 mm, representing the superficial layers of epidermis [34]. More recently, immunotherapy with topical imiquimod 5% cream at least three times each week for a minimum of 8 weeks, and as long as 16 weeks, of treatment has been shown to be successful for the treatment of EMPD limited to the skin [38]. It has been suggested that topical imiquimod can be used as monotherapy or as an adjunctive treatment before subsequent surgical intervention or other modalities for persistent disease [38].

The reports of the median time to recurrence after MMS for primary and recurrent tumors range from 29 to 36 months [45] with some reports indicating recurrences as long as 15 years after initial treatment [34]. Follow-up should be long-term to exclude local recurrence and development of associated malignancy. Specific recommendations for perianal EMPD include annual complete exam and proctosigmoidoscopy, punch biopsy of any new lesions [34], and colonoscopy repeated every 2–3 years. Vulval EMPD should be followed with regular inspection of the vulva, pelvic exam with PAP smear, punch biopsy of new lesions, and regular pelvic ultrasound and hysteroscopy [34].

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E. Stockfleth et al. (eds.), Managing Skin Cancer,
DOI: 10.1007/978-3-540-79347-2_11, © Springer-Verlag Berlin Heidelberg 2010
11.1 Immunosuppression

M. Ulrich and C. Ulrich

Core Messages

- Skin cancer is the most common neoplasm in organ transplant recipients (OTR)
- Actinic keratosis and squamous cell carcinoma represent the most common malignant skin tumour in OTR
- Risk factors include increased age at time of transplantation, chronic sun-exposure, skin type and immunosuppressive medication (type, duration, level/dosage)
- Sun protection including the use of highly protective sunscreen is very important and represents the basis of management
- Interdisciplinary management and close collaboration with transplant physicians is necessary which include the optimization of immunosuppressive medication

11.1.1 Introduction

During the past decades, the population of immunosuppressed patients has increased worldwide. Solid organ transplantation has successfully been performed for a variety of end-stage organ diseases and the development of new and potent immunosuppressive drugs has led to a prolonged long-term survival after transplantation. Prevention of allograft rejection and maintenance of organ function are achieved by effective systemic immunosuppression. However, side effects associated with immunosuppressive medication occur and may effect survival in these patients. Skin cancer is the most common neoplasm in organ transplant recipients (OTR) and may show an aggressive course with potential lethal outcome. Therefore, prevention, early recognition, and effective treatment of cutaneous malignancies are of special importance in these patients.

Besides medical immunosuppression after transplantation or for the treatment of autoimmune disorders, diseases with impaired immune function like HIV, lymphoma, and leukemia may increase the susceptibility for skin cancer. Herein, we will focus on the different cutaneous neoplasm in organ transplant patients.

OTR have an increased risk for developing skin cancer when compared to the normal, immunocompetent population. In fact, nonmelanoma skin cancer (NMISC) represents the most common tumor occurring after organ transplantation.

A report from the United States examining the rates of malignancies of 35763 first-time renal transplant recipients using Medicare billing claims showed a cumulative NMISC incidence of 7.43% after 3 years posttransplantation [1]. In the same study, the total number of tumors after kidney transplantation excluding skin cancer was 7.45% after 3 years. This analysis illustrates the high incidence and importance of skin cancer among transplant patients. Different factors have an impact on the development of skin cancer in OTR, including the patients age; previous and current sun-exposure; type, duration, and level of immunosuppression; human papillomaviruses; and individual susceptibility.

11.1.2 Squamous cell carcinoma

The most common invasive cutaneous tumor after transplantation is squamous cell carcinoma (SCC). Compared with the normal population, the incidence of SCC shows a 65–100-fold increase in OTR [2, 3]. Furthermore, the SCC:BCC (basal cell carcinoma) ratio is reversed in OTR with SCC being 2–4 times more frequent than BCC. In the normal population BCC occurs four times more frequently than SCC. Besides its common occurrence, SCC in transplant recipients shows a different biologic behavior and a more aggressive course with higher recurrence rates, increased risk of metastasis, and development of multiple and subsequent SCCs.

Well-known risk factors of SCC include chronic UV-exposure, fair skin type, and advanced age, and do apply to the general and the transplant population.
However, special risk factors are important post-transplantation. Patients of older age at the time of transplantation have a greater risk and show earlier occurrence of SCC. Furthermore, the type, duration, and level of immunosuppressive medication have an influence on the development of SCC.

Patients with higher levels of immunosuppression bear a greater risk of developing SCC and patients with transplanted organs that generally require higher maintenance dosages like heart or lung transplant patients have increased risk of skin cancer. Furthermore, the risk increases with the duration of immunosuppression. Data from Australia showed that the incidence of NMSC increased from 29% after 5 years to 52% after 10 years, and 82% after more than 20 years [4]. Regarding the type of immunosuppressants, multiple studies have been performed, but no concordant results have been reported. However, besides the immunosuppressive effect of these drugs that may lead to greater susceptibility for UV-damage by impaired immunologically driven repair function, direct carcinogenic effect of some immunosuppressants has been demonstrated. In this context it has been shown that Azathioprine acts via intercalation in the DNA and leads to misreading and inhibition of DNA repair. Furthermore, it has been shown that the accumulation of 6-thioguanine in the DNA caused by azathioprine in combination with UVA exposure causes reactive oxygen species and therefore has indirect carcinogenic potency [5]. Cyclosporine has also been proposed to have direct carcinogenic effects by induction of growth factors and a subsequent effect on angiogenesis, tumor growth, and metastasis. Recently, novel pharmaceutical agents, namely mTor inhibitors, have been introduced for posttransplant immunosuppression. Two mTor inhibitors, sirolimus and everolimus, are currently approved as immunosuppressants after organ transplantation. In contrast to Calcineurin inhibitors, mTor inhibitors have antitumoral properties via direct inhibition of cancer cell replication and induction of apoptosis and also indirectly inhibit tumor growth by inhibition of vascular endothelial growth factor (VEGF) expression [6]. Furthermore, Sirolimus has been shown to inhibit UVR-related carcinogenic mechanism including the expression of Matrix-Metalloproteinases (MMP), TNFα, and p53 [7, 8]. Clinical studies have been performed and support the antineoplastic properties of mTor inhibitors in transplant recipients. A study evaluating patients under combination of Sirolimus and Cyclosporine showed a significantly lower skin cancer incidence of 2.4% after a median follow-up of 62 months [9].

An association of human papilloma viruses (HPV) and posttransplant SCC has been proposed and several HPV-types have been detected, prevalences of up to 90% have been reported in posttransplant SCC with PCR [10]. Furthermore, the co-existence of viral warts, actinic keratoses (AK), and SCC in areas of sun-exposed skin has led to the concept of progression from warts into SCC. However, several studies failed to prove this theory. Furthermore, HPV may, to a lower extent, also be found in healthy skin and has also been detected in BCCs of transplant patients. Therefore, the role of HPV in the carcinogenesis of posttransplant SCC remains controversial, and unlike HPV and cervical cancer, no clear association has been shown for SCC (Fig. 11.1).

Patients with a previous history of SCC are at special risk as this has been shown to be the best predictor for the development of subsequent SCCs after transplantation [4]. The clinical presentation may differ from SCCs occurring in the immunocompetent population. SCC typically presents as scaly or hyperkeratotic, erythematous nodule or plaque that occurs in areas of sun-damaged skin, often adjacent to AK. Ulceration, crusting, or even a cutaneous horn may occur. The most common location is on the head and neck, followed by the dorsum of the hand and forearms. The problem of SCC in OTR is the tendency of developing multiple SCCs. After the first SCC the risk of developing subsequent SCCs is 60% [11]. The biologic behavior of SCC in

![Fig. 11.1 Verrucous carcinoma (VC) in a 68 year old heart transplant recipient located on the left malleolus medialis. VC is considered as a well-differentiated variant of squamous cell carcinoma with low risk for metastasis and HPV-association]
OTR is more aggressive with approximately 14% of kidney transplant patients showing local recurrence and up to 9% of cases developing metastasis from SCC. High risk SCCs clinically appear as large, deeply infiltrating tumors with ill-defined borders, rapid growth, and ulceration. Histologically, high risk tumors show poor differentiation and/or perineural and/ or vascular invasion and infiltration of the subcutaneous fat [12].

Any lesion suspicious for SCC requires a biopsy for histological confirmation. The gold standard of treating SCC is Moh’s or micrographic controlled surgery. If simple excision is performed, a minimum of 4–6 mm margin should be performed. Other treatment modalities may be performed in special cases including cryotherapy or shave biopsy [12]. Management of patients who develop multiple SCCs, high risk SCCs, or metastasis often remains challenging and does require a multidisciplinary approach. In these patients, reduction of immunosuppression and/or switch to mTor inhibitors should be considered and discussed with the responsible transplant physicians. Treatment of coexisting AK is required in order to reduce the risk of these carcinomata in situ to develop into SCC. Sentinel lymph node biopsy (SLNBx) is recommended in high risk SCC, and in case of positive SLNBx, node dissection or radiotherapy should be performed. Furthermore, chemoprevention with systemic retinoids may be beneficial, and in case of metastasis, combination of surgery, radiotherapy, and chemotherapy may be required (Fig. 11.2).

**Actinic keratoses (AK)** have recently been defined as in situ SCC of the skin [13]. Long-term ultraviolet radiation is the most important risk factor for AK and leads to field damage with subsequent malignant transformation of keratinocytes in areas of chronic UV-exposure. Therefore, AK do usually not occur as single lesion, but multiple in actinically damaged skin, and in this regard, the term “field cancerization” has been defined [14]. AK are very common post transplantation. Data from the UK show a prevalence of 38% 5 years after renal transplantation [15]. In areas of greater sun exposure, the rates of AK are much higher; a study from Australia showed that 56.6% of patients developed AK 7 years post transplantation.

AK clinically present as erythematous, rough plaques with scaling, crusting, and hyperkeratosis on sun-exposed skin sites (scalp, face, dorsum of the hands, forarms, etc.). Flat lesions may be better felt than seen and typically show a rough, sandpaper-like appearance on palpation. Regarding the high incidence of AK in OTR and the potential of progression into SCC, effective treatment of the whole actinically damaged areas is recommended. Different treatment modalities have been used and a summary is given below. Cryotherapy with liquid nitrogen has widely been performed for AK. However, only single lesions are treated and the recurrence rates are high. Side effects include pain, burning, crusting, and scarring, and hypopigmentation frequently occurs. Topical 5-FU may be used for multiple AK in OTR. It does, however, lead to significant irritant toxic skin reactions and recurrence frequently occurs. Side effects include crustung, burning, crusting, blistering, and scarring, and hypopigmentation frequently occurs. Photodynamic therapy has been used for the treatment of AK in transplant recipients. Initial clearance rates have been shown to be similar to those in the immunocompetent population, but drop to 48% complete cure rate after 48 weeks, compared to 72% in control patients [16]. Most common side effects are pain, burning, and stinging during the therapy. Erythema is common and crustung may occur. The cosmetic outcome is usually very good. Imiquimod 5% cream is commonly used for the treatment of AK in the immunocompetent population. It has recently been shown to be effective and safe in transplant recipients. In a multicenter study including 43 patients, a complete clearance of 62.1% was achieved. No alteration regarding organ function was observed and no rejection occurred. The topical

![Fig. 11.2 Field cancerization Clinical presentation of actinic field cancerization in an immunosuppressed patient with multiple actinic keratosis and an invasive squamous cell carcinoma in the center of the image](image)
immunomodulating effects of Imiquimod do not seem to influence the systemic immunosuppression, and therefore, organ function remains unaffected [17]. *Three percent Diclofenac in 2.5% hyaluronic acid* has been evaluated in a preliminary study for the application in OTR. In a case series of 6 patients, 50% of patients had complete clearance after 16 weeks and this response rate is similar to the control population. Mild local reaction with erythema and scaling was observed, close monitoring of laboratory parameters including creatinine did not reveal any pathological findings [18]. *Systemic retinoids* have been introduced for the chemoprevention of AK and invasive SCC in organ transplant patients. Dosages of 0.2–0.4 mg/kg/day have been recommended and a decrease in AK numbers of 50% has been reported. However, another study showed only a relative decrease of 13.4%. Side effects including xerosis, peeling, cheilitis, hyperlipidaemia, and musculoskeletal symptoms are common and limit the use in OTR.

### 11.1.3 Basal Cell Carcinoma (BCC)

BCC is the most common cancer in humans, but only the second most common skin cancer in OTR. The incidence is increased about tenfold compared to the normal population [19]. Furthermore, organ transplant patients develop BCC earlier than the immunocompetent population (54.6 vs. 69.8 years). Further differences include the predominance of superficial BCCs and a location on trunk and extremities [20]. The clinical appearance is consistent with BCCs in the immunocompetent population, and in contrast to SCC, BCC do not tend to be more aggressive posttransplantation. The treatment of BCC is similar to that in nonimmunosuppressed patients (Fig. 11.3).

### 11.1.4 Merkel Cell Carcinoma (MCC)

Merkel cell carcinoma (MCC) is a rare neuroendocrine skin neoplasm that shows increased incidence postorgan transplantation and aggressive biologic behavior with high mortality of 60% [21]. The ratio between MCC and Melanoma is 1:6 in the normal population and this ratio is reversed to 65:1 after solid organ transplantation. MCC most commonly occurs on sun-exposed skin sites and has a clinically unspecific appearance that often resembles insect bites or cysts. Metastasis frequently occurs in MCC; at presentation about 30% of patients have positive Sentinel lymph nodes. The treatment of MCC does not differ from the one applied in immunocompetent patients and includes surgery and adjuvant radiotherapy. However, decrease of immunosuppression and switch to mTor-inhibitors should be considered and performed if possible. In kidney transplant patients and high risk tumors or metastasis, a cessation of immunosuppression may also be considered (Fig. 11.4).
11.1.5 Malignant Melanoma

Besides the development of de novo malignant melanoma post transplantation, other aspects have to be considered in OTR: a history of malignant melanoma prior to organ transplantation and a transmission of melanoma from the donor organ to the recipient.

11.1.5.1 De Novo Malignant Melanoma in Otx

Regarding the incidence of malignant melanoma in organ transplant patients, different rates have been reported. Recent reports from the U.K. and Ireland have reported a 7–8 fold increase of malignant melanoma in OTR [22–24], whereas in a dutch and swedish study, no significant increase of melanoma incidence occurred [25, 3]. Various reasons might be responsible for these inconsistent findings, including differences in sun habit, level of immunosuppression, skin types, or different immunosuppressive regimens. Notably the immunosuppresion in the London cohort consisted of prednisolone and azathioprine (with or without cyclosporine) and the regimens in the Netherlands of Cyclosporine, mycophenolat mofetil, and prednisolone. Further studies have to be performed in order to increase the knowledge on melanoma incidence in the transplant population.

De novo MM seems to occur more frequently in male than in female [26] and pediatric patients are at risk with 4% of melanomas occurring in children. In the normal population only 0.4% of cases affect children; therefore, MM occurs ten times more frequently in immunosuppressed than in immunocompetent children [27].

Duration of immunosuppression and subsequent increase in melanocytic nevi have been proposed as risk factors and one case series reported that the majority (10/14) melanomas arose on a previously existing nevus [28]. However, recent reports did not confirm these observations [23, 24]. On histopathological exams, MM in OTR characteristically shows a marked decrease of inflammation; the Breslow thickness is less than 1 mm in the majority of cases. Melanoma generally occurs after 3 or more years posttransplantation with great variations [29].

Clinical presentation is similar then in the immunocompetent population and the ABCDE rule, and dermoscopy aids in diagnosing MM. Staging and treatment follows established guidelines for immunocompetent patients. However, special considerations including reduction of immunosuppression or conversion to mTOR inhibitors should be considered as part of the management.

High mortality rates and worse prognosis have been reported in the literature. However, recent studies do not support these findings. Le Mire et al. reported that only one of ten patients in their cohort died from melanoma after a median follow-up of 3.7 years [24]. The 5-years disease specific survival for all patients has been estimated to be 80–85% [30]. Earlier recognition as a result of effective pre and posttransplant dermatologic care might be responsible for these observations, but other factors as lower doses of immunosuppressants may also be of importance.

11.1.5.2 History of Melanoma Prior to Transplantation

Patients with a melanoma prior to transplantation who develop recurrence posttransplantation have a very bad prognosis. Thus, the risk for recurrence is within the expected range and does not seem to be greater in the transplant population. Data from the Cincinnati Tumor Registry reported a 19% recurrence rate of MM posttransplant.

Generally a 5 year interval is recommended between occurrence of primary melanoma and organ transplantation. The decision should be based on considerations of different aspects of like Breslow depth, Sentinel lymph node involvement, or metastasis. In this regard organ transplantation may be considered in patients with in situ MM or low risk MM < 1 mm without a waiting time of 5 years. Contrariwise, organ transplantation may be postponed or contraindicated in patients with a history of high risk melanoma.

11.1.5.3 Transmission of Melanoma from the Donor Organ

Malignant melanoma represents the most common donor derived malignancy and shows high mortality rates ranging from 50 to 100% [31–33]. The largest case series consists of 20 recipients who received organs from 11 donors. Of these 20 recipients, 85% (17/20) developed melanoma, 16 metastatic melanoma,
and one melanoma limited to the graft. 11/20 (65%) died from melanoma. In four renal transplant patients, a complete remission was achieved by transplant nephrectomy, cessation of immunosuppression, and, in one patient, adjuvant interferon α. Thus, careful examination should be performed prior to organ donation. In donors with a history of brain tumor or cerebrovascular accident, an autopsy is recommended in order to rule out unknown MM as these scenarios were responsible in the majority of transmitted MM.

11.1.6 Kaposi’s Sarcoma

Kaposi’s sarcoma (KS) is a malignant vascular tumor that has been classified into four categories: classic or sporadic KS, endemic KS, an epidemic form that has been associated with AIDS, and an iatrogenic form under immunosuppression. The risk of KS posttransplantation is increased up to 128-fold [34].

KS is one of the tumors associated with viral infection, and a correlation of all forms of KS and Human Herpes Virus 8 (HHV-8) has been shown. It has been supposed that this viral association may be responsible for the high incidence of KS after organ transplantation. Immunosuppression may lead to a reactivation of the virus and subsequent development of KS. In a study, 400 patients were monitored for anti-HHV-8 antibodies at the time of transplantation and 32 patients were found to be positive. Of these 32 patients, 28% developed KS within 3 years posttransplantation. None of the HHV-8 negative patients were found to have KS and the incidence was increased in males [35]. The fact that not all of the HHV-positive patients actually developed KS is highly suggestive of other pathogenetic factors involved. Furthermore, HHV-8 may also be transmitted from the organ donor to the recipient.

On clinical exam, patients present with red to violaceous plaques and nodules on skin and mucosa. The size of the single lesions and the distribution may greatly vary and the presentation is similar to KS in AIDS patients. Internal organs may be involved, including most frequently the gastrointestinal tract, lungs, and lymph nodes. Clinical diagnosis is confirmed by biopsy and histologic exam. Detection of HHV-8 can be achieved either by immunohistochemistry or in situ hybridization. Following a full body examination, ultrasound of lymph nodes and abdomen and chest X-ray are recommended for staging. Further imaging by CT, MRI, or endoscopy may be performed.

Reduction of immunosuppression should be the first therapeutic step as it has been shown that regression is achieved in up to 46% of cases [36]. In renal transplant recipients, cessation of immunosuppression and return to dialysis may become necessary if reduction of immunosuppression fails to achieve remission. Another possibility is the cessation of proliferative immunosuppressants and switch to antiproliferative substances. Recently a new class of immunosuppressants, the so called m-TOR inhibitors, have been introduced as immunosuppressant agents after organ transplantation. Besides their immunosuppressive properties, m-TOR inhibitors have been shown to have antiangiogenetic and direct antitumoral effects. Therefore, switching to m-TOR inhibitors may lead to complete remission of KS in OTR. Both commercially available m-TOR inhibitors, Sirolimus and Everolimus, have been shown to induce regression of Kaposi sarcoma. After withdrawal of Calcineurin inhibitors along with switch to m-TOR-inhibitors, regression of KS lesions in 11 of 12 patients has been reported within a few months. [37]. Sirolimus and Everolimus are usually well tolerated, and stable renal function is achieved in the majority of patients. Therefore, these agents have to be considered if Kaposi sarcoma occurs after organ transplantation. Other treatment modalities might be considered and include surgery, cryosurgery, or laser in single lesions or chemotherapy in disseminated disease. Interferon has been used in the immunocompetent population, but should not routinely be considered after transplantation as it induces allograft rejection.

Complete withdrawal of immunosuppression and return to dialysis may be considered in cases that do not respond to the above mentioned treatment modalities.

11.1.7 Sunscreens

Prevention with regard to UV exposure is very important in the transplant population. A recent study evaluating a liposomal highly effective sunscreen (Daylong actinica®) in 120 OTR showed a decrease in AK and no new SCC with daily application of this sunscreen for 24 months [38, 39]. Daylong actinica® was the first sunscreen that has been shown to decrease the number
of AK in the high risk group of organ transplant recipients, and therefore, proves the value of sun-protection in high risk populations.

References

11.2 HIV

Anja V. Potthoff, Norbert H. Brockmeyer and the Competence Network for HIV/AIDS Germany

Core Messages

Life expectancy of HIV infected patients has immensely increased with the advances of antiretroviral therapy. While less patients die from opportunistic infections, we see a growing problem in the manifestation of malignancies. In the beginning of the HIV epidemic, Kaposi’s sarcoma was a common stigma in AIDS patients, now it is rare in patients taking antiretroviral therapy. The incidence of human papilloma virus (HPV)-related tumours (e.g. anal cancer and its precursor lesions) is rising in the HAART era. Other skin tumours (e.g. basal cell carcinoma, squamous cell carcinoma, and melanoma) show a more aggressive behavior and differential diagnosis can be challenging. Generally, treatment should be performed according to guidelines for HIV-negative patients in close cooperation with the HIV specialist.

11.2.1 Skin Cancer Under Special Circumstances

Advances in treating HIV have led to an increased interest in both the early and long-term complications of immunosuppression. It is known that decreased CD4 cell counts, even outside the context of HIV, lead to an increased risk of malignancies [1]. Chronic
inflammatory conditions are known to be associated with the development of malignant diseases. They are proangiogenic, suppress cell-mediated immune response, and increase humoral responses. Chronic immune activation leads to inhibition of apoptosis through suppression of p53 activity [2].

In the beginning of the HIV epidemic, Kaposi’s sarcoma was a common stigma in AIDS patients and one of the leading causes of death. While Kaposi’s sarcoma is less frequently seen after the introduction of antiretroviral therapy, other malignancies are increasingly challenging. A survey in French clinics specialized in HIV showed that 28% of all HIV-positive patients’ deaths were tumour-related. Forty-five percent of those were non-AIDS-defining tumours [3]. The differential diagnosis is broadened, e.g. bacillary angiomatosis can mimic Kaposi’s sarcoma and hypertrophic herpes simplex (Fig. 11.5) can be simulating anal neoplasia [4]. Treatment should be performed according to guidelines for HIV-negative patients in close cooperation with the HIV specialist.

11.2.2 Kaposi’s Sarcoma

Kaposi’s sarcoma is the most common AIDS-defining tumour. It affects patients between 30 and 40 years. Staging considers location and grade of immunodeficiency (Table 11.1). The mucosa is involved in 30% of the patients. Disseminated affection of the skin and involvement of the lung and gastrointestinal tract are common. In patients with severe untreated immunodeficiency, aggressive tumours with a life expectancy of less than a year have been reported. Before introduction of highly active antiretroviral therapy (HAART), Kaposi’s sarcoma occurred in 25% of all HIV-infected men who had sex with men (MSM) [5]. Today, 5–7% of this population is affected [6]. By inducing an inflammatory-angiogenetic stage, human herpes virus (HHV) 8 is the most important pathogenetic factor of carcinogenesis in Kaposi’s sarcoma. HHV8 specific pathways like G protein-coupled receptors, viral IL6, viral chemokine homologues and cellular growth, and angiogenic pathways are potential targets for therapy [7]. In addition, genetic host factors (e.g. HLA-DR5) and viral proteins of HIV (e.g. HIV tat) contribute to carcinogenesis [8]. HHV8 is transmitted by sexual intercourse and blood. Shedding was detected in 32% of saliva samples, 28% of mouth swabs, 4% of cervical swabs, 2.3% of vaginal swabs, 9% of plasma samples, and 18% of PBMC samples in a study with 174 HHV8 seropositive women [7]. Clinical symptoms are asymptomatic red lesions that can transform to a nodul with hyperkeratosis and ulcerate later (Fig. 11.6). In Black people the lesions can be very dark, almost black (Fig. 11.7). Associated lymphatic edema is common.

As a differential diagnosis for the early manifestation of Kaposi’s sarcoma, one should consider granuloma pyogenicum, histiocytomas or hemangiomas. Acroangiodermatitis, bacillary angiomatosis, angio- or lymphangiosarcomas are differential diagnosis for later stages [9]. The proliferation of endothelial-like cells and fibroblast can be detected histologically. Vascular structures with erythrocyte extravasate and hemosiderin deposits are formed. Tumour cells are vimentin positive and CD30 positive. Early lesions express factor VIII. For staging, a complete inspection of the oral and genital mucosa should be performed. Staging is completed by lymphnode and abdominal ultrasound, gastroduodenoscopy, colonoscopy, and chest X-ray [10]. The prognosis without treatment depends on tumour spread, the immunosystem, and

**Fig. 11.5 Ulcerating herpes simplex**
additional systemic disease (see ACTG classification, Table 11.1, [11]).

In many cases Kaposi’s sarcoma resolves with antiretroviral therapy [12, 13]. Some cases of Kaposi’s flare during immune reconstitution inflammatory disease have been reported [14]. Treating cutaneous lesions for cosmetic reasons is justified and strongly recommended. The social stigmatization and constant reminder of a fatal illness evoke severe psychological stress. Recurrence is common after topical treatment. Local therapeutic options include excision, laser, cryosurgery, and radiation [15]. Since 2000, alitretinoin gel is approved in local therapy for small lesions of HIV-associated Kaposi’s sarcoma. It is applied twice daily. Response can be seen after 2 weeks [16]. Intrallesional chemotherapy with vinblastin or vincristin (0.1 mg/cm² of lesion) achieves response rates of 60–80%. Intrallesional application of interferon-α-2b (0.5 U/cm²) reduces KS-lesions, but complete remission is rare and

**Table 11.1** Staging of HIV-associated Kaposi’s sarcoma (AIDS Clinical Trial Group)

<table>
<thead>
<tr>
<th>Stage (T)</th>
<th>Description</th>
<th>Immunsystem</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Tumour restricted to the skin, lymphnodes and oral mucosa</td>
<td>I0 (good risk)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour involving visceral organs, edema or ulceration, bulky masses</td>
<td>I1 (poor risk)</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>CD4+ cells &gt;200/µL</td>
<td></td>
</tr>
<tr>
<td>S0</td>
<td>No opportunistic infection or oral candidiasis in medical history, no constitutional symptoms</td>
<td>Karnofski-Index &gt;0.7</td>
</tr>
<tr>
<td>S1</td>
<td>Opportunistic infections, oral candidiasis or other HIV-related diseases in medical history, constitutional symptoms or Karnofski-Index &lt;0.7</td>
<td>Karnofski-Index &gt;0.7</td>
</tr>
</tbody>
</table>
side effects are common. Camouflage can be psychologically helpful [9]. Kaposi’s sarcoma is a radiation sensitive tumour. After a cumulative dose of 20–30 Gy (single dose 4–5 Gy), a regression rate of 80–90% can be achieved in isolated lesions [17]. Lymph nodes should be irradiated with 40 Gy (5×2 Gy/week) [15]. Compression therapy is an important part of the therapeutic concept in lymph edema.

Systemic treatment is indicated in disseminated skin disease, Kaposi’s sarcoma of the face, for painful lesions, e.g. palm and sole or visceral involvement. Immunomodulation with interferon-alpha in combination with HAART [18] can induce apoptosis in tumour cells. In addition, it inhibits angiogenesis by inhibition of expression of fibroblast-growth-factors-β. In patients with <200/μl CD4, lymphocytes response rate is poor, while in patients with >400/μl CD4+ lymphocytes remission rates up to 45% with interferon-alpha 3×3 Mio i.E. s.c./week [6] have been reported. Highest remission rates can be seen after treatment with liposomal anthracyclins [19]. A remission rate of 80% has been documented after treatment with liposomal doxorubicin 20 mg/m² every 2–3 weeks in combination with HAART [9, 20–23]. It is still first-line therapy in patients with advanced Kaposi’s sarcoma and is well tolerated. Main side effects were neutropenia, leucopenia, nausea, fatigue, and elevated liver enzymes [19, 20]. Palmar-plantar erythrodysesthesia, also called hand-foot syndrome, is seen in up to 50% of patients, but seldom leads to treatment withdrawal. The pathophysiology is not well understood. Data support the roles of drug excretion in sweat and local pressure as contributors [24]. Liposomal Daunorubicin (40 mg/m²) is well tolerated, but less effective [20]. Paclitaxel (100 mg/m² i.v. every 2 weeks) is also very effective in Kaposi’s sarcoma. Patients who failed another chemotherapeutic regime benefit from this therapy, but it is limited by toxicity [25]. Growing understanding of the pathogenesis of Kaposi’s sarcoma leads to new targets in treatment. The phosphatidylinositol 3-kinase (PI3K)/Akt (protein kinase B, PKB)/mammalian Target Of Rapamycin (mTOR) signalling pathway plays a critical role in many cellular functions which are elicited by extra cellular stimuli. Blocking the PI3K/AKT/mTOR signal transduction network could be an effective new strategy for targeted anticancer therapy. Pharmacological inhibitors of this signalling cascade are powerful antineoplastic agents in vitro and some of them (e.g. sirolimus) are now being tested in clinical trials [26]. The proteasome inhibitor bortezomib induces immediate-early, early and late HHV8 gene expression. The ability to induce lytic gene expression supports the role of proteasome-regulated signalling pathways in HHV8 reactivation and prompts further investigation of bortezomib as therapeutic agents in Kaposi’s sarcoma [27]. Another approach is the inhibition of HHV8 growth factors, e.g. VEGF with sorafenib [7]. The tyrosinkinase inhibitor imatinib was used successfully in a pilot study with ten patients [28]. The combination of imatinib with antiretroviral therapy can be problematic because it is metabolised mainly by the cytochrome (CYP) P450 3A4 and can competitively inhibit the metabolism of drugs that are CYP3A4 substrates [29]. Drug interactions with the other new agents are not fully investigated yet. Matrixmetalloproteinase inhibitor Col-3 is an angiogenesis inhibitor. In a trial with 75 pre-treated patients, remission was seen dose dependant in 29–41% [30]. A combination of the new substances with or without conventional chemotherapy may be a promising option for patients failing on other regimes.

11.2.3 Lymphoma

HIV-associated lymphomas are the second most-common AIDS-defining neoplasias. On first diagnosis, disseminated disease is seen in 90% of patients with non-Hodgkin-lymphoma (NHL). Involvement of the gastrointestinal tract, the bone marrow, and the liver are common. Up to 30% affect primarily and secondarily the central nervous system. Body-cavity lymphomas (primary effusion lymphoma) clinically appear as pleura effusion or ascites. This aggressive tumour is almost exclusively seen in HIV-positive patients. An association with Epstein–Barr virus (EBV) has been described. Most HIV-related NHLs are highly-malignant blastic B-cell lymphoma. HIV is associated with a TH2 cytokine profile that is associated with B-cell proliferation. These cytokines also enhance HIV proliferation, immune evasion, angiogenesis, and transcription of oncogenes [2]. Elevated serum IL10 or the IL10 promoter 92 C/C genotype are also associated with the development of AIDS lymphoma [31]. Long-term persistence of HIV-1 structural protein and glycoproteins in the germinal centres of lymph nodes play a potential role in chronic antigenic stimulation and subsequent lymphoma
formation. They could be found in the absence of detectable virus replication in patients under HAART [32]. It can be difficult to distinguish between HIV-related lymph adenopathy and lymphoma (Fig. 11.8). A lymph node biopsy is mandatory. Most NHLs occur in patients with about 100/μl CD4 cells, but sometimes helper cells could be much higher. Lymphomas in HIV-positive patients rarely affect the skin.

11.2.3.1 CD30+ Large Cell Lymphoma

Patients with CD30+ large cell lymphoma typically present with a rapidly growing deep skin nodule or plaque. Histologically, there is a predominance of the T-cell lineage in HIV-associated cutaneous CD30+ large-cell lymphoma in contrast to B-cell types that occur in HIV-negative patients [33, 34]. In NHL, early therapeutic intervention is necessary because of the fast progression of the tumour. Diagnosis and treatment do not differ from HIV-negative patients. Prior to antiretroviral therapy, patients with CD30+ large-cell lymphoma had a very poor prognosis. Improved survival has been reported with the addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in patients with HIV-associated diffuse large B-cell lymphoma [35]. A previous study had seen a higher rate of treatment-related infectious deaths [36].

11.2.3.2 Cutaneous T-Cell Lymphoma (CTCL)

Mucosis fungoides and Sezary-syndrome are rare conditions in HIV-infected persons. In most cases, the immune system is still relatively intact. Standard therapy and antiretroviral therapy should be applied. Immunosuppressive substances such as methotrexate should be avoided if possible, because of their potential to worsen the immune status. Interferon alfa-2a has been used safely for other indications in HIV-infected persons.

11.2.4 Human Papilloma Virus (HPV)-Related Tumours

Human papilloma virus (HPV) is known to induce not only warts, but also tumours and its precursor lesions. Association with high-risk HPV-types (e.g. 16, 18) has first been described in cervical cancer ([37], see also Sect. 11.3). All HIV-positive women should be screened carefully for cervical intraepithelial neoplasia (CIN) and AIDS-defining cervical cancer. The relative risk for developing cervical cancer in HIV-positive women compared with HIV-negative women varies widely across the globe [38]. The incidence of HPV-related anal carcinoma and its precursor lesions is rising dramatically in HIV-infected patients. Compared with the general population, concomitant HIV-infection drastically increases the relative risk for anal intraepithelial neoplasia AIN and anal cancer (60.1 and 37.9, respectively) [39]. Perianal HPV-infections have been detected in up to 86–93% of men who are HIV-positive and a high incidence of high-grade AIN has been reported.
Kreuter et al. found AIN in 19.4% of his patients. With high resolution anoscopy, this number increases to up to 40–50% [40–42]. Screening programs with high resolution anoscopy and cytology as they are already established for cervical carcinoma should be implemented. HIV-positive men also carry a 36-fold higher risk of developing penile cancer. Regular clinical screening is suggested.

An evidence-based therapeutic concept has not been established. In a recent study, the efficacy of imiquimod for the treatment of external genital warts in HIV-positive subjects was compared to a group of patients with normal immune function [43]. Thirty-one percent of all HIV-positive patients achieved a complete clearance; a partial response was obtained in 24%. In the immunocompetent control group, a total clearance was obtained in 62% of subjects and a partial response in 24%. Recurrences occurred in 17% of HIV-patients and 7% of immunocompetent patients within 3 months of follow up. This compares favorably with ablative techniques alone, where 66% recurrences in immunocompromised patients were observed in a study performing surgical ablation of genital warts [44]. Imiquimod has also shown good clearance rates and safety when applied in the form of anal tampons and for anal intraepithelial neoplasia [45].

There is no clear relationship between anal, penile or cervical cancer incidence and lower CD4 levels.

HAART does not lead to a reduction of intraepithelial dysplasia [42]. So far, there are no studies with the new HPV-vaccines in HIV-infected patients. Vaccination has to be considered on an individual basis.

11.2.5 Nonmelanoma Skin Cancer (NMSC)

An increase of basal cell carcinomas, squamous cell carcinoma and Merkel cell carcinoma (MCC) in persons with HIV-infections has been observed. For basal cell carcinoma, the age-adjusted rate in Caucasian males was 795/100,000 person years compared to 475/100,000 in HIV-negative persons. The rate for squamous cell skin carcinoma was 159/100,000, which is also higher than the general Caucasian United states population [46]. HIV-positive patients with NMSC tend to be younger than HIV-negative patients.

11.2.5.1 Basal and Squamous Cell Carcinoma

Basal cell carcinoma in immunosuppressed patients appears to show a more aggressive behavior [44]. The risk factors including sun exposure, blond hair, blue eyes, and a family history of skin cancer are the same as in HIV-negative persons. Higher exposure to recreational UV radiation in homosexual men has been reported [47, 48]. Patients with HIV-infection more commonly experience treatment-associated complication such as infection and recurrence.

11.2.5.2 Squamous Cell Carcinoma

The ratio of squamous cell carcinoma to basal cell carcinoma in HIV-infected patients is approximately 1:7, whereas in organ transplant recipients it is 1.8:1 [49]. An uncontrolled retrospective case series reports a strikingly aggressive nature of squamous cell carcinomas in HIV-infected patients. The authors suggest adjunctive modalities, such as sentinel lymph node biopsy for high-risk tumours. Primary prevention with the avoidance of UV-radiation and aggressive management of precancerous lesions should be recommended [48]. Infection with unusual HPV-types is more common in HIV-related squamous cell carcinoma of the anogenital region, the nail unit, and in epidermodysplasia verruciformis [50].

11.2.5.3 Merkel Cell Carcinoma

Several cases of MCC in persons with HIV-infection have been described [51–55]. The patients’ mean age was 48 years, while 85% of MCC patients uninfected by HIV-1 are over 60 years old. The relative risk of MCC compared with the general population was 13.4 (95% confidence interval 4.9–29.1). It can develop before AIDS-diagnosis. The role of sun-exposure in addition to the immune deficiency is discussed. The tumour is particularly aggressive in HIV-positive patients, resulting in a poor prognosis [54]. A standard therapy has not been established. Surgical removal in combination with radiation with or without chemotherapy is indicated in localized tumours. A safety margin of at least 3 cm including the fascia should be chosen where possible. When distant metastases are diagnosed, only palliative care is possible.
11.2.6 Melanoma

It is not clear whether melanoma is more common in HIV-infected patients [46, 57]. However, they tend to have an atypical appearance. A number of case reports have been published [58, 59]. Metastatic disease with poor prognosis is common. In a case-control study, 17 HIV-positive patients were matched with HIV-negative patients. HIV-positive patients had a significantly shorter disease-free survival (\(p = 0.03\)) and overall survival (\(p = 0.045\)). Low CD4 cell counts led to earlier melanoma recurrence [59]. Standard guidelines for melanoma treatment including surgical margins for excision procedures have been proposed. Adjuvant treatments with chemotherapy or interferon-alpha should be considered on a case-by-case basis [58]. Collaboration with an oncologist who has experience with HIV-patients is highly recommended. The safety of adjuvant interferon-alpha has been documented in the treatment of HIV-related Kaposi’s sarcoma [6, 18].

Therapeutic options should be chosen according to the stage of the disease. Antiretroviral therapy should be continued if possible. Interaction between HAART and chemotherapy has to be considered. Treatment should be confined to specialized centres.

References

11.3 Genital Skin Cancers

Anja V. Potthoff and Norbert H. Brockmeyer

Core Messages

- Differences in biological behavior make familiarity with and accurate diagnosis of genital tumour essential. It is well established that high-risk human papilloma virus (HPV) plays an essential role in the carcinogenesis of tumours of the anogenital tract. Annual clinical examination with high-resolution colposcopy, vulvoscopy, and proctoscopy can help identify precursor lesions of invasive squamous cell carcinoma in patients at risk. Early diagnosis and treatment allow minimal invasive treatment with a good cosmetic and functional result. Differential diagnosis of rare anogenital tumour like melanoma, basal cell carcinoma, Paget’s disease or Kaposi’s sarcoma may be challenging. Biopsies can help distinguish between benign and malignant lesions.

11.3.1 Human Papilloma Virus (HPV)-Related Tumours

It is well established that high-risk human papilloma virus (HPV) plays an essential role in the carcinogenesis of tumours of the anogenital tract. Among other mechanisms, HPV oncogenic proteins E6 and E7 bind to host regulatory proteins, especially tumour gene products p53 and phosphorylated retinoblastoma protein (pRb). This results in a loss of tumour suppressor function.

The primary screening tool for HPV-associated diseases is cytology. The Bethesda grading system is

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commonly used (Table 11.2, [1]). The diagnosis has to be histologically confirmed before treatment. Recently, two prophylactic HPV-vaccines based on virus-like particles have been approved for the prevention of cervical neoplasia in women. A quadrivalent vaccine (against HPV 6, 11, 16, and 18) [2, 3] also covers the most common causative HPV types for condyloma; a second bivalent vaccine (against HPV 16 and 18) uses with monophosphoryl lipid A a different adjuvant [4, 5].

### 11.3.1.1 Anal Cancer

Anal intraepithelial neoplasia (AIN, Fig. 11.9) represents a precursor lesion of invasive squamous cell carcinoma with a clear association to high-risk HPV-types. The histological grading system is analogue to cervical intraepithelial neoplasia. The incidence of HPV-related anal carcinoma and its precursor lesions is rising dramatically in immunosuppressed patients (organ transplant recipients [6] and HIV-positive, see Sect. 11.2). Topical therapy is sufficient for most AIN I lesions (e.g. podophyllotoxin, trichloro acetic acid (TCA), imiquimod, cryosurgery). Electrocautery, infrared coagulation or surgical excision is used in AIN grade II and III. After ablation treatment with imiquimod or interferon gel can reduce the risk of recurrence [7–9]. An evidence-based therapeutic concept has not been established. Compromised wound healing with following stenosis and incontinence has been described [7, 10].

### Table 11.2  Algorithm for diagnosis and follow-up of anal intraepithelial neoplasia

<table>
<thead>
<tr>
<th>Normal cytology</th>
<th>ASCUS</th>
<th>LSIL or HSIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical and cytologic screening (once a year)</td>
<td>Repeat smear</td>
<td>Perform HRA</td>
</tr>
<tr>
<td>Next Clinical and cytologic screening (after 6 month)</td>
<td>LSIL and no visible lesions</td>
<td></td>
</tr>
<tr>
<td>Treatment and next clinical and cytologic screening (after 6 month)</td>
<td>LSIL with clinical lesions</td>
<td></td>
</tr>
<tr>
<td>Biopsy in case of AIN: treatment in case of normal histology: next clinical and cytologic follow-up (after 3 month)</td>
<td>HSIL and no visible lesions</td>
<td></td>
</tr>
<tr>
<td>Treatment and next clinical and cytologic screening (after 3 month)</td>
<td>HSIL with clinical lesions</td>
<td></td>
</tr>
</tbody>
</table>

Anal cytology is classified using the Bethesda system: *ASCUS* atypical squamous cells of unknown significance; *LSIL* Low grade squamous intraepithelial lesion; *HSIL* high grade squamous intraepithelial lesion; *HRA* high resolution anoscopy.
guidelines. Surgical treatment is the standard of care for tumours up to 2 cm diameter. Chemoradiation therapy is applied for tumours over 2 cm with 50.4 Gy (1.8 Gy per dose), together with 5FU (5-fluorouracil 1,000 mg/m² day 1–5 and 29–33) and mitomycin C (10 mg/m² day 1 and 29) [10].

Proctoscopy should be performed annually in all patients at risk. Patients with AIN grade II and III should be screened every 3 months (Table 11.2, [11]), since rapid progression from initial dysplasia to invasive cancer has been described especially in immunocompromised patients [12].

11.3.1.2 Penile Cancer

Penile cancer (Fig. 11.11) is in the majority of cases of squamous epithelial origin. Early treatment can be lifesaving and is essential for functional and cosmetic outcome. While the tumour is rare in Europe and America, it is very common in the third world. In the USA, penile cancer accounts for 0.3–0.6% of all cancer in men; in some African and Asian countries, the incidence is as high as 10–20%. Known risk factors are HPV infections, phimosis and lichen sclerosus (see below). Poor hygiene, ultraviolet light, some chemicals, chronic irritation and smoking seem to be cofactors that enhance the oncogenic properties of low-risk HPV types. Carcinogenic nitrosamines may concentrate in the smegma and immune surveillance is impaired in heavy smokers. Circumcision can prevent some cases of penile cancer. Men with a history of anogenital warts have a risk of penile cancer that is 5–6 times higher. Prevalence of HPV infection in penile carcinoma ranges from 15 to 71% in different studies [13].

The diagnosis can be confirmed by excision biopsy. Additional imaging techniques such as ultrasonography and CT or MRT are recommended. In situ carcinomas of the penis are also known as erythroplasia of Queyrat and Bowen’s disease. Like all preneoplastic disorders of the penis, they are now classified as penile intraepithelial neoplasia (PIN I–III) similar to the classification of the cervix and the anus. Progression from untreated penile in situ neoplasia to invasive cancer is common (up to 30%). In situ carcinoma can be treated locally. Treatment options include topical 5-fluorouracil, laser surgery, cryosurgery, curettage combined with electrocautery. Imiquimod 5% cream and 5-aminolevulinic acid have shown encouraging results. Excision and circumcision have the advantage of histological confirmation of tumour clearance. Small (<2 cm) invasive tumours may be managed by excision. Laser therapy has a high risk of recurrence. Radiation therapy (60 Gy) is an option to preserve sexual function. Larger tumours should be treated with partial or total penectomy. Verrucous carcinoma is generally managed with wide local excision and shows excellent treatment outcomes. When the dermis is invaded, lymph node metastasis may be detectable in
20–37% of patients. Patients with high-grade squamous cell cancer and extensive penile shaft involvement with a flat grown pattern are at greater risk to develop lymph node metastasis. Lymphadenectomy can be curative in 40–50% of cases. Sentinel lymph node dissection can be helpful, but 22% of patients develop regional lymph node metastasis, in spite of negative sentinel node. Distant metastasis is found in the bone, the brain, the skin, the kidney, the heart, the thyroid and the adrenal glands in the late stages of the disease. A curative effect of combined surgical and cytotoxic management can only be achieved in patients with locoregional metastasis, but not in patients with systemic spread. Standard therapeutic guidelines to the best treatment strategy of different stages have not been established. Clinical differential diagnosis include psoriasis, circinate balanitis, basal cell carcinoma, fungal infections, lichenoid chronic dermatosis, syphilis, Zoon balanitis, anogenital warts and others [13].

11.3.1.3 Vulvar Cancer

The incidence of vulvar cancer rises from 0.4/100,000 in 30-years old women to 20/100,000 in over 70-years old women. In vulvar squamous cell carcinoma, HPV can be detected in up to 71% of biopsy samples. It develops slowly from premalignant vulvar lesions (VIN I–III) similar to anal, cervical, and penile lesions. Multilocal (vulvar, anal, cervical) HPV-related intraepithelial neoplasia at the same time should be considered. Risk factors (immunosuppression, especially HIV, smoking etc.) are the same as in anal and cervical cancer. An HPV–independent pathway has also been described [14].

Symptoms are not characteristic. Diagnosis should be confirmed by biopsies. Staging includes a complete gynecological examination, chest X-ray, and abdominal ultrasound. In stage III disease, cystoscopy and rectoscopy are also recommended. The primary treatment of localized microinvasive vulvar cancer is excision with a safety margin of 1 cm. Histologically confirmed premalignant lesions can also be treated with destructive methods (CO₂-Laser, electrocautery, cryosurgery). Additional inguinofemoral lymph-node dissection is recommended in FIGO (Federation Internationale de Gynecologie et d’Obstetrique) stage I disease. FIGO stage II and III are treated with radical vulvectomy with inguinofemoral lymph node dissection and partial resection of vagina or urethra depending on localization. Neoadjuvant radiochemotherapy can be considered in extensive stage III and in stage IV disease.

Radiation therapy is indicated when two or more lymph node metastasis are found and in cases of infiltration or penetration of lymph node capsule or surrounding tissue. The pelvis minor should be irradiated in patients with extensive inguinal lymph node metastasis. Radiation can be considered if lymphadenectomy was not performed (e.g. because of impaired operability). Short-time remission is seen in 30% of patients after chemotherapy with 5FU, cisplatin, mitomycin C, and bleomycin. Recurrent disease can be treated by excision, radiation, chemotherapy or an individualized combined treatment. Follow-up includes vulvoscopy, cytology, and biopsies of suspicious areas every 3 months for the first 3 years and then every 6 or 12 months. Hormone substitution is not contraindicated [15].

11.3.2 Squamous Cell Carcinoma and Lichen Scleroses

Lichen sclerosis is a chronic sclerosing inflammatory disease that can involve the vulva, the perianal region, the penis, and, sometimes, extragenital skin (Fig. 11.12). The association between lichen sclerosis and vulvar cancer is well documented and is observed in 3–6% of affected patients. Whether penile lichen sclerosus is also associated with an increased risk of malignant transformation is a matter of debate. Multiple factors are increasing the risk of penile cancer: chronic inflammation, phimosis, and a high-risk HPV that can be found more frequently in patients with lichen sclerosus (17.4 vs. 8.7%). The average leg time for cancer development is usually long (10–34 years). Malignant transformation should be suspected in nonhealing ulcerated or warty nodules or plaques [16]. Differences of vascular endothelial growth factor and COX-2 expression may identify precursor lesions with greater potential to evolve into squamous cell carcinoma [17]. There is still a debate about whether topical calcineurin inhibitors are save in the management of lichen sclerosis. Some authors suggest that they should be restricted to patients that are not adequately controlled with topical corticosteroids [18, 19]. Genital lentigines and melanocytic nevi with associated lichen sclerosis may show features that mimic malignant melanoma [20].
11.3.3 Melanoma

Genital melanomas are rare and biologically aggressive neoplasms. Of all primary mucosal melanomas, 18% are located in the female genital tract, 23.8% in the anal/rectal region and 2.8% in the urinary tract [21]. The median age at presentation is about 70 years and women are at greater risk. The aetiology is unknown. HPV 16 and epidermodysplasia verruciformis-associated types (e.g. HPV 38) have been identified in some cutaneous and mucosal melanomas, suggesting it might play a role in the pathogenesis or progression of melanoma [22]. Multiple local recurrences are common. About a third of patients have lymph node metastasis at presentation. Sentinel node biopsy is now a standard procedure in most cutaneous melanomas with more than 1 mm depths. It has not yet been established for genital melanoma. A false negative rate of about 15% suggests that careful consideration is necessary before using sentinel lymph node biopsy in genital melanoma [23]. Therapeutic options do not differ from other localizations of melanoma. For vulva melanoma, <1 mm excision with 1 cm safety margin is recommended. Tumours infiltrating more than 1 mm should be treated by en-bloc resection with regional (femoral and inguinal) lymph nodes. Initial surgical modality does not influence long-term survival, but can affect disease-free survival significantly [24]. Sugiyama et al. identified 644 vulvar melanoma patients. Their median age was 68 years and most women were White (572). Three hundred and two women had localized disease, 268 had regional disease and 28 had distant disease. 27.8% had lymph node resection and 33 had concurrent radiation therapy. Lymph node metastases were identified in 58 (9%) of the patients.

The 5-year survival rates for those with localized, regional, and distant disease were 75.5, 38.7, and 22.1%, respectively \( p < 0.001 \). Younger patients had a better prognosis. Patients with involvement of more lymphnodes had a significant lower 5-year survival rate (19.5%) [25].

11.3.4 Basal Cell Carcinoma

Basal cell carcinoma is the most common skin cancer. Genital localization, however, is very rare. Case reports describe basal cell carcinoma of the perineum, the perianal region, the penis, and the vulva [26–28]. The aetiology is not known. Biopsy of suspect lesions is advisable. Mohs micrographic surgery is the preferred treatment. In penile basal cell carcinoma, circumcision can be considered. Although genital basal cell carcinoma sometimes has a large average size, they are not considered aggressive because the lesions are well-circumscribed and the growth patterns are noninfiltrative.

11.3.5 Paget’s Disease

Paget’s disease is an intra-epidermal adenocarcinoma seen over the nipple/areola (mammary Paget’s disease) or in extramammary body zones, such as the anogenital and perineal skin and the axilla [29]. Other malignancies are found in ca. 30% of patients. The most frequent localizations of the other cancers are
the colorectum, the prostate, the breast, and the extragenital skin [30]. Exposure to chemicals (e.g., engine oil) has been suggested to be a pathogenetic factor [31]. A combination of single-photon emission computed tomography (SPECT) and multidetector computed tomography (MDCT) can help to identify the sentinel lymph nodes in the patient with extramammary Paget’s disease of the scrotum [32].

Radiotherapy is a first-choice, curative treatment for in situ extramammary Paget disease. There are case reports of complete clearance after topical imiquimod 5% cream treatment [33]. In a pilot study, photodynamic therapy was successfully used [34]. Further topical treatment options are 5-fluouracil and retinoic acid [35]. Frozen section-guided wide local excision is recommended in patients with penoscrotal and invasive vulvar extramammary Paget disease. In a study by Zhu et al., 32% had positive frozen section results and extended surgery. In 40% of the patients, there was a microscopic positive margin, when a 2 cm clinical tumour-free border was maintained. After a medium follow-up of 33 months, 16% had recurrent disease. 10% had systemic progression [36]. Combination chemotherapy with mitomycin C, epirubicin, vincristine, cisplatin, and 5-fluorouracil or monochemotherapy with doxetaxel (60 mg/m²/every 4 weeks) has been used in advanced extramammary Paget’s disease with persistent partial response for more than 12 months [37, 38]. The overall relative 5-year survival for invasive tumours is approximately 72%.

11.3.6 Kaposi’s Sarcoma

Genital localization is uncommon in classic Kaposi’s sarcoma, though there are several case reports [39–41]. In contrast, genital involvement (Fig. 11.13) is common in HIV-associated Kaposi’s sarcoma [42, 43] (see also Chap. 11). Therapeutic options do not differ from other localization. Low dose radiation (6–30 Gy, fractions of 1.5–8 Gy) has been used successfully for penile and scrotal lesions with complete response rates of 60.4% [44]. Additional radiation in recurrent disease can be successful [45]. Meatal obstruction can be treated by urethral serial dilation [46]. Chemotherapy with liposomal doxorubicin is well tolerated and very effective. All HIV-positive patients should be treated with antiretroviral therapy.

11.3.7 Angiomyxoma, Angiomyofibroblastoma

Angiomyxoma is an infiltrative lesion with a tendency of recurrence. Histology shows a paucicellular and extensively myxoid stroma [47]. Although pathogenesis remains unclear, chromosomal abnormalities have been described in aggressive angiomyxoma [48]. Angiomyofibroblastoma is a rare, usually small benign mesenchymal tumour that occurs in vulvar lesions of premenopausal women [49].

11.3.8 Differential Diagnosis

11.3.8.1 Hidradenitis Suppurativa

Hidradenitis suppurativa is a chronic inflammation of the skin and subcutis that is located in intertriginous regions. Some case reports suggest that it may be associated with cancer when located in the genital and perianal region. Surgery remains the treatment of choice for chronic and severe cases of hidradenitis suppurativa and has the advantage of histological control.

11.3.8.2 Hypertrophic Herpes Simplex

Especially in HIV-infected patients, herpes simplex can cause painful verrucous perianal lesion simulating neoplasia [50]. Histology shows epithelial hyperplasia
and dense inflammation composed mainly of lymphocytes and plasma cells. Diagnoses can be confirmed by immunohistochemistry or PCR.

11.3.8.3 Syringoma

Syringoma are benign tumours of the eccrine sweat glands. They are most common in the peri orbital region, but may also occur in anogenital localization. They may sometimes cause pruritus, but most lesions are asymptomatic. A hormonal influence has been postulated because of increased symptoms in puberty, pregnancy, and menstruation. Treatments for symptomatic patients include topical corticosteroids, systemic and topical antihistamines, laser and excisional surgery, cryotherapy, and topical atropine, with variable results [51].

11.3.8.4 Angiokeratoma

Angiokeratomas are rare benign dermal lesions of the external genital system and occur before the age of 50 years [52]. It is sometimes associated with increased venous pressure (varicocele). Treatment is only indicated if the lesions are symptomatic (e.g. bleeding, pruritus) or if malignancy cannot be ruled out.

11.3.8.5 Hemangioma

Vascular tumours are rare in the genital tract. Symptoms can be abdominal pain, genital masses, and postcoital bleeding. The differential diagnosis of the vascular tumours must be made mainly from endometriotic lesions and melanomas. Immunohistochemistry (S-100, CD31, CD34, cytokines, epithelial membrane antigen (EMA)) aids in the diagnosis. Local excision is adequate for the benign vascular lesions [53, 54].

11.3.8.6 Angiofibroma

Angiofibroma of the vulva is a rare tumour that affects middle-aged women [55]. Characteristic histological features are fusiform cells forming small fascicles, numerous blood vessels, and adipose tissue. Stroma cells are positive for vimentin and negative for CD34, S-100 and desmin. Differential diagnoses include aggressive angiomyxoma, angiomyofibroma, perineuroma, Bartholin’s glandular cyst and leiomyoma. Local excision is the appropriate treatment of this benign tumour.

References


11.4 Skin Cancers in Children

G. Schäfer-Hesterberg and Theodore Rosen

Core Messages

- Malignant tumors in children are extremely rare events
- Encountered entities can be atypical Naevus Spitz, childhood melanoma, rhabdomyosarcoma and Dermatofibrosarcoma protuberans
- Prognosis of childhood melanoma and rhabdomyosarcoma in advanced stage are mostly fatal
- Treatment should be performed at experienced cancer centers, if possible closely related to the international or national guidelines
- BCC might be found in cases of Gorlin Golz Syndrome
- Avoidance of intensive sun exposure is the only and therefore most important principle in primary prevention.
- Patients with large congenital naevi should be registered at www.naevus.org

11.4.1 Introduction

Most skin tumors in children are benign entities. Fortunately malignant neoplasms are very rare events, but when such lesions are encountered, they are difficult for both the parents and the treating physician. This chapter will concentrate on those skin cancers which are more frequent, such as melanoma in childhood and atypical Spitz nevi. Squamous cell carcinoma is not known in children, except for the occurrence in association with xeroderma pigmentosum. Similarly,
rare cases of basal cell carcinoma can be found in the context of the Gorlin–Goltz-syndrome. In both instances, the appearance of multiple tumors should strongly suggest a syndromal etiology, and an appropriate genetic analysis should be conducted.

Most entities can be readily diagnosed on a clinical basis. All unclear or partially suspicious lesions need to be biopsied for dermatopathological analysis. Dermatopathological evaluation should be performed by well-versed specialists who are familiar with the entities under consideration.

Moreover, from a philosophical viewpoint, physicians are charged with protecting children from the damaging effects of cumulative UV-radiation by encouraging primary prevention, parental counseling on sub protective measures, and participating in educational campaigns. We clearly know that excessive exposure to UV-radiation in childhood causes an increased risk of melanoma and other skin cancers in adulthood.

11.4.2 Melanoma

11.4.2.1 Definition/Epidemiology/Pathogenesis

The appearance of melanoma in childhood is extremely rare. It accounts for only 1–3% of all pediatric malignancies [1]. Melanoma in the prepubertal age group contributes about 0.3–0.4% of all melanomas [2]. There is a slight increase of the incidence among adolescents (3%) and in children (age below 10 years; 1.5%) [3]. There does not seem to be a difference in the prognosis of melanoma in younger children (under 12 years of age) compared to adolescent patients [4].

Acquired melanocytic nevi prove to be precursor lesions of melanoma in about 50% [5–7]. The highest risk factor for a later occurrence of multiple melanocytic nevi has been found to be early and repetitive intense exposure to sunlight and/or sunburns in early childhood [8, 9]. Aside from multiple melanocytic nevi, other high risk factors for the occurrence of melanoma in childhood include: the atypical nevus syndrome, the autosomal recessive genodermatosis xeroderma pigmentosum, immunosuppressive therapy, a family history of melanoma, and the preexistence of large congenital nevi [10] (Fig. 11.14).

11.4.2.2 Clinical Features

Pediatric melanomas follow the same patterns of growth as in adult lesions, so that they can be identified easily using the common clinical “ABCDE” features. Data indicate that the histological appearance of nodular melanomas is more frequent than in adults, and therefore, greater Breslow thickness is found, whereas the distribution on body surface and sex in all age groups seems to be similar [10–13].

As noted previously, large congenital nevi covering more than 5% of the body surface or with a greatest diameter of more than 20cm are considered risk factors for melanoma development in childhood [14]. This is especially the case when there are multiple satellite melanocytic lesions and if the nevus is located on the dorsal axis of the body [15]. At highest risk are a group of children with neurocutaneous melanosis, in which the first symptom is often the development of a
hydrocephalus. Neurocutaneous melanosis is more frequent in patients with congenital nevi and many satellite lesions or multiple small to medium congenital nevi. Literature reports the development of leptomeningeal melanoma with fatal outcome in about 2/3 of the cases [16]. For the purpose of gathering longitudinal data, patients with large congenital nevi should be encouraged to register at: www.nevus.org.

11.4.2.3 Diagnosis

Whenever clinical examination of a pigmented lesion is equivocal, dermatoscopy should be employed to establish a suspicion for malignancy. For any remaining uncertain case, surgical excision will provide definitive diagnosis. Histological evaluation should be performed by a specialized dermatopathologist in a comprehensive cancer center in order to reliably differentiate between the multiple subtypes of melanoma, atypical nevi, and Spitzoid lesions. In a multicenter study, formerly diagnosed childhood melanomas were found to often be the result of “false positive” histological interpretation rendered by insufficiently experienced pathologists [17].

11.4.2.4 Treatment

In those cases where dermatoscopy could not rule out malignant melanoma, surgical removal with histology should be performed. If clinical suspicion is not very strong, delay in excision is advisable due to the higher risk of postsurgical keloids in children. In cases with a strong positive family history of melanoma, early prophylactic excisions of suspicious moles must be recommended, since those children also have a significantly greater risk for developing a melanoma [18]. Larger congenital nevi, especially any nodular components, should be excised due to a high risk of melanoma transformation [19]. Depending on the size and location of a giant congenital nevus, removal may need to be accomplished via a staged excision with use of tissue expanders. At present, in some countries it is a trend to treat the visible portion of giant congenital nevi with laser. For cases in which total surgical removal cannot be achieved, this reflects a feasible way to improve cosmetic aspects, especially in teenage girls and young women. Still, this should – in the authors’ opinion – only be offered to patients who are known to be reliable enough not to let go of the important, regular aftercare appointments. One must always bare in mind that laser treatment is the application of high energy light on skin and all long-term effects may not yet be known.

As in adults, surgical margins are determined by staging (per AJCC 2002 revised staging criteria) and as recommended in the 2007 edition of the NCCN Practice Guidelines. Sentinel node identification and evaluation can be recommended likewise for subjects with a lesion thickness over 1 mm or when other specific risk factors are present (such as ulceration or regression) [20]. Regular sonographic examinations, depending on the stage, every 3–6 months, of the regional lymph nodes and the intransit region should be performed in order to identify possible metastases early [21].

There is no standard treatment for pediatric melanoma patients. Chemo or Immunotherapeutic approaches, just as vaccination strategies, should carefully be decided on a case to case basis and decisions must be based on significant results from adult trials; since the incidence of pediatric melanoma will always be too small, trials would always remain underpowered. Data indicate that children with stage IIc and III might be treated with interferon in an adjuvant setting, as reports about side effects are not worse than those in adults. The potential effect on overall survival remains unclear [22]. To the authors, in case of distant metastases, all treatments with tolerable toxicities are justified. If the status “no evidence of disease” can be achieved by radical surgery, this should always be favored. As today, none of the available drugs proved reliable benefit in stage four disease in large adult trials, there is certainly no knowledge about the benefit in any of the therapies in childhood melanoma.

Considering the limited utility of chemotherapeutic agents against melanoma, no specific recommendation can be made, except that treatments and experimental protocols should be performed in cancer centers by experienced oncologists. All treated cases should be well documented, followed-up and possibly – if not included in a trial – be shared as a case report publication.

11.4.3 Spitz Tumor/Reed Nevus

11.4.3.1 Definition/Epidemiology/Pathogenesis

Spitz tumor is currently recognized as a distinct entity. It was first characterized by the American pathologist
Sophie Spitz as “juvenile melanoma” with a rarely fatal outcome [23]. Subsequently, she showed that the lesions are better considered to be benign tumors. Some years later, the tumors were defined as spindle cell and/or epithelioid cell nevi. The few fatal cases described were found in young pubertal or postpubertal females. Atypical Spitz tumors seem to be a borderline entity of biologic behavior residing between benign Spitz nevi and overt malignant melanoma.

Another phenotype of a pigmented nevus is the so-called Reed nevus, which may be a variant of the Spitz tumor [24, 25]. Because of the difficulties in the distinction between Reed nevus and pigmented Spitz tumor, Ferrara et al. proposed to group them together as the pigmented Spitz-Reed nevus [26].

11.4.3.2 Clinical Features

The Spitz tumor is a distinct, usually acquired form of a melanocytic nevus with characteristic clinical features. This tumor appears primarily in young children on the head and neck region or on the extremities. It presents as a solitary, symmetric, red or pink to light brown, papular to nodular lesion less than 10 mm diameter. Associated pruritus has been described. The first growth phase can be alarmingly rapid. The Reed nevus is usually found on the lower extremities, and presents as papular, dark pigmented lesion which follows a rapid growth phase. Both entities can be diagnosed with the help of dermatoscopy that demonstrates a typical pattern including starburst pattern with pigmented streaks and brown/black globules of variable size.

11.4.3.3 Diagnosis

Due to the occasional resemblance to malignant melanoma, the clinical diagnosis of a Spitz nevus is always to be handled with caution. After excision and histopathological exclusion of a melanoma, Spitzoid lesions can be classified into low, intermediate, and high risk lesions, with a scoring system devised by Spatz and coworkers [27]. Defined risk factors for malignancy are age (older than 10 years), size (>10 mm), depth of invasion (into subcutaneous tissue), presence of ulceration, and a mitotic index >6/mm² [27]. Nonetheless, the ultimate biological behavior of each specific lesion remains uncertain.

CD99 (MIC2) was recently shown to be of potential use to differentiate Spitz nevi from Spitzoid melanoma. More than 50% of Spitzoid melanomas express CD99, whereas only about 5% of Spitz nevi expressed this transmembrane glycoprotein [28]. Another potentially helpful approach to differentiate between typical and atypical Spitzoid lesions and melanomas is the immunohistochemical staining for the expression of Ki67, a marker for proliferation rate of cells (within the G0 state cells do not express Ki67); therefore, positive cells represent the proliferating fraction within the tissue. It may usually be found in an increasing amount from Spitz nevi to malignant melanoma, i.e., increasingly from benign to malignant lesions. Similarly, the expression of Telomerase activity showed to discriminate between Spitz nevi, acquired nevi, and melanoma. Expression of HMB-45 in nevi and calm melanocytes is usually negative, whereas HMB-45-positivity can be found in about 85% of melanomas. Also the method of CGH (comparative genomic hybridization) can help to discriminate between melanoma and Spitz nevi, since the latter, just as other benign forms of nevi, hardly present any alterations of DNA copy number [29, 30].

11.4.3.4 Treatment

A surgical approach is the treatment of choice for all Spitz tumors with full resection and complete histopathological examination. The literature does not contain data supporting a specific, acceptable surgical margin. A safety margin of 2 mm is proposed by many authors, but the decision lies with the treating physician [31]. All Spitz tumors with an atypical appearance such as asymmetry, enlargement (>10 mm), or ulceration must be entirely removed with histological assessment. The need for re-excision in case of an incomplete removal remains controversial and might not always be mandatory [32, 33]. It seems appropriate to apply a wider safety margin (5–10 mm) for atypical Spitzoid lesions in accordance to the recommended margin for low-risk melanomas. Since definite histological diagnosis requires examination of lesion edges and entire dermal component, it seems even more appropriate to completely excise all Spitzoid tumors [34].

Concerning performance of SLNB, the numbers are too small to make clear recommendations, but considering the tolerability of this procedure it should, in the authors’ opinion, always be considered. SLNB seems
reasonable if there is any ambiguity regarding a diagnosis of melanoma. It might also be performed if the lesion turned out to be of a high-risk according to the Spatz scoring system [27]. Patients should be followed regularly by a dermatologist, and the regional lymph nodes can be examined once per year by sonography.

11.4.4 Rhabdomyosarcoma

11.4.4.1 Definition/Epidemiology/Pathogenesis

The appearance of rhabdomyosarcoma in children and adolescents is more frequent than in adults, accounting for 5–8% of all malignant tumors in childhood [35]. A primary presentation in the skin remains extremely rare. Among neonates, a slight predominance of males has been noted (1.8:1). Neither histology and mitotic count, nor tumor size allows outcome predictions as found in a subgroup analysis of 14 neonates in the Intergroup Rhabdomyosarcoma Study [36]. This tumor primarily is encountered on the head and neck, in genitourinary tract, and within the soft tissue of the extremities. Five different subtypes of rhabdomyosarcomas are known, of which the alveolar type is the most common in childhood. The other types are: embryonal, botryoid, spindle cell, and pleomorphic. The incidence of the latter generally increases with age [37]. Rhabdomyosarcomal cells are derived from embryonic mesenchymal precursor of striated muscle [38].

11.4.4.2 Clinical Features

Rhabdomyosarcoma is characterized as a rapidly growing, skin-colored to erythematous tumor with a potential for ulceration. Although the head and neck region predominates in children, location is inconsistent in the few cases of this tumor arising in adults.

11.4.4.3 Diagnosis

The clinical diagnosis is difficult since various types of sarcoma and other skin tumors must be considered. The diagnosis is generally only established following histopathological evaluation, including a panel of immunophenotyping.

11.4.4.4 Treatment

Wide surgical excision of both the tumor and the adjacent soft tissue needs to be performed. In advanced cases, radiotherapy and chemotherapy can be utilized postoperatively. A report of postoperative administration of poly-chemotherapy (vincristine, actinomycin, and cyclophosphamide) showed promising results [38]. The overall prognosis is poor. About 50% of rhabdomyosarcoma cases have a fatal outcome [36].

11.4.5 Dermatofibrosarcoma Protuberans: DFSP

11.4.5.1 Definition/Epidemiology/Pathogenesis

Dermatofibrosarcoma protuberans (DFSP) in adults was first described in 1890 [39] and named by Hoffmann in 1925 [40]. DFSP is characterized as a locally destructive tumor without metastatic spread being common. Nevertheless, the tumor’s high rate of recurrence justifies its classification as a semimalignant entity. Data indicate an overall incidence of 1/100,000 per year. In childhood, DFSP is also known as giant cell fibroblastoma (GCF), and it may occur congenitally. Translocations on chromosomes 17 and 22 have been found, resulting in a COLIA1-PDGFB fusion, which leads to an ongoing activation of the PDGF receptor beta tyrosine kinase [41–43].

11.4.5.2 Clinical Features

The presentation of DFSP and GFC is an extensive, slowly growing, and infiltrating tumor within the dermal or subcutaneous tissue. The tumor can eventuate into a firm and fibrous, multinodular appearing lesion with an irregular contour. DFSP is usually of erythematous to light-brown hue, though surface pressure leads to cutaneous pallor. Initially movable over deeper structures, DFSP eventually becomes bound down as it infiltrates the underlying subcutaneous fat and fascial planes. Even the adjacent skeletal muscle can be rarely infiltrated by the tumor [44]. DFSP can be mistaken for a keloid or hypertrophic scar. With progredient growth, the covering tissue becomes stretched, thinner, and ulcerations will occur. Typical locations for DFPS
include the upper thorax and abdomen. There is a male predominance. There are usually no subjective symptoms, such as pain or itching.

A specific, pigmented form of the juvenile dermatofibrosarcoma is the Bednar tumor, which represents in about 5% of all DFSP [45]. Melanin pigment can be found in parts of the tumor.

### 11.4.5.3 Diagnosis

Histologically, these tumors present with atypical spindle-shaped fibrocytes organized in the so-called stellate or cartwheel pattern. Nevertheless, diagnosis depends upon clinico-pathological correlation since this histologic picture can also be found in other entities [46]. Distant metastases are rare, but hematogenous spread is reported to occur in cases which had a mitotic rate above eight per ten high power field (HPF), while DFPS usually present only 0–4 mitoses per HPF [46]. Cells are usually CD34 positive and S100 negative.

Discrimination of the GCF from DFSP is not always possible and recurrences might present characteristic patterns of DFSP. One proposed typical pattern for GCF seems to be a peculiar perivascular lymphocytic infiltration, described by Jha et al. [44]. Differentiation into separate entities does not seem logical since the genetic background as well as most clinical and histological features are identical. Tumor cells in both entities are of histiocytic or fibroblastic origin [47].

### 11.4.5.4 Treatment

Standard therapy of choice is surgical excision with at least 1 cm of histologically-verified clear margin. Excisional specimens need to be carefully examined because the high recurrence rate is largely due to an incomplete removal at the sides or at the deep, fascial border. Results of recent perioperative poly-chemotherapy trials for multiply recurrent DFSP are promising. The administration of vinblastine (6 mg/m²) and oral methotrexate (20 mg/m²) led to tumor reduction with well-tolerated toxicity in case of a 9 year old girl [48].

Most recently, the tyrosine kinase inhibitor imatinib mesylate (Gleevec®/Glivec®) offers a new option for adjuvant therapy or primary therapy of problematic and metastatic DFSP in adults and children [49, 50].

### References

11.5 Nail Apparatus Cancer

Robert Baran

11.5.1 Acrokeratosis Paraneoplastica

Core Messages

- Paraneoplastic acrokeratosis is a specific sign of cancer of the upper airway and upper digestive tract. The distinctive cutaneous changes include erythematous to plum-colored scaly acral lesions, paronychia, dystrophic nail, and keratoderma.
- The lesions resolve on therapy of the tumour.

Key-Points

- Men over 40 years
- Nail changes may precede the malignancy
- The cancer of upper G-I tract resolves on therapy of the tumour
- Red, keratotic lesions on hands, feet, ears and sometimes nose
- Nails, either thin, soft, fragile and crumbling develop subungual hyperkeratosis resembling severe psoriatic dystrophy

11.5.1.1 A Cutaneous Marker of Malignancy

Bazex and Dupre's Syndrome

Paraneoplastic acrokeratosis is a specific sign of cancer of the upper airway and upper digestive tract. The distinctive cutaneous changes include erythematous to plum-colored scaly acral lesions, paronychia, dystrophic nail and keratoderma [1–3].

1. The condition affects males almost exclusively, nearly always over the age of 40. It is exceptional in non-Caucasians.
2. It appears to be associated only with neoplasia of the pharyngo-laryngeal region, oesophagus, tongue, lower lip, upper third of the lungs, or with neoplasia metastasizing to the cervical region.
3. The initial lesions start on the extremities and affect particularly the fingers, toes (Fig. 11.15), nose and ears. They are psoriasiform and usually symmetrical.

Typically three stages can be recognized:

First stage
The eruption starts as erythema and psoriasiform scaling on the fingers and toes, soon spreading to the margins of the aural helices, and as violaceous erythema and pityriasiform scaling over the bridge of the nose. The nail folds are prominently involved and may be tender. Elsewhere, the eruption is symptomless. Nail changes are frequent and consist of dystrophy with subungual hyperkeratosis and onycholysis progressing to complete destruction of the nail plate. At this stage the neoplasm is frequently undetected, but may have already metastasized to the cervical glands.

Second stage
The eruption spreads from the nail folds to the whole of the hands and feet producing keratoderma with a violaceous colour. The skin appears oedematous and the palms may have a honeycomb appearance. Red scaly lesions involve the whole of the pinna, and on the face, the eruption spreads from the bridge of the nose.

Fig. 11.15 Bazex disease
sometimes reaching the upper lip. The neoplasm at this stage often gives rise to localizing signs and systemic symptoms.

**Third stage**

If the neoplasm is not treated, the rash extends locally or new lesions appear in other sites such as the legs, knees, thighs and arms. On the trunk, the lesions resemble psoriasis, but the plaques are always ill-defined and never progress to erythroderma. On the face, the lesions mimic seborrhoeic eczema or lupus erythematosus, and on the scalp, the scaling is pityriasisiform. In some cases the extent of the rash does not correlate with the extension of the malignancy. With successful treatment of the tumour the rash usually clears, but changes in the nails may persist.

**References**


### 11.5.2 Epidermoid Carcinoma

#### 11.5.2.1 Bowen’s Disease: Squamous Cell Carcinoma

**Core Messages**

- Bowen’s disease of the nail apparatus is a distinctive type of squamous cell carcinoma (SCC) that differs from other variants. The malignant process may develop in the epithelium of the periungual area, as well as in the subungual tissues, and most commonly originates in the nail folds or nail grooves. The clinical presentation is protean and several new signs have been added to the classical one. Bowen’s disease has been reported in individuals between the ages of 13 and 90. New treatment possibilities enlarging the range of the treatments offered to the patient have not superseded Moh’s micrographic surgery.

- Bowen’s disease of the nail apparatus is a distinctive type of SCC that differs from other variants. Some authors prefer to avoid the use of the term Bowen’s disease for in situ epidermoid carcinoma occurring beneath the nail plate, because it is not always easy to distinguish invasive from in situ carcinoma, and it cannot be overemphasized that a biopsy specimen showing Bowen’s disease does not exclude the possibility of invasive carcinoma in another area of the lesions.

- The malignant process may develop in the epithelium of the periungual area as well as in the subungual tissues and most commonly originates in the nail folds or nail grooves.

- Bowen’s disease has been reported in individuals between the ages of 13 and 90, the incidence being highest in the 50–69 year range.

**Classical Clinical Patterns**

Classical patterns in periungual involvement include hyperkeratotic or papillomatous, and even warty proliferation; erosions, scaling of the nail fold; whitish cuticle; periungual swelling from deep tumor proliferation, a paronychia with erythema caused by
inflammation due to infection; and fissure or ulceration of the lateral nail groove, sometimes crusted with granulation-like tissue beneath the scab.

Subungual involvement is the most common finding. It may present with onycholysis, and clipping away of the nonadherent portion of the nail plate shows partial or extensive hyperkeratosis of the nail bed. Onycholysis associated with oozing erosion or ulceration of a sometimes crusty nail bed can be observed.

Localized pain may be noted, for example, when the patient uses a keyboard.

The nail plate may become dystrophic, ingrown. The presence of ulceration, bleeding, or nodule formation indicates that the carcinoma has become invasive. One of the most important clinical features of Bowen’s disease of the subungual tissues is associated with partial or total nail loss (Fig. 11.16). Bone involvement is seen in less than 20% of patients. Metastases have been reported in patients with hereditary ectodermal dysplasia, but also in patients without ectodermal dysplasia. The rate of metastases, however, appears to be low. Nodal involvement is reported in only 2% of patients with subungual squamous cell carcinoma (SCC).

The key to diagnosis is the histologic examination. The picture is identical to that of Bowen’s disease in other skin areas. The most important feature is the intact basement membrane.

The tumor grows slowly, and the duration of signs and symptoms from onset to the time of diagnosis has varied from several months to 30 years. The diagnostic biopsy is often delayed because of the patient’s reluctance, technical difficulties, or because the physician has failed to suspect the disease. The toes are significantly less frequently affected than the digits of the hands, especially the thumb that is probably the most common involved area, despite some publications indicating that the second, third, and fourth fingers are more often diseased.

New Described Clinical Patterns

Identification of longitudinal melanonychia, with a classical band pattern [1, 2] that may be isolated [3], or present with an irregular appearance of the dark streak [4–6], is a recent clinical finding confirmed by numerous authors. Lifting the nail plate, subungual pseudo-fibrokeratoma is an uncommon pattern [7]. It may be pigmented, appearing as a longitudinal melanonychia [8, 9]. Pseudo-Hutchinson’s sign is particularly misleading, as it is similar to melanoma when it affects only one digit [10, 11], but several digits may even be simultaneously involved. Longitudinal erythronychia associated with subungual Bowen’s disease [12–14] is a recent finding.

Bowen’s disease of the fingernail structures should always be regarded as a potentially polydactylous process [15–17]. Adequate follow-up observation of uninvolved nails of all digits, with prompt evaluation and treatment of suspicious changes, is therefore mandatory.

Leuconychia may involve verrucous carcinoma [18] and seven patients out of 35 SCCs have been reported by french authors [13].

Differential Diagnosis

Bowen’s disease is a protean tumor that often appears as a clinically misleading “benign” lesion which delays diagnosis. The lesions are sometimes mistaken for chronic inflammatory conditions, including bacterial infections. However, in rapidly enlarging growth of the proximal nail fold [19], SCC must be considered in the differential diagnosis of nail fold neoplasm. An immunocompromised condition such as HIV/AIDS may predispose to malignant degeneration of lesions caused by infection with HPV.

Differential diagnosis includes pyogenic granuloma, verruca vulgaris, onychomycosis, subungual exostosis, melanoma, glomus tumor, epidermoid cyst, and subungual kerato-acanthoma that may pose a diagnosis difficulty radiologically and histopathologically, and even in acquired ungual fibrokeratoma. Pigmented onychomatricoma may be difficult to rule out without the histologic malignant patterns [20]. Metastatic SCC

![Fig. 11.16 Bilateral Bowen’s disease. (Courtesy, L. Requena, Spain)](image-url)
of the nail bed as a presenting sign of lung cancer is rare [21, 22]. It may be impossible to differentiate radiologically between necrotic bone caused by infection and neoplastic bone caused by malignancy. But early X-ray examination may be useful to determine whether the SCC is a primary lesion or rather a secondary complication of chronic infection.

**Etiology**

The etiology of subungual epidermoid carcinoma remains unclear. Arsenic, for example, cannot be excluded in old psoriatic patients. Trauma, infection, and chronic paronychia, but above all, exposure to X-ray (physicians, dentists, patients) have been cited as etiological factors. This may be followed by radiodermatitis which, together with discovery of HPV-infection, is the most common factor for the development of SCC. HPV 16, 34, and 35 have been detected in in situ and invasive epidermoid carcinoma. HPV genome was found in eight out of ten periungual lesions by dot-blot analysis of frozen tissue, and six of them were related to HPV16.

A human papillomavirus-associated digital SCC review [23] suggests the possibility of genital-digital spread as a mechanism of tumor genesis. HPV has never been found in association with SCC developing on toenails. HPV-associated with digital SCC is more likely to recur after surgical treatment than previously reported.

### 11.5.2.2 Verrucous Carcinoma

Epithelioma cuniculatum is a rare, slow-growing but locally destructive low grade cancer of squamous cell origin. It has been reported in several patients with thumb involvement. Progressively, the inflammatory features are accompanied by paronychia, subungual purulent material leading to disappearance of the nail plate. In carcinoma cuniculatum, the nail bed is covered with multiple holes extruding toothpaste-like, foul smelling yellow–white material [24, 25].

### 11.5.2.3 Keratoacanthoma

The lesion is most often seen on the thumb or index fingers in patients 40–60 years of age. Keratoacanthoma (KA) of the nail apparatus may present with pain, swelling, and erythema. Bony destruction by overlying pressure effect is frequent. The rapid growth contrasts with the lack of spontaneous regression as is typical in KAs in other location.

The possibility that KAs are a variant of SCC has been repeatedly raised. Because absolute differentiation between malignant SCC and benign KA is not currently possible, it may be best to consider KA as a very low grade of SCC especially in the nail region [26].

**Classical Treatment**

The need for complete removal of the lesion cannot be overemphasized:

1. The best treatment is *Mohs’ micrographic surgery* allowing adequate excision with maximum preservation of normal tissue and function. This can be performed with routine instrumentation as well as with the CO₂ laser in a focused beam incisional mode, which avoids bleeding and ensures minimal postoperative discomfort for the patient.

2. *Excisional surgery* may be used in some cases or for complete removal of the nail apparatus, with healing by secondary intention, grafting, or repair with a bridge flap.

3. *Electrosurgery* is a therapeutic alternative in very few specific cases.

4. *Liquid nitrogen* may give good results in experienced hands. However, both electrosurgery and liquid nitrogen do not allow adequate histological control of tumor margins.

A perionychial SCC without bone involvement requires complete removal with margins of one-half to one cm, and usually requires coverage with a skin graft. If there is bone involvement or extensive soft tissue involvement, amputation of the distal interphalangeal joint or more proximally should be considered. Lymph node dissection is indicated if palpable lymph nodes do not disappear within 3–4 weeks after amputation or excision, as many lymph nodes enlargement are due to chronic inflammation. A multidisciplinary approach to resection and reconstruction is mandatory.

**Recent Alternatives**

1. **Imiquimod**

Imiquimod topical treatment has been used with good results in genital or extragenital Bowen’s disease in
immunocompetent or immunocompromised patients. It was, therefore, logical to manage the digits of patients affected by Bowen’s disease [27].

2. 5-aminolevulinic acid

There has been some success using photodynamic therapy [28, 29].

3. Intraarterial infusion with methotrexate

Intraarterial infusion of chemotherapy [30] has been considered as a simple and effective alternative method for big toe SCC with the preservation of organ and function.

4. Radiation therapy

Radiation therapy should be considered as a treatment option for nail bed SCC before suggesting

5. Amputation

Amputation and, perhaps, for all unresectable lesions (Table 11.3).

### Table 11.3 Treatments for epidermoid carcinoma

<table>
<thead>
<tr>
<th>Classical treatment</th>
<th>Recent alternatives</th>
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<tbody>
<tr>
<td>Moh’s micrographic surgery</td>
<td>Imiquimod</td>
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<tr>
<td>Excisional surgery</td>
<td>5-aminolevulinic acid</td>
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<tr>
<td>Electro or Radiosurgery</td>
<td>Methotrexate intraarterial infusion</td>
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<tr>
<td>Liquid nitrogen</td>
<td>Radiotherapy</td>
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<td>Amputation</td>
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</table>

### References

11.5.3 Basal Cell Carcinoma

Basal cell carcinoma (BCC), the most frequent malignant neoplasm of the skin, is rare in the nail region (about 25 cases published) but may not be as rare as previously thought [1, 2]. The tumor occurs three times more often in fingers than in toes, and has a slight predilection to occur in men [3].

Clinically, there are three main types of presentation [1, 3] that are sometimes associated:

- Ulceration, sometimes painful and noted in more than one-half of the patients, is the most common presentation on the proximal or lateral nail fold [3] (Fig 11.17);
- Partial or complete nail destruction [4];
- Pigmentation of the nail as longitudinal melanonychia [5] or as brownish nail pigmentation mimicking melanoma [6].

Nonpigmented lesions developing on the fingers could easily be misdiagnosed as chronic dermatitis (peri-ungual eczema) or chronic paronychia. This explains that BCC is usually present for many years.

The diagnosis can only be made by histologic examination; therefore, adequate biopsy of the lesion is associated to rule out infections processes, other malignant
tumors, or benign neoplasms. BCCs reported in the nail area often have a metatypical histologic pattern, i.e., they have a component of squamous cell carcinoma [1, 3, 7]. Recently, special emphasis was given on superficial multicentric histopathologic type with jagged borders in the superficial neoplastic buds that may be a hallmark for superficial BCC of the nail apparatus [3].

Mohs micrographic surgery may be a very effective modality for treatment, and second intention healing may provide excellent cosmetic and functional results after tumor removal. Curettage and electrosurgery or local excision was also curative.

Photodynamic therapy might be commonly used in the future.

References


11.5.4 Metastatic Tumors

Core Messages

Metastases to the nail region are quite rare. They may be the first manifestation of a visceral neoplasm. Multiple sites may be involved. Most metastatic tumors primarily affect the bone with subsequent spread to soft tissues, but primary soft tissue involvement of the distal digit may secondarily involve the bony phalanx. The appearance of pigmented streaks in the nail plates is an unusual metastatic manifestation of melanoma.

They may be the first manifestation of a visceral neoplasm [1, 2] (Fig. 11.18). Multiple sites may be involved (see Table 11.4). Most metastatic tumors primarily affect the bone with subsequent spread to soft tissues, but primary soft tissue involvement of the distal digit may secondarily involve the bony phalanx [1, 3]. The appearance of pigmented streaks in the nail plates is an unusual metastatic manifestation of melanoma.

The symptoms and signs of metastases are variable. They include dusky red painful or painless swelling, expansible pulsation, pseudo-clubbing, nail dystrophy, and changes simulating acute infection or chronic paronychia. Whatever symptoms occur, the signs increase out of proportion to the pain. In the absence of injury or infection, this suggests the possibility of metastases. With time, a reddish-purple nodule in the

![Fig. 11.17 Basal cell carcinoma (Courtesy, Verret, France)](image1)

![Fig. 11.18 Colon metastasis (Courtesy, Brownstein, USA)](image2)
Table 11.4  Reported sites of primary tumor in patients with nail unit metastasis (adapted from Cohen and Spencer) [5]

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Site</th>
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<tbody>
<tr>
<td>Lung</td>
<td>Sarcoma</td>
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<tr>
<td>Genitourinary</td>
<td>Chondrosarcoma</td>
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<tr>
<td>Kidney</td>
<td>Sarcoma, type not specified</td>
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<tr>
<td>Testes</td>
<td>Melanoma</td>
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<tr>
<td>Chorioepithelioma</td>
<td>Gastrointestinal</td>
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<tr>
<td>(placenta)</td>
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<tr>
<td>Bladder</td>
<td>Colon</td>
</tr>
<tr>
<td>Cervix</td>
<td>Rectum</td>
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<tr>
<td>Uterus</td>
<td>Stomach</td>
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<tr>
<td>Breast</td>
<td>Liver</td>
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<tr>
<td>Head and neck</td>
<td>Skin</td>
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<tr>
<td>Parotid</td>
<td>Neuroblastoma</td>
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<tr>
<td>Hypopharynx</td>
<td>Plasmacytoma</td>
</tr>
<tr>
<td>Larynx</td>
<td>Adrenal glands</td>
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<tr>
<td>Oral cavity</td>
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distal subungual tissues may become ulcerated. X-rays usually show an osteolytic focus.

Bronchial carcinoma represents 50% of phalangeal metastases and breast 15% in woman followed by genitourinary tract.

Table I provides the list of the other primary tumors reported.

The appearance of pigmented longitudinal streaks in the nail plates is an unusual metastatic manifestation of melanoma [4].

Biopsy is mandatory, but may fail to reveal the true nature of the primary lesion.

References


11.5.5 Nail Apparatus Melanoma

Core Messages

- Nail apparatus melanoma (NAM) is rare and accounts for less than 3% of melanomas in Whites. The relative incidence of NAM is much higher in non-Whites; up to 25% are located in the nail apparatus especially on the thumbs, index fingers, and big toes. The mean age at diagnosis is 60–70 years. Acrolentiginous melanoma (ALM) is the most frequent type; superficial-spreading melanomas and nodular melanomas are encountered less frequently. A delay in the diagnosis of NAM is common and is associated with poor prognosis. Delays can be attributable to the patient and to the medical staff. Medical misdiagnosis occurs in 52% of the cases and is responsible for an 18-month median delay. This misdiagnosis is true particularly for amelanotic melanoma, which represents at least 25% of NAM.

The ABCDEF rule, as well as dermoscopy, to improve early clinical detection of subungual melanoma is useful.

NAM is rare and accounts for <3% of melanomas in whites. The relative incidence of NAM is much higher in non-Whites; up to 25% are located in the nail apparatus, especially on the thumbs, index fingers, and big toes. The mean age at diagnosis is 60–70 years. ALM is the most frequent type; superficial-spreading melanomas and nodular melanomas are encountered less frequently. A delay in the diagnosis of NAM is common, and is associated with poor prognosis. Delays can be attributable to the patient and to the medical staff. Medical misdiagnosis occurs in 52% of the cases and is responsible for an 18-month median delay [1]. This misdiagnosis is true particularly for amelanotic melanoma, which represents at least 25% of NAM [2].

The ABCDEF rule to improve early clinical detection of subungual melanoma may be of use [3].

The most salient features of subungual melanoma can be summarized according to the newly devised
criteria that may be categorized under the first letters of the alphabet, namely ABCDEF of subungual melanoma. In this system, A stands for age (peak incidence being in the 5–7th decades of life and African, Americans, Asians, and native Americans in whom subungual melanoma accounts for up to one third of all melanoma cases. Nail plate pigmentation, usually LM, is the first manifestation of NAM in 38–76% of the cases, but only one third of patients consult a physician at this stage [4, 5]. B stands for brown to black band with breadth of 3 mm or more and variegated borders. C stands for change in the nail band or lack of change in the nail morphology, despite, presumably, adequate treatment. D stands for the digit most commonly involved; E stands for extension of the pigment onto the proximal and/or lateral nailfold (i.e., Hutchinson’s sign or pseudo-Hutchinson sign); and F stands for family or personal history of dysplasic nevus or melanoma (Table 11.5).

Atypical melanocytic hyperplasia shows an increased number of melanocytes with larger, hyperchromatic, pleomorphic nuclei, more prominent nucleoli, increased mitoses, and long branching dendrites. Thus, atypical melanocytic hyperplasia may be considered to be incipient malignant melanoma in situ.

Melanomas of the nail region are now better understood since the identification and analysis of ALM, the most frequent type. Superficial spreading melanoma (SSM) [6] is infrequent and nodular melanoma is very rare in subungual area despite Milton’s et al.’s findings [7] in Australia (7 cases out of 30 individuals) and Miura & Jimbow’s [8] questionnaire survey of 108 cases of subungual melanomas in Japan, indicating that ALM was present in 80% of cases, nodular melanoma in 15%, and SSM in 5%.

Melanomas are often asymptomatic, pain and bleeding being rare. The clinical appearance of the tumor varies, but half the patients note a mass below the nail, usually associated with partial destruction of the nail or total loss.

Periungual infection, ulceration of the nail bed, and granulation tissue occur in about one-third of the patients. In another third, discoloration of the nail area is the presenting sign.

1. Some lesions begin as a longitudinal melanonychia [9, 10]. This pigmented (brown to black) linear streak of variable width runs through the whole length of the visible nail. It was the first feature in six out of ten patients with malignant melanoma in a Belgian study [11]. After some months or years, the borders of the band widen, become blurred, and ulceration appeared. It must be stressed that neither the width nor the intensity of the brown pigmentation are proof of, or exclude, subungual melanoma. The appearance of pigmented streaks in the nail plate may even be an unusual metastatic manifestation of melanoma [12].

Dermoscopy is useful for the evaluation and etiological diagnosis of longitudinal melanonychia.

The following criteria can be evaluated by dermoscopy [13]:

- Gray pigmented band composed of multiple thin homogeneous grayish lines.

This pattern is usually a result of epithelial hyperpigmentation without accompanying melanocytic hyperplasia as is seen in a lentigo, drug-induced pigmentation, and ethnic pigmentation.

- Brown pigmented band. The brown pigmented band is usually composed of multiple thin brown lines. These lines can be regular or irregular and are caused by melanocytic hyperplasia as seen in a nevus or melanoma. There are two main patterns seen within brown pigmented bands.

- Regular pattern: Brown longitudinal parallel lines with regular spacing and thickness. They are usually associated with a brown homogenous color of the background band.
• Irregular pattern: The band comprises multiple longitudinal brown to black lines with irregular spacing and thickness, and disruption of parallelism.
• Free edge of the nail: apart from the examination of the nail plate, perionychium, and hyponychium, dermoscopy can also be used to examine the free edge of the nail plate which allows the determination of the exact anatomic location of nail matrix pigmentation in vivo.

2. A spot can appear in the matrix or nail bed. This may vary in color from brown to black, and may be homogeneous or irregular. It is seldom painful.

3. Less frequent is Hutchinson’s sign [14], an irregular brown black pigmentation of the matrix, nail bed, nail plate, and surrounding tissues. It represents the radial growth phase of subungual melanoma and has proved to be a valuable clue to the clinical diagnosis of malignancy after pseudo-Hutchinson’s sign [15, 16] has been ruled out. The latter can be observed in benign conditions, nonmelanoma, malignant tumors, and illusory category. The presence of Hutchinson’s sign means that the entire nail apparatus must be removed (without prior incisional biopsy) [17]. This technique enables serial sections to be examined, which is particularly important in acral lentiginous melanoma in which histology may be difficult to be interpreted. The radial growth phase of malignant melanoma in the subungual region is easily confused histologically with junctional nevus and the clinician must be wary of a benign histological report in any subungual lesion showing Hutchinson’s sign. The vertical phase with its abrupt onset when compared temporally with the slowly evolving radial growth phase is manifested by the focal appearance of a discrete blue, black, or pink nodule in tumors of subungual site causing partial or total permanent destruction of the nail plate.

Approximately 25% of melanomas are amelanotic (Fig. 11.9) and may present as pyogenic granuloma, granulation tissue, ingrowing nail, and mycobacterial infections with nail dystrophy. The risk of misdiagnosis is, therefore, particularly high in these cases.

At the Sydney Melanoma Unit, the mean Breslow thickness of NAM at diagnosis is 3.05 mm compared with a mean of <1.0 mm for cutaneous melanoma, and significantly fewer patients present with local disease without metastasis [5]. In a British study of 105 patients [18] who had NAM, the mean Breslow thickness was 4.8 mm. The 5-year survival rate was 88% for a Breslow thickness of 2.5 mm or less and only 40% for a thickness >2.5 mm.

It should be mentioned that nail melanoma is extremely rare in children but does occur.

11.5.5.1 Differential Diagnosis

Nail melanoma must be considered in the differential diagnosis in all patients affected by unexplained chronic paronychia, whether painful or not; torpid granulomatous ulceration of the proximal nail fold; pyogenic granuloma; pseudo-verrucous keratotic alterations of the nail bed and lateral nail groove; and persistence of a lesion following trauma of the nail. Pathologic fracture secondary to subungual melanoma may be the presenting sign.

Subungual melanoma may be mimicked by subungual hematoma, which is not rare and may even be present without a history of severe trauma. It may follow repeated minor trauma which escapes the patient’s attention such as in tennis toe or following trauma from hard ski boots or windsurf board. Hematoma following isolated trauma usually grows out in one piece rather than as longitudinal streak due to continuous production of pigment, but subungual melanoma following a single injury to the digit was observed in several cases after an interval of between 9 months and 7 years. Repeated trauma may cause difficulties in differential diagnosis when a nonmigrating hematoma is present. The pigmented nail should then be clipped and tested with the argyrophil stain in order to rule out melanin
pigmentation. As subungual hemoglobin is not degraded to haemosiderin and remains, therefore, Prussian blue negative, scrapings or small pieces of the nail boiled with water in a test tube give a positive benzidine reaction with conventional hemostix. However, it has to be stressed that any erosive bleeding tumor will also give a positive benzidine reaction. Consequently, a diagnostic nail biopsy should be performed for the investigation of any persistent, clinically suspicious, pigmented nail lesion. The difference between blood and melanotic pigment, sometimes rather difficult to discern by routine histological methods, is easily seen by ultrastructural techniques – since hem pigment is intercellular while melanin is mainly intracellular [19].

_Pseudomonas, Proteus spp, and Trichophyton rubrum nigricans_ may cause black nails [17, 20]. It is also very important to stress that a major proportion of patients suffering from subungual melanoma have undergone some minor form of surgery before the diagnosis of subungual melanoma has been made. This is not only the consequence of patients’ neglect, but also of physicians’ misdiagnoses, false biopsy techniques, and insufficient histopathological techniques and knowledge. Thus, the importance of proper biopsy and histopathology for the prognosis cannot be overestimated. Recent series as well as our own experience has shown that LM in young people is mostly due to lentigines or junctional nevi. Histopathology, thus, shows melanocytes and nevus cells mainly in the basal zone of the matrix epithelium. Therefore, a biopsy technique was developed that ensures almost scarless healing and gives excellent tissue specimens for histopathological work-up. This is essentially a superficial, tangential excision of the pigmented lesion of the matrix performed after lifting the nail plate at its proximal third [10].

Migration of melanoma cells into suprabasal epidermal layers is a characteristic feature also seen in acral lentiginous melanoma. These cells and cell clusters eventually reach the horny layer or nail plate, respectively. Therefore, clippings of subungual melanoma nail plate sometimes contain pycnotic tumor cells which retain their protein S-100 positivity.

There is usually no difficulty making the histopathological diagnosis of advanced invasive subungual melanoma. Most subungual ALMs exhibit a lentiginous pattern with pleomorphic, often dendritic atypical melanocytes being arranged singly or in irregular clusters in the basal and suprabasal epithelial layers. Sheets of melanoma cells, either spindle, epithelioid, polygonal, small, dendritic, or bizarre and pleomorphic, extend from the epithelium into the dermis. Large round melanoma cells are dispersed throughout the entire epidermis in a pagetoid (SSM-like) pattern. The nodular pattern is rare and shows subepidermal tumor cells usually with little junctional cell complexes, and at least part of the overlying epithelium is necrotic. Subungual nodular melanoma appears to be primarily located rather in the nail bed than the matrix [17]. Mixed features of lentiginous and pagetoid patterns are not rare. Especially the lentiginous type of subungual melanoma may exhibit a dense population of atypical melanocytes in the basal epithelial layers, which may give rise to artificial bulla formation due to lack of cohesion between melanoma cells and nail bed and matrix epithelium upon sectioning and is also one cause of nail atrophy in subungual melanoma. Subungual nodular melanoma with no junctional component may be difficult to distinguish from lymphoma, anaplastic, and small cell carcinoma as well as other malignant tumors including metastases, all of which are rare in this location. Several cases of dermoplastic subungual melanoma have been reported, some with perineural extension. SM also masquerades as fibrous histocytic tumors and has even been observed to produce cartilage. Immunohistochemical demonstration of S-100 protein or another melanoma marker such as HMB-45 aids in making the correct diagnosis.

**11.5.5.2 Immunohistochemistry**

Immunohistochemistry may be helpful in ambiguous cases. S-100, HMB-45, and Mart-1 are all accurate markers for cells of melanocytic origin in nail neoplasms. The distribution of melanocytes in vertical sections of the matrix has shown located in a suprabasal (rather than basal) position, which again may be misrepresented as pagetoid upward growth and malignancy when it is simply the normal histologic pattern. This distribution of melanocytes in the matrix justifies the tangential biopsy recently advocated [10]. In that sense then, immunohistochemistry may be good at identifying the cells in question, but more traditional criteria including cellular morphology, necrosis, and mitotic activity can be more crucial to diagnosing melanoma.

Once the diagnosis of melanoma of the nail unit is made, the patient must be staged. Quantifying the extent of melanoma is essential for determining the appropriate treatment and assessing prognosis [21].
11.5.5.3 Management of NAM

The diagnosis of NAM should lead to further surgical procedures. Total excision of the nail apparatus is enough for in situ melanoma. Mohs micrographic surgery has been advocated [22]. In invasive melanoma, amputation of the distal phalanx is usually recommended.

The necessity for lymph node dissection and its timing are controversial. The use of sentinel node intraoperation biopsy may determine whether lymph node dissection should be carried out.

References

11.6 Ethnic Skin

Kenneth W. Neal Jr and Hugh M. Gloster Jr

Core Messages

- Skin cancer in persons of color is less common than in light-skinned Caucasians, but is often associated with a higher rate of morbidity and mortality. To greatly improve the likelihood of early detection of these tumors, it is vital that physicians gain more knowledge about skin cancer in people of color. Squamous cell carcinoma (SCC) is the most common skin cancer in dark-skinned ethnic groups; SCC and melanoma usually occur on sites that are not exposed to sunlight; and with the exception of basal cell carcinoma (BCC), ultraviolet radiation is not an important causative factor for skin cancer.

- Races of intermediate pigmentation, such as Hispanics and Asians, share clinical and epideimiologic features of dark-skinned ethnic groups and Caucasians. Clinicians should focus on preventive measures such as regular skin exams, self-examination, public education, and screening programs because skin cancers pose a significant risk in ethnic groups, who have greater morbidity and mortality than Caucasians.

The most common tumor in the United States is skin cancer. Multiple reports have shown that it accounts for approximately 20–30% of all tumors in Caucasians, 2–4% of all tumors in Asians, and 1–2% of all tumors in Blacks and Asian Indians [2–13]. Since nonmelanoma skin cancers (NMSCs) are not commonly reported to tumor registries, the actual incidence cannot be estimated with certainty. Due to the rarity of skin cancers in Blacks, Hispanics, and Asians compared to Caucasians, it is difficult to interpret the clinical and histopathologic differences between the races. Special surveys and tumor registries evaluating select populations provide the majority of skin cancer incidence data. Based on data from 1978 for the annual age-adjusted incidence of skin cancer for Caucasians (232 per 100,000 population) and for Blacks (3.4 per 100,000 population), Caucasians are approximately 70 times more likely to develop skin cancer [2, 14]. Skin cancer incidence rates have increased at a rate of 5–8% annually since the 1960s among predominately Caucasian populations [15–17]. According to one study, BCC incidence in Japan has been on the rise from 1976–1980 to 1986–1990; however, SCC incidence has continued to be stable [18]. NMSC incidence among the Japanese is 1.2–5.4 per 100,000 population [19]. Skin cancer incidence rates have also increased among Chinese Asians between 1968 and 1997 (6 per 100,000 population to 8.9 per 100,000 population) according to the data in the Singapore Cancer Registry [8]. In a review by several authors, skin cancer incidence rates for Blacks, and specifically, SCC and BCC incidence rates among southeastern Arizona Hispanics have remained quite stable [2, 5, 20].

Although skin cancer incidence has remained stable in Blacks, the skin cancer mortality rate for Blacks has been relatively high in contrast to the stable skin cancer incidence rate among Blacks [21]. However, the NMSC mortality rate has decreased among Caucasians [21]. Overall, for Blacks and Caucasians, the NMSC mortality rate has decreased approximately 20–30% from 1969 to 1988, but the decline has been variable for Blacks [21]. During the 1980s and 1990s, there was a high incidence of AIDS-related Kaposi Sarcoma among Blacks, which may have negatively skewed the data for NMSC in Blacks compared to Caucasians, who have a much higher incidence of non-AIDS-related NMSC [22].

It is critical that physicians gain more awareness about skin cancer in non-Caucasians because it is estimated that by the year 2050 50% of the US population will mostly be composed of Hispanics, Asians, and Blacks [23]. It is paramount that physician awareness is significantly improved when also considering that darker skinned individuals have a lower incidence of skin cancer, yet the morbidity and mortality rates are disproportionately higher in comparison to lighter-skinned individuals, such as Caucasians.
11.6.1 Role of Ultraviolet Light

A number of authors have noted that Blacks have an inherent sun protection factor of up to 13.4 due to increased epidermal melanin, which is also found in other darker-skinned ethnic groups and plays a key factor in the lower incidence of skin cancers in comparison to Caucasians [3, 24]. Melanocytes in Caucasians are small and grouped together with decreased activity, whereas the melanocytes in darker-skinned ethnic groups are larger and dispersed with increased activity [3, 25, 26]. Due to these differences in melanocytes among darker-skinned ethnic groups, less ultraviolet light is transmitted in the darker-skinned individuals because the melanocytes absorb and scatter more light energy compared to Caucasians. Several authors confirmed that the melanin in the epidermis of Blacks filters two times the amount of ultraviolet (UVB) radiation than Caucasians [3, 14]. The researchers also found that only 7.4% of UVB and 17.5% of ultraviolet A (UVA) radiation are transmitted through the epidermis of Blacks vs. 24% of UVB and 55% of UVA in the epidermis of Caucasians [3, 14]. The minimal erythema dose (MED), which is the minimal dose of ultraviolet radiation necessary to induce mild erythema, is approximately 6–33 times greater in Blacks than in Caucasians [27]. There are very rare occurrences of SCC and melanoma, but no documented cases of BCC among the deeply pigmented Melanesians in the North Solomons of New Guinea [28]. Possibly, due to the protective effects of the brown pigmentation, Japanese in Hawaii have a NMSC calculated incidence that is 40 times less than the Caucasians who reside in the same area [19].

UVR does not appear to play an important role in the development of skin carcinomas of darker-skinned ethnic populations due to the melanin that protects against the carcinogenic effects of solar UVR radiation.

The major risk factor for skin cancer in Caucasians is UVR, which has increased over the past two decades due to a significant reduction in the total ozone column [19, 29–31]. Other factors that play a role in increasing the development of skin cancer with UVR include lighter skin pigmentation, decreasing latitude, and amount of sun exposure [32]. For example, Caucasians develop NMSC from long-term sun exposure on sun-exposed areas of the body, and melanomas from repetitive, intense sun exposure early in life [33, 34].

UVR also plays an important role in the development of skin cancers in Asians. Ethnic Japanese residents of Kauai, Hawaii have a BCC incidence that is twice that of Japanese residing in Japan due to the greater intensity of sun exposure and the prominence of outdoor activities in Hawaii [35]. Fairer skinned Chinese that participated in the Singapore Cancer Registry from 1968 to 1997 had a twofold higher skin cancer incidence than darker Malays or Indians in the same study [8].

With the exception of BCC, which most commonly develops on sun-exposed areas in Blacks, UVR is not clearly defined as a causative factor in the development of skin cancer among Blacks [2, 3, 36]. Blacks with a light complexion have been found to have an increased risk of developing BCC [2, 3]. Out of 23 Blacks with BCC in a study at Howard University Hospital, 60% had fair or olive skin [3]. The incidence of NMSC increased with decreasing latitude in one US study for Blacks, and a number of studies have noted a US geographical variation in the relative rates of skin cancer that approach those of Caucasians [37, 38].

Although studies in Africa demonstrate a greater incidence of BCC in albino Blacks than in normally pigmented Blacks [39–41], UVR does not appear to be an important etiologic factor in Blacks for the development of SCC and melanoma due to their tendency to occur more commonly on nonsun-exposed sites in darkly pigmented ethnic groups.

The importance of UVR as an etiologic factor for BCC and SCC in various races and ethnic groups is exemplified in how these tumors are distributed on the body. A study noted that the scalp and nose were the most common sites for NMSC on the head-and-neck region in 44% of Blacks and 76% of Caucasians [42]. BCC most commonly occurs on the head-and-neck region in Blacks, Asians, Caucasians, and Hispanics [2, 20, 43–45]. The authors found that although the ratio of BCC to SCC in both Blacks and Caucasians is 4:1 on the head and neck, the ratio on covered sites was 1:1 in Caucasians and 1:8.5 in Blacks, which further supported the notion that UVR is not an important factor in the etiology of SCC in Blacks.

A review by Hu et al. of cancer registries in 6 states consisting of New York, New Jersey, Illinois, California, Texas, and Florida noted that melanoma incidence was correlated with UV index and latitude for Blacks, Caucasians, and Hispanics, but was only statistically significant for Black men, Caucasian men, and Caucasian women [46]. This study along with another study that found similar cytotoxic damage in cultured melanocytes of Blacks and Caucasians who were
exposed to simulated sunlight [3, 47] provide support to the speculation that solar radiation has a role in the etiology of melanoma in darker-skinned ethnic groups and emphasizes the necessity for sun protection and risk education in these populations.

In contrast, investigators of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute evaluated data from 1992 to 2001 comparing the correlation of melanoma incidence with UV index and latitude with racial and ethnic groups [48] and found evidence to dispel the role of UVR in the development of melanoma. Data from the SEER-11 Program, which was an expanded SEER program of 11 cancer registries representing approximately 14% of the US population, found an association of melanoma incidence with increased UV index and lower latitude in non-Hispanic Caucasians only [48]. The data from the SEER-11 Program did not find supportive evidence for the association of UV exposure and melanoma incidence in Asians, Blacks, and Hispanics [48].

It has been shown that albinos in Africa compared to African Blacks of normal pigmentation do not have the same increase in incidence of melanoma as seen with actinic keratoses (AKs), BCC, and SCC, leading others to challenge the notion that skin pigmentation protects Blacks from melanoma [49].

11.6.2 Squamous Cell Carcinoma

Thiry percent of skin cancers among Blacks and 65% of skin cancers among Asian Indians are SCC in whom it is the most common cutaneous neoplasm [2–5, 7, 13, 50]. However, only 15–25% of skin cancers are SCC in Caucasians for whom it is the second most common cutaneous tumor [2–5, 7].

Data compiled at Charity Hospital in Louisiana (176 SCCs in Black patients) also showed SCC to be the most common cutaneous neoplasm in Blacks with BCC occurring 20% less commonly vs. SCC [4].

SCC incidence rates among Caucasians are dependent upon the amount of UVR intensity in their region of residency. Documented SCC incidence rates for Caucasian residents in Kauai, Hawaii are 118 per 100,000; Caucasian women (17–150 per 100,000); Caucasian men (30–360 per 100,000); Japanese residents of Kauai, Hawaii (23 per 100,000); New Mexican Hispanics (21 per 100,000); Hispanic residents of southeastern Arizona (13.8–32.9 per 100,000); and Blacks (3 per 100,000) [20, 32, 35, 51, 52].

SCC accounts for 30% of all skin cancers in Japan and is the second most common skin cancer among Japanese and Chinese Asians [8, 53]. The incidence rate of SCC among Chinese (2.6–2.9 per 100,000) has been on the decrease from 1968 to 1997 by 0.9% annually [8]. It is theorized by some authors that seborrheic keratoses are a potential risk factor for AKs among Japanese [54] and this precancerous form of SCC is more common among Japanese men than Japanese women because men have a greater tendency to engage in outdoor activities [55]. The incidence of AKs is approximately 414 per 100,000 in Japan and the amount of AKs has increased significantly between 1987 and 1996 [19, 53, 54].

UVR has been discredited as an important etiologic factor in SCC development among Blacks in whom it develops most commonly on nonsun-exposed sites, whereas among Caucasians SCC develops most commonly on sun-exposed sites such as the head and neck [2–5, 32, 42, 51, 56–58]. SCC was the most common skin cancer in a review of skin cancer in Black patients at Howard University Hospital from 1947 to 1985, which found that 65% of the SCC cases were on non-sun-exposed sites that included the legs and 23% of the SCCs in Black women that occurred on the anus [2]. Fifty-four percent of the 524 SCC cases involved the lower limb, making it the most common location, in a Nigerian review of SCC in Black Africans with the head and neck being the second most common location in this review [59]. Fleming et al. had similar findings in their report on 58 cases of skin cancer in Blacks, of which 66% were SCCs and 61% of them involved nonsun-exposed areas [5]. The Tanzanian Cancer Registry in Africa also found SCC to be the most common skin cancer in its registry with the lower limb being the most common location followed by the head and neck and its peak in 40–49 year old age group [50]. Mora’s review of 163 Black patients with SCC at Charity Hospital between 1948 and 1979 in New Orleans also found that the nonsun-exposed areas of the body were most commonly affected in Blacks, which included the lower extremity and the hair-covered scalp [4]. Skin cancers that develop on sun-exposed areas in Blacks most commonly occur on the nose, forehead, and lower lip.

Researchers at Grady Hospital in Atlanta, Georgia reviewing cases of SCC from 1996 to 2001 in Blacks
found a total of 35 SCCs, with 24 out of 35 (69%) developing on fairly sun-protected areas of the body such as the anogenital area, the legs, and the feet [57]. Sixty-three percent of these patients were elderly women with 46% of them having involvement of the lower extremities [57]. The SCCs in this study were pigmented and only occurred on the legs of the female patients with three of them having positive history of leg warming and skin changes consistent with erythema ab igne and dyspigmentation of the perilesional skin. The authors determined that the combination of hyperkeratotic neoplasms and mottled pigmentation of the legs of Black individuals should alert the physician to the possibility of SCC.

The anogenital area is affected in 10–23% of SCC cases in Blacks [4, 57, 60]. This finding is supported by the Howard University study where 23% of SCCs affected the anus in women [2] and the Tanzania Cancer Registry in Africa where the penis and vulva were the third most affected areas [50]. Penile SCC prevalence is roughly equal for Whites and Blacks; however, Blacks present with a higher stage of disease at a younger age and have a statistically significant shorter survival period [60].

In Blacks, SCC in situ, also known as Bowen disease, is uncommon and usually presents as a nonspecific scaly, hyperkeratotic, sharply demarcated plaque that often pigmented and may be velvety, flat, or verrucous [2, 3, 61–63]. Bowen disease affects older people after the sixth decade in most series and is slightly more common in Black men than in Black women [2, 63, 64]; however, one study showed females to be affected twice as often as males [58]. Similar to SCC in Blacks, Bowen Disease tends to develop more often on nonsun-exposed skin, particularly the lower extremities [2, 3, 58]. In dark-skinned patients, pigmented Bowen disease may mimic melanoma [2, 3] and it also has been reported in the anogenital region of Black patients [62]. Arsenic has been hypothesized to be a predisposing factor in the development of Bowen disease in Blacks, since 3 of 7 patients had histories of arsenic exposure [64]. In Blacks, internal malignancy in association with Bowen disease has been reported [58], but no such association was noted in other series [2, 61, 64]. Invasive lesions, which are capable of metastasis, may develop in some patients [58].

Chronic scarring processes and areas of chronic inflammation are the most important risk factors for the development of SCC in Blacks (Fig. 11.20) [3, 4, 50] and have been documented in 20–40% of the SCC cases in Blacks [2, 4, 5]. In Blacks, SCC has developed in burn scars [2, 3, 65], areas of past physical or thermal trauma [3, 57, 66, 67], prior sites of radiation therapy [2, 3, 65], and areas of chronic inflammation such as ulcers [2, 3, 57, 65], discoid lupus [2, 65, 68], lupos vulgaris [4], granuloma annulare [4], leprosy [69], lymhphogranuloma venereum [4], osteomyelitis [3, 67], and hidradenitis suppuritiva [3, 4]. In Nigerian Blacks, chronic leg ulcers were the most common predisposing factor in a review of 524 cases of SCC, with most tumors arising from postburn scars [35]. A review of the Tanzania Cancer Registry in Africa revealed that chronic traumatic injuries and chronic ulcers were the main predisposing factors for SCC on the lower limb and scalp, whereas the major risk factor for head and neck lesions was UVR [50]. Other risk factors for SCC not associated with scarring or inflammation include a history of albinism [2, 57], human papillomavirus [2, 67], epidermodysplasia verruciformis [3], immunosuppression [3], and chemical carcinogens such as arsenic and tar [64, 67]. Because of the previously mentioned predisposing factors for the development of SCC in Blacks, nonhealing ulcers or nodules in close proximity to an area of chronic scarring or inflammation should be subjected to biopsy to exclude malignancy. Despite reports of SCC in Blacks associated with non-UV-light risk factors (e.g., immunosuppression) and comorbidity with other diseases (e.g., discoid lupus erythematosus), it is difficult to make resolute conclusions about these risk factors because of the isolated number of reported cases and the lack of large series in the literature.

SCCs developing within a chronic scarring process, the most common scenario in Blacks, tend to be more
aggressive and are associated with a 20–40% risk of metastasis, compared with the 1–4% metastatic rate of sun-induced SCCs in Whites [4, 70]. Also, SCC that occurs on nonsun-exposed sites may have greater probability for metastasis [2, 3]. The disparity in metastatic rates of SCC between Blacks and Whites may reflect the tendency for Blacks to present with more progressive disease, presumably as a result of delays in diagnosis, or it may be related to the presence of inherently more aggressive tumors [2, 3]. Mora reported that mortality was greater among patients with SCC that arose in a chronic scarring process and was highest among those with perianal tumors [71]. SCC in Blacks is associated with mortality that ranges from 17 to 30% in most series [2, 4, 5, 71]. Therefore, compared with sun-induced SCC in Caucasians, SCC in Blacks is associated with increased morbidity and mortality, which gives emphasis to the vital need for earlier diagnosis and treatment.

11.6.3 Basal Cell Carcinoma

BCC is the most common cutaneous malignancy in Caucasians, Hispanics, Chinese Asians, and the Japanese [3, 8, 45]. However, BCC is the second most common cutaneous malignancy in Blacks and Asian Indians [3, 13]. A low percentage of BCCs, approximately 1.8%, occur in Blacks and BCCs are approximately 19 times more common in Whites [72, 73]. Based on data from 6 large medical centers, the prevalence of BCC in North American Blacks averages 1–2% per year [2, 5, 74]. In one study, which was a survey of 101 institutions from 1987 to 1996, BCC was the most common skin tumor in Japan, accounting for 47% of all cutaneous malignancies [53]. BCC is rare in dark skin due to the inherent photoprotection of melanin and melanosomal dispersion [7, 72].

The incidences of BCC per 100,000 population have been reported in different races as follows: Black men (1), Black women (2), Kenyan Africans (0.065), Chinese men (6.4), Chinese women (5.8), Japanese (15 to 16.5), Japanese residents of Kauai, Hawaii (29.7), Japanese residents of Okinawa (26.1), New Mexican Hispanic women (113), New Mexican Hispanic men (171), southeastern Arizona Hispanic females (50), southeastern Arizona Hispanic males (91), Caucasian men (250), Caucasian women (212), and Caucasians in Kauai, Hawaii (185–340) [3, 8, 18, 20, 35, 52, 75, 76]. The highest reported incidence of BCC for Caucasians in the United States is in Kauai, Hawaii [35].

The ratio of BCC to SCC in Japan in the 1960s was 1–1.4:1 [77], whereas in the 1990s the ratio increased to 4.5:1 [55], indicating an increasing trend of BCC in Japan. Among Asian residents of Singapore, the incidence of BCC increased at a rate of 2–8% annually from 1968 to 1997 [8].

In southeastern Arizona, BCC among Hispanics was 14 times less in incidence than that among non-Hispanic Whites [20]. Some of the highest skin cancer rates in the world were reported in a 1969 survey of southeastern Arizona dermatology practices [78]. Therefore, the high incidences of BCC among New Mexican and Arizona Hispanics probably reflect high rates of UVR exposure among those who live in that region of the United States. Interestingly, there were no changes in the incidence of BCC among southeastern Arizona Hispanics between 1985 and 1996 [20]. Some studies report a higher incidence of BCC among Black females than among Black males [43, 72]; however, other studies have shown a near equal incidence between the two sexes [3, 73]. In Asians, the male-to-female ratio of BCC in two large series ranged from 0.94 to 0.97 [45, 79]. In Hispanics and Whites, BCC tends to be more common among males, with an even higher male-to-female ratio in studies of White and Hispanic populations in tropical areas [20, 52, 76, 80].

BCC represents 65–75% of skin cancers in Caucasians [81], 20–30% of skin cancers in Asian Indians [13], 12–35% of skin cancers in American Blacks [2, 5, 7, 74, 82, 83], and 2–8% of skin cancers in African Blacks [39, 40, 84]. Data from 1968 to 1997 in the Singapore Cancer Registry showed that fairer-skinned Chinese had a two-fold increased incidence of BCC compared with darker-skinned Malays and Indians [8]. At Howard University from 1960 to 1986, the majority of BCCs occurred in light-complexioned, as opposed to darker, Blacks [2]. Hence, the incidence of BCC appears to be directly correlated with the degree of pigmentation in the skin, being most common in fair Caucasians and least common in African Blacks.

BCC is primarily related to prolonged, intensive UV light exposure in Caucasians, Blacks, Hispanics, Chinese Asians, Japanese, and Asian Indians [2–5, 7, 8, 13, 45, 79]. Thus, BCC occurs most often in people after the fifth decade on sun-exposed areas of the head and neck, regardless of the degree of pigmentation of
the skin [2, 43, 45, 79]. Similar to Caucasians, 70–90% of BCCs occur on sun-exposed skin in Blacks, Japanese, and Asian Indians (Fig. 11.21) [2, 3, 13, 40, 43, 45, 74, 84, 85]. Hence, the emphasis on sun protection should not be disregarded by darkly pigmented people.

BCC may occasionally occur on nonsun-exposed sites in all races [13, 44]. Sites, such as the nipple, penis, anus, groin, popliteal space, ankle, and hairy scalp, are rarely affected [5, 7, 13, 43, 44, 74, 93]. Some series indicate that the incidence of BCC on covered sites is the same for Caucasians and for Blacks [2, 74], although others have shown a higher percentage of BCCs on nonsun-exposed regions in Blacks than on similar areas in Whites [43, 44, 86]. Ten to fifteen percent of BCCs arise on the trunk in Caucasians [7, 88]. A similar percentage of BCCs develop on the trunk of Blacks [5, 7] and a slightly lower percentage of Asian Indians [13]. In all ethnic groups, it is interesting that BCCs are rare on heavily sun-exposed areas of the hands and the dorsal portions of forearms [89].

As stated previously, the most common etiologic factor for BCC is UVR exposure in Caucasians, Blacks, Chinese Asians, Asian Indians, Japanese, and Hispanics [2–5, 7, 8, 13, 45, 79]. A past medical history of radiation therapy may also increase the risk of BCC in Black patients [90, 91]. However, the risk of developing BCC is much higher in previously irradiated Caucasian patients [90, 91], which underlines the importance of UVR as a cofactor in the development of BCC, since the pigmentation of black skin provides some protection from UVR.

Other possible risk factors for BCC in Blacks include albinism [7, 39, 41, 43, 92], scars [2, 43, 74, 93], ulcers [43, 74, 93, 94], chronic infections [74, 93], sebaceous nevus [44], arsenic ingestion [95], immunosuppression [95], previous radiation treatment [90], xeroderma pigmentosum [96], and trauma (physical and thermal) [2, 13, 73, 97–99]. In Asian Indians, one study showed physical and thermal trauma to be particularly important risk factors for BCC [13]. BCC that arises in scars typically develops in sun-exposed areas on older patients [13, 98]. This finding implies a synergistic role between trauma and UVR [13].

Blacks, Asians, and Caucasians have similar clinical presentations and histologic features for BCC [44, 45, 73, 99, 100]. However, in a study by Kidd et al., Blacks compared to Caucasians had a higher percentage of BCCs that stain for the carcinoembryonic antigen, which suggests a greater tendency of differentiation toward follicular, eccrine, or sebaceous structures [101]. The elderly are most commonly affected in ethnic populations and usually present with asymptomatic, translucent, solitary nodules with central ulceration [2, 43], although the telangiectasias and a pearly, rolled border in pigmented BCCs or in dark skin may sometimes be difficult to distinguish. A characteristic clinical feature of BCC in Asian races is the so-called “black pearly” appearance, which has been reported clinically to appear brown to glossy black [45, 79]. Lesions can occur as papules, nodules, plaques, ulcers, or undulated or pedunculated masses [44]. BCC, unlike SCC, is not associated with increased morbidity in Blacks in comparison with Caucasians [2, 3].

Reports of multiple tumors, metastases, and coexisting malignancies have been documented in Blacks [43]. Basal cell nevus syndrome, an autosomal dominantly inherited genodermatosis, is due to a mutation in the patched (PTCH) gene linked to chromosome 9q22.3-q31, which functions in human beings as both
a developmental gene and a tumor suppressor gene [102, 103]. Although basal cell nevus syndrome has been reported in Blacks [104], the expression of BCC is diminished compared to that in Caucasians owing to the photoprotection in darker-skinned people [2, 3]. Features of basal cell nevus syndrome include the presence of multiple BCCs, hypertelorism, a short fourth metacarpal, a broad nasal root, frontal bossing, palmar or plantar pits, medulloblastomas, ectopic calcification of the falx cerebri, bifid ribs, odontogenic keratocysts, and a variety of internal neoplasms [105]. Basal cell nevus syndrome should be in the differential diagnosis for any Black patient who presents with a BCC, especially multiple BCCs.

Metastatic BCC is rare in all races and only a few cases have been reported in North American Blacks [43, 94, 97, 106–108], but 3 of the 4 documented cases had preexisting conditions. Two of the metastatic BCCs developed from long-standing venous stasis ulcers [43, 94] and the third one from a gunshot wound scar on the shoulder [97]. The incidence of metastatic BCC is approximately 0.0028% in general dermatology patients and 0.1% in surgical centers [101].

Epidemiologic evidence indicates that people with BCC or SCC of the skin are at elevated risk for the development of other malignancies [109, 110]. Women with a history of NMSC (n = 7,559) were 2.3 times more likely to report a history of coexistent cancer; breast cancer was the most common type, from a cross-sectional assessment of the association of NMSC with another malignancy in the Women’s Health Initiative Observational Study composed of 93,676 women between the ages of 50–79 years old [111]. A subgroup analysis in this study also found that Black women with NMSC compared to Black women without NMSC were 7.46 times more likely to report a second malignancy [111]. The age-adjusted odds ratio for other ethnic groups was 3.67 (Hispanic), 4.51 (American Indian), and 5.64 (Asian, Pacific Islander). The authors proposed multiple mechanisms that may account for the association of NMSC with a second malignancy, such as UVR-induced depression of cell-mediated immunity, UVR-induced p53 suppressor gene mutations, and a predisposition of certain people to p53 mutation or abnormal DNA repair capacity. Possible underlying ethnic immunologic differences could imply that Black women with a history of NMSC may be at even greater relative risk for another cancer than are White women with NMSC.

Transurocanic acid, a photoreceptor in the skin that may initiate photoimmune suppression, [112] has been found in higher concentrations in the skin of Blacks compared to Caucasians [113]. Since evidence has shown that Blacks have more total urocanic acid in the skin, it is hypothesized that Blacks would consequently have an increased susceptibility to a second tumor due to transurocanic acids ability to initiate photoimmune suppression.

Mora et al. reported that 16.5% of Black patients with a BCC had a second, noncutaneous tumor that was represented by lung cancer in 65% of the cases in their study [7]. Lung cancer in association with BCC has been documented in other cases as well [101, 114]. Burns et al. reasoned that impaired tumor immunity and altered tumor surveillance might be important etiologic factors for BCC in Blacks that could increase the risk of developing concurrent malignancies upon their discovery of depressed cellular immunity by means of T-cell assay in 17 Blacks with BCC [115].

More than 50% of BCCs have pigmentation in Blacks, Hispanics, and Japanese [2, 13, 43–45, 116, 117]. In contrast, pigmentation is present in only 6% of BCCs in Caucasians [13, 118–120]. The presence of pigmentation in some ethnic populations may make it difficult to differentiate BCC from other lesions, such as seborrheic keratoses, epidermal inclusion cysts, nevocellular nevi, blue nevi, Bowen disease, lentigines, or malignant melanoma [3, 44, 61, 72]. Nodular BCC is the most common histopathologic type of BCC in Whites, Blacks, and Asians [43, 45, 73, 79, 121]. In Blacks and Asians, there may be a comparatively higher incidence of the adenoid type [122, 123]. In Blacks, the morpheaform variety of BCC is rare and develops less frequently than in Caucasians [43, 72, 73]. The presentation of morpheaform BCC in Blacks is very similar to Caucasians, with it presenting as a porcelain-colored plaque with indistinct, smooth borders that may be indurated, flat, or depressed, smooth, shiny, or atrophic [72].

11.6.4 Melanoma

Malignant melanoma is the sixth most common cancer in the United States [124] and the incidence of malignant melanoma is increasing faster, at a rate of 6% per year, than that of any other cancer [125]. Melanoma
will be diagnosed in approximately 59,580 Americans in 2005 [125], with estimates of 1 in 50 people in the United States to be diagnosed with melanoma during their lifetime by 2010 [125]. Melanoma is the third most common cutaneous malignancy in Blacks, Asians, Hispanics, and Caucasians [2, 3, 126]. It represents 1–8% of all skin cancers in Blacks [2, 127], 10–15% of skin cancers in Asian Indians [13], and 19% of all skin cancers in Japanese [53]. The Black-to-White ratio of melanoma incidence in the United States is approximately 1:16 [128]. The age at presentation of melanoma in darker-skinned ethnic groups ranges from 50 to 70 years [53, 127, 129–135].

The range of melanoma age-adjusted incidences reported in the literature is slightly lower in Caucasian women (7.6–12.9 per 100,000) than in Caucasian men (8.4–18.9 per 100,000) [36, 126, 135–139]. The incidences of melanoma are also slightly lower in Black women (0.6–0.9 per 100,000) than in Black men (0.8–1.5 per 100,000) [36, 126, 127, 136–140]. As a result, melanoma is approximately 10 to 20 times more frequent in Caucasians than in Blacks [46, 117, 130, 137].

Melanoma incidences in Hispanics range from 1.2 to 4.0 per 100,000 males and 1.3 to 3.0 per 100,000 females [126, 132, 139, 141, 142]. Bergfelt et al. found that fairer New Mexican Hispanics had a higher melanoma incidence per 100,000 (1.5 in males, 2.9 in females) than darker Puerto Ricans (1.3 in males, 1.3 in females) [143]. Melanoma is 3–7 times more common in Caucasians than in Hispanics [46, 117, 137, 141, 143, 144] and 1–4 times more common in Hispanics than in Blacks [137]. The incidence of melanoma among Hispanics is intermediate between that among Whites and that among Blacks, a finding that parallels their intermediate skin pigmentation [137].

Incidence trends of melanoma vary among different ethnic groups. The literature suggests that the incidence of melanoma is increasing at a rate of 3–7% per year in Caucasian populations, and there are strong signs from birth cohort analyses that incidences will continue to rise in the future [22, 36, 147]. Between 1973 and 1994, melanoma incidence in the United States increased 6.8 per 100,000 person years to 17.3 per 100,000 person years for males and 6.1 (1973) to 11.6 (1994) per 100,000 person years for females [17]. In Canada, from 1973 to 1987, the incidence of melanoma increased by 12.5% in males and 10.35% in females [148].

Over the past 30 years, incidences for Blacks, Asians, Chinese Asians, Asian Indians, and Hawaiians have remained relatively stable [8, 22, 36, 147, 149]. SEER population-based data from 1973 to 1987 showed a 12% decrease in the incidence of invasive melanoma in Blacks [130]. Penello et al. used the nine areas of the SEER program to tabulate data on melanoma between 1973 and 1994 and found no significant increases in incidences of melanoma in Black males and females [22, 36]. Between 1968 and 1977, the incidence of melanoma among Asian residents of Singapore remained constant at 0.5 per 100,000 [8]. Modest increases in incidence have been noted in Japanese (0.1–0.2% per year) and Hispanics of Puerto Rican and South American descent [53, 132, 147]. The incidence of melanoma in Puerto Ricans increased from 0.92 to 1.59 per 100,000 from 1977 to 1987 [132]. In contrast, Hispanics residing in New Mexico have seen a significant increase in the incidence of melanoma [147].

Melanoma mortalities increased by 34.1% from 1973 to 1992, making it the third highest increase of all cancers [134], but there are variations in mortality trends among different races. Swerdlow found that mortality from melanoma is increasing at a rate of 3%
per year in Caucasians and Japanese, but is remaining relatively stable in Blacks, Chinese, Indians, Hawaiians, and Hispanics, with the exception of Puerto Ricans, in whom there was a very slight increase [147]. Estimated percentage changes in mortality from SEER data (1973–1996) indicate a 1.0% decrease for Black males and no change for Black females [36], which may indicate an improvement in early diagnosis and treatment for Black males. The 5-year mortality in Blacks is high, although relatively stable, with a range of 37.5–85% in multiple studies [2, 5, 150, 151]. Japanese individuals had a greater mortality increase per year (3%) than incidence increase (0.1–0.2% per year) in contrast to Caucasians, whose annual incidence increase (3–6%) was greater than the increase in mortality (3% per year) [53, 147, 152].

Risk factors for melanoma vary among Caucasians and Blacks. UVR exposure, specifically intense early sunburns and blistering sunburns, is closely linked with the development of melanoma in Caucasians [46, 125, 144, 153, 154]. Other risk factors for Caucasians include atypical and multiple nevi, family or personal history of melanoma, intermittent sun exposure, and Fitzpatrick types I and II [46, 125, 144, 153–155].

In contrast, UVR does not appear to be a significant risk factor for melanoma in Blacks and other ethnic groups, who tend to develop melanoma on non-sun-exposed sites such as palmar, plantar, and mucosal surfaces [56]. Other reported risk factors for melanoma in Blacks include albinism, burn scars, radiation therapy, trauma, immunosuppression, and preexisting pigmented lesions (especially on acral and mucosal regions) [3, 78, 150]. Studies suggest that more than 90% of Blacks have at least 1 nevus [78, 156]. Melanocytic nevi in Blacks are predominantly acral, which may account for the high number of acral melanoma in Blacks [78, 156].

A family history of melanoma does not appear to be a major predisposing factor in Blacks in contrast to Caucasians [56]. Other unknown factors, such as immunologic and environmental, may possibly play a role in the development of melanoma in Blacks.

Although less significant than in Caucasians, UVR may still play a role in the development of melanoma in ethnic skin. Hu et al. analyzed six US cancer registries and found that there were higher melanoma incidences in Hispanics and Blacks of both sexes at lower latitudes of residency and with increasing UV index; however, this correlation was statistically significant only in White men, White women, and Black men [46]. Data from nine areas of the SEER program from 1973 to 1994 indicated a significant increase in age-adjusted mortality for Black males with increasing levels of surface radiation, but failed to show significantly increased incidences with increasing UVB radiation exposure in Blacks [22, 36]. No such corresponding increase in mortality was found for Black females, possibly because males spend more time outdoors. Also, several studies have shown evidence that migrant populations who move closer to the equator developed higher rates of melanoma compared with people in their country of origin [157–159]. The most important etiologic factors for melanoma in dark-skinned populations remain to be documented.

In Caucasians, more than 90% of melanomas are on sun-exposed areas of the trunk in men and on legs in women [66, 126, 160]. Melanomas in Blacks [126, 127, 129, 134, 160, 161], Asians [53, 126, 152, 162, 163], Filipinos [164, 165], Indonesians [166], and native Hawaiians [167] most often arise on non-sun-exposed skin with less pigment, particularly acral areas of the lower extremities. In non-Caucasians, mucous membranes and acral areas are the most common sites of melanoma with up to 60–75% of tumors arising on the palms, soles, mucosal locations, and subungual regions [56, 134, 137, 160–162]. Tumors usually present as dark, rapidly spreading patches. These tumors arise within prior pigmented lesions in 25–50% of cases [162]. A review of 9,000 cases of melanoma at Duke University between 1970 and 1996 revealed 93 cases of subungual melanoma. Interestingly, 12% of the cases occurred in Blacks, although they comprised less than 1% of the 9,000 cases [168]. The majority of cases presented as a pigmentation of the nail bed. Oral melanomas represent approximately 7.5% of all melanomas in Asians, and two-thirds of these tumors arise from oral melanosis [162]. At Charity Hospital from 1975 to 1997, Bellows et al. found that mucosal melanoma represented 20% of cases in 27 Blacks [134]. Melanoma occurred on the lower extremity of 9% of Whites, 20% of Hispanics, 36% of Asians, and 50% of Blacks among men in the California Cancer Registry from 1988 to 1993 [126]. The frequency of lower-extremity melanomas in races of intermediate pigmentation has a propensity to fall between that of Whites and that of Blacks [126, 162].

There are variations in the distribution of melanoma in Hispanics with some studies showing similarities to Caucasians [126], whereas other investigators have
found that the distribution more closely parallels that of darker ethnic groups [132, 137]. Data from the SEER program from 1973 to 1981 demonstrated that lighter-skinned New Mexican Hispanics tended to develop melanomas on the trunk in men and on legs in women, similar to findings for Caucasians [137]. The California Cancer Registry data from 1988 to 1993 revealed that 20% of melanomas occurred on the lower extremities in Hispanics, compared with 9% in Whites [126]. The trunk was the most common site found in both Hispanic men and women in the New Mexico Tumor Registry from 1969 to 1977 [142]. In contrast, darker Puerto Rican Hispanics developed acral tumors predominantly on the lower extremities (notably the feet), similar to Blacks and Japanese [132, 137, 169]. Hispanics in the New Mexico melanoma Registry from 1970 to 1986 developed melanomas on acral sites in 23% of cases, compared with 3% in Caucasians [141, 170]. Variations in distribution of melanomas in Hispanics are possibly due to the wide variety in the degree of pigmentation in Hispanic people.

In non-Caucasians, the plantar portion of the foot is often the most common site with involvement in 30–60% of cases [4, 53, 90, 129, 131, 132, 140, 150, 160, 162, 171–175]. In Blacks, 30–70% of melanomas arise on the sole of the foot [4, 134, 140, 160, 175]. The most common location of melanoma in Japanese is the sole of the foot, accounting for 25–35% of cases [53, 176, 177]. Other common sites reported in Japanese include subungual areas and mucosal membranes [53, 176, 177]. In a study of more than 1,000 melanoma patients in Japan between 1987 and 1996, the most common site in both males and females was the sole of the foot [53], accounting for 32% of cases [53]. Krishnamurthiy et al. reviewed cancer registry data in six different parts of India from 1964 to 1984 and found that the sole of the foot and internal mucous membranes were the major anatomic sites of involvement for melanoma [149]. Fifty-six percent of tumors arose on the foot, with 83% on the plantar surface in a study of 43 cases of melanoma in Chinese Asians at the University of Hong Kong from 1964 to 1982 [162]. Forty-seven percent of these tumors developed within a prior pigmented lesion, and 100% of subungual tumors were on the nail bed of the great toe or thumb. The authors concluded that the frequency of plantar melanoma in Chinese, like other racial groups of intermediate pigmentation, was between those of Whites and Blacks. In a study of five lower-extremity melanomas in Hispanic Puerto Ricans, the foot was the most common site, particularly minimally pigmented zones of the sole, heel, and nail bed [178]. At Howard University, Byrd et al. found that the most common location of melanomas in Black men between 1981 and 2000 was the foot (38.9%), compared with 2.4% in Whites [160]. The high incidence of involvement of the sole of the foot may indicate that trauma is a significant predisposing factor for melanoma in ethnically darker skin [3, 179]. Plantar involvement may be more common in Black men than in Black women. Of 80 Black patients with melanoma at Charity Hospital in New Orleans since 1948, only 32% of primary lesions among women were on the foot, compared with 73% in men [161]. It is interesting that Black women also had a higher rate of extracutaneous melanoma than did Black men or White men and women, a finding that had a negative impact on survival rates for Black women with melanoma. Bellows et al. also found that Black males were four times more likely than Black females to present with a cutaneous lesion [134].

The predominance of plantar melanoma in non-Caucasians may not be due to an increased incidence in comparison with that of Caucasians, but rather a decreased incidence of melanoma at other sites [179]. One study showed that Blacks and Whites in the United States have similar melanoma incidences when it comes to the sole of the foot [179].

The most common histologic subtype in Asians and Blacks is acral-lentiginous melanoma (ALM); in contrast, the most frequent subtype in Caucasians is superficial spreading melanoma (SSM) [53, 56, 126, 127, 129, 131, 133, 134, 137, 150, 161, 162, 171, 175, 180]. ALM represents 35–90% of melanomas in Blacks and Asians, but only 2–8% of melanomas in Caucasians [6, 127, 134, 150, 163]. ALM represented more than 50% of all melanomas in a study of more than 1,000 melanoma patients in Japan between 1987 and 1996 [53]. However, there was an increased incidence of SSM in Japanese in 1975–1986 to 1987–1996 from 12.3 to 17.5%, possibly reflecting recent westernization of the Japanese lifestyle (i.e., more vacations to sunny destinations, resulting in increased intermittent exposure to sunlight, which may be a major risk factor for SSM) [53, 152]. In Chinese Asians at the University of Hong Kong from 1964 to 1982, 52% of tumors were ALM and 21% were SSM [162]. ALM may arise in preexisting nevi, and this phenomenon has been documented in Asians [162, 181].
Singluff et al. reviewed 185 patients with ALM and found that 17% of them were Black [182]. In contrast, only 0.7% of 2,274 patients with nonacral tumors were Black. The authors concluded that ALM was the most common subtype in Blacks (Figs. 11.22 and 11.23), whereas lentigo maligna was the least common. In the same study, SSM was most common in Caucasians and ALM was least common. In a study of melanoma patients at Charity Hospital in New Orleans from 1975 to 1997, ALM (39% in Blacks, 2% in Whites) was most common in Blacks and SSM (18% in Whites, 4% in Blacks) was most common in Caucasians [134].

SSM is more common overall than ALM in Hispanics and members of some other ethnic groups [126, 132]. However, the incidence of ALM is greater than in Caucasians. In a study of the New Mexico Melanoma Registry from 1970 to 1986, ALM represented 2% of melanoma in Caucasians and 15% in Hispanics [141, 170]. Similar results were found in a study of Hawaiians from 1994 to 2002 by Johnson et al., with the incidence of ALM being 1% in Caucasians and 18% in non-Caucasians (Japanese, Filipinos, and native Hawaiians) [167]. In a review of the Puerto Rican Cancer Registry from 1981 to 1987, SSM was most common and ALM was second most common [132].

Blacks tend to present with more advanced, thicker tumors, and as a result, tend to have a poorer prognosis with higher mortality compared to Caucasians [4, 131, 134, 150, 160, 171, 172, 174]. Multiple studies have demonstrated that 5-year survival rates of Blacks are consistently lower than those of Caucasians. Fleming et al. reported melanoma lymph node metastases in 11 of 13 Blacks, with only 2 patients surviving [4]. In a review of melanoma at Charity Hospital in New Orleans from 1975 to 1997, Bellows et al. found that 56% of Blacks presented with ulcerated tumors and stage 3 and 4 disease, whereas Caucasians were 3.6 times likely to present without ulceration and with stage 1 or 2 disease [134]. The mean Breslow depth was 6.15 mm in a study of 45 Black patients at the University of Capetown [131]. Fifty-one percent of patients presented with stage 3 or 4 disease and none of these patients survived beyond 38 months in a study of 63 Black South Africans with melanoma from 1972 to 1985 [175]. At Howard University, Byrd et al. found that Blacks presented with in situ disease in 39.3% of cases and stage 3 or 4 disease in 32.1% of cases [160]. In contrast, 60.4% of Caucasians presented with in situ melanomas and 12.7% with stage 3 or 4 disease [160]. Hudson et al. had similar results with 50% of Blacks, 33% of mixed-raced patients, and 4% of Caucasians who presented with stage 3 or 4 tumors [172]. There was also a significant difference in the primary tumor mean Breslow depth at presentation in Blacks (7.1 mm), mixed-race (3.6), and White patients (3.3 mm) [172]. At the University of Capetown, Swan and Hudson found that Blacks of mixed ancestry presented with stage 3 or 4 disease in 35% of cases [129]. The likelihood of diagnosis after metastasis was 4% for Caucasians and 14% for Blacks in the SEER registry from 1986 to 1991 [138]. Ulceration, a known poor prognostic indicator, was found at the primary site in 41% of Blacks vs. 24% of Whites in the Duke University Melanoma Clinic Registry, which was composed of 7,500 patients with melanoma, 79 of whom were Black [6]. On a positive
note, the same Duke University Melanoma Clinic Registry found an improvement in survival in Black patients with melanoma from 35 (prior to 1980) to 49% (1989 and 1990), perhaps because of improved awareness among patients and physicians [6].

Plantar melanoma, the most common site of involvement in non-Caucasians, often has a poor prognosis. Between 1958 and 1990, researchers at Tulane University in New Orleans examined 92 ALM patients and found that all Black men had foot lesions and the poorest survival rate (13% at 10 years) [183]. Hudson et al. reviewed 85 cases of plantar melanoma from 1977 to 1991 at the University of Capetown in South Africa and found that significantly more Blacks had metastatic disease and presented with deeper tumors (7.1 vs. 3.3 mm) than did Whites [172]. The 5-year survival statistics for plantar melanoma in Hudson’s study was 60% for Whites and 26% for Blacks.

Other ethnic groups besides Blacks tend to present with more advanced tumors than Caucasians. Johnson et al. found in a study of Hawaiians from 1994 to 2002 that Caucasians presented with a mean tumor thickness of 1.62 mm, whereas non-Caucasians (Japanese, native Hawaiians, and Filipinos) presented with a mean tumor thickness of 2.59 mm [167]. In a study of 81 melanomas in New Mexican Hispanics, a large proportion of tumors arose on the palms, soles, and subungual regions and tended to be advanced in stage and to metastasize compared with those in Whites who lived in the same area [141]. In a review of data from the California Cancer Registry, Cress and Holly showed that the likelihoods of diagnosis after metastasis in various races were 6% (Caucasian men), 4% (Caucasian women), 15% (Hispanic men), 7% (Hispanic women), 13% (Asian men), 21% (Asian women), 12% (Black men), and 19% (Black women) [126]. In a study of 43 melanomas in Chinese at the University of Hong Kong (1964–1982), 82% of volar and subungual tumors presented at a thickness of more than 3 mm, and 37% were thicker than 9 mm [162]. Taiwanese Asians with melanoma were found to have a propensity toward presentation with advanced stages and poor prognoses [133]. Hispanics in the New Mexico Cancer Registry from 1970 to 1986 had a higher proportion of late-stage tumors than did Caucasians [141]. Finally, about 50% of the 1,000-plus Japanese melanoma patients analyzed by Ishihara et al. between 1987 and 1996 presented with stage 1 or 2 disease, yet the incidence of metastatic disease was around 30% [53].

Probable causes for a poorer prognosis in non-Caucasians include delays in diagnosis and management and the frequent presence of thick primary lesions and intrinsically more aggressive acral tumors, which tend to present at a more advanced stage [131, 134, 160]. Multiple investigators have found that volar and subungual sites are usually thick and deeply invasive by the time treatment is sought [162, 184, 185]. Bellows et al. found that Blacks with stage 1 and 2 melanoma had a shorter survival time than did Whites with the same stages, implying that melanoma in Blacks may indeed follow a more virulent course [134]. Probable reasons for delayed diagnosis and management are less accessibility to medical care and preventive screenings, as well as the false notion that darker races, particularly Blacks, never develop skin cancer, which leads to a low level of awareness and a lack of public and physician education directed toward non-Caucasians. Also, there is a predominance of lesions in unforeseen sites in non-Caucasians such as the palms, soles, subungual areas, mucosal regions, and lower extremities. These areas of the body are not often emphasized in skin screening programs and there may be a tendency to overlook dark lesions in dark skin. Thus, the patient and physicians do not suspect melanomas in unusual areas, which leads to a delay in diagnosis and management and subsequent decreased survival.

Finally, normal variations in Blacks, such as longitudinal melanonychia and hyperpigmented macules of the creases of the palms and soles, can make the diagnosis of melanoma difficult [171]. Hints to the diagnosis of subungual melanoma include width greater than 3 mm, variable pigment, rapid size increase of lesion, Hutchinson’s sign, and the presence of solitary lesions, especially on the thumb [171].

Improved preventive strategies will allow melanoma to be diagnosed at an earlier stage, thereby improving survival. First, physicians and patients should maintain a high index of suspicion for melanomas, regardless of patient’s race or ethnic background. Second, patients of darker-skinned ethnicities should be encouraged to perform skin examinations themselves and to seek regular full skin examinations, with careful attention paid to the palms, soles, fingers, toes, subungual areas, and mucosal surfaces. A dermatologist skilled in differentiating malignant from benign pigmented lesions should perform full skin examinations. Current public education programs for skin cancer and melanoma are directed toward Whites, particularly high-risk people.
with fair skin, blue eyes, and red or blond hair. Physician training, patient education, and public awareness campaigns should be directed to all ethnic groups.

11.6.5 Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a rare tumor of intermediate malignancy that represents less than 0.1% of all malignancies and is characterized by slow growth and a tendency to recur after local excision, yet it rarely metastasizes in spite of its locally aggressive behavior [186]. It characteristically presents on the trunk or extremity of adults between 20 and 50 years of age as a flesh-colored or hyperpigmented, indurated plaque that with time develops protuberant nodules (Fig. 11.24). In Blacks, DFSP should be considered in the differential diagnosis of atypical-appearing keloids [2, 3].

There is controversy as to whether DFSP is more common in Blacks [2]. Garg et al. concluded that it is more common in Blacks [187]. DFSP accounted for 12.1% of 132 skin cancers in a study of Black patients at Howard University from 1947 to 1986, which represented a higher frequency of skin cancer than melanoma [2]. The authors theorized that DFSP was more common in Blacks than in Caucasians, yet acknowledged that such generalizations may not be valid because of the small number of patients in their study. Although DFSP has reported in all races, it is difficult to establish racial incidences, since race is not mentioned in many of the larger series of patients in the literature [3]. Lastly, the Bednar tumor, an unusual pigmented variant of DFSP, occurs primarily in Blacks, although it represents less than 5% of cases of DFSP overall [3, 188].

11.6.6 Kaposi Sarcoma

Before 1980, Kaposi sarcoma occurred most frequently in Italian and Eastern European elderly men and was rare in the United States before the onset of the AIDS epidemic in 1981 [189, 190]. In addition, an endemic form of KS exists in equatorial Africa, where it represents 10% of all cancers [191]. The incidence of KS has increased considerably since the onset of the AIDS epidemic with the incidence and demographic patterns closely emulating trends in AIDS patients [3, 192]. Mora and Lee reported a series of 19 Blacks with KS from 1948 to 1983 [122], none of whom had AIDS. Their male-to-female ratio was equal, 75% of patients were at least in their 6th decade, and almost all patients had lower extremity involvement. The overall mortality was 21%. KS represented 3.8% of cutaneous neoplasms in Halder and Bang’s review of skin cancer cases in Blacks from 1947 to 1985 [2]. Only one of these cases occurred before 1982 and was not associated with AIDS. In recent years, KS is frequently associated with AIDS, primarily in young homosexual males [2].

There were 12,162 cases of KS between 1972 and 1998 with 88% occurring in Caucasian men [192]. Between the early 1980s and 1989, the incidences of KS in Caucasian men rose from 0.3 per 100,000 to a peak of 8.1 per 100,000, respectively [192]. Similar incidences were noted in Black men, but with a 2 year lag in comparison with Caucasian men [192]. Peak rates for Black men were 8.6 per 100,000 in 1992 and 8.0 per 100,000 in 1994 [192]. There was a precipitous fall in KS incidences between 1995 and 1998 to 0.9 per 100,000 in Caucasian men and 2.4 per 100,000 in Black men [192], apparently owing to improved treatment for AIDS patients.

Among Caucasian women, there was modest change in KS incidences from 1979 through 1998 (0.07 per 100,000 to 0.09 per 100,000) [192]. Among Black women, KS incidences increased from 0.07 per 100,000 in 1987 to a peak of 0.49 per 100,000 in 1996 [192]. Several studies found that women have a lower incidence of KS because of a lower risk of HIV.

![DFSP on torso](image-url)
infection and a lower prevalence of KS type 8 herpesvirus [123, 193, 194].

KS usually presents as painless, violaceous plaques and nodules. The violaceous hue may sometimes be difficult to detect in dark-skinned people. Increased morbidity has been documented in Blacks, who tend to have more diffuse tumors, lower cure rates, and decreased survival rates [2, 3, 122].

### 11.6.7 Cutaneous T-Cell Lymphoma

Mycosis fungoides is a chronic cutaneous T-cell lymphoma that is more common in Blacks than in Caucasians, regardless of sex and age [3, 195–197]. Blacks are considered to be affected twice as often as Whites [197]. Mycosis fungoides represented 12.1% of all cutaneous neoplasms in one series of 132 Black patients with skin cancer [2]. The basis for the racial difference in incidence is not known [197]. Mycosis fungoides represents approximately 5% of all cutaneous malignancies and is the fourth most common skin cancer among Japanese [53].

The hypopigmented variant of cutaneous T-cell lymphoma has ill-defined, often pruritic, hypopigmented macules and patches and tends to present in a younger patient population than typical forms of the disease and occurs almost solely in dark-skinned people [3, 56, 195, 198, 199]. A history of prolonged eczematous or psoriasiform dermatitis may be seen in up to 75% of patients with this variant [2]. Hypopigmented mycosis fungoides is commonly misdiagnosed because it is easily confused with other dermatoses such as vitiligo, pityriasis alba, tinea versicolor, hypopigmented sarcoïd, and postinflammatory hypopigmentation [3, 180]. Misdiagnosis often causes delays in diagnosis and treatment ranging from 7 months to 10 years from disease onset to histologic diagnosis [200]. Cutaneous T-cell lymphoma usually responds well to therapy with psoralen plus UVA light, UVB light, and topical mechlorethamine; however, recurrences are common [195]. The prognosis overall is good and analogous to that of nonhypopigmented stage 1a mycosis fungoides [195–197].

In Blacks, cutaneous T-cell lymphoma may follow a more aggressive course than in Caucasians. There was a 44% mortality among Blacks in a series of patients at Howard University [2]. Moreover, diagnosis tended to occur at a later stage in Blacks, emphasizing the necessity for earlier diagnosis, as earlier stages of cutaneous T-cell lymphoma are more easily treatable. Later forms of the disease with erythroderma and nodal involvement do not respond as well to the usual therapeutic modalities [201].

### 11.6.8 Other Tumors

Many other cutaneous neoplasms have been reported in darker skin, yet their occurrence is so rare that their exact incidence in skin of color is not known. Such rare malignancies include trichilemmal carcinoma [202, 203], Merkel cell carcinoma [135, 204, 205], and microcystic adnexal carcinoma [92, 206, 207]. The annual age-adjusted incidence from 1986 to 1994 of Merkel cell carcinoma in Blacks was 0.01 per 100,000 compared to 0.23 per 100,000 in Whites [135]. Merkel cell carcinoma in Japanese people is not as rare as in Blacks and occurs on the face in 74% of cases [135]. In contrast, Merkel cell carcinoma occurs on the face in only 36% of cases in Whites [135].

### 11.6.9 Conclusion

Although uncommon, skin cancers do occur in darker-skinned ethnic groups and pose a significant health risk because numerous studies have shown that this patient population has a higher incidence of morbidity and mortality from skin cancers than do Caucasians. Clinicians should take into account the potential for skin cancer in people of color and should initiate preventive measures such as public education in ethnic communities, regular skin examinations, and self-conducted skin examinations. Performing these steps will assist in earlier diagnosis and treatment of skin cancer, which will ultimately lead to a decline in the morbidity and mortality seen in the non-Caucasian population.

### 11.6.10 Pearls

- Although skin cancer is less common in people of color than in light-skinned Caucasians, skin cancer in people of color is often associated with a higher rate of morbidity and mortality.
• Squamous cell carcinoma is the most common skin cancer in dark-skinned ethnic groups.
• BCC is the most common skin cancer in Caucasians, Hispanics, Chinese Asians, and the Japanese.
• Races of intermediate pigmentation, such as Hispanics and Asians, share clinical and epidemiologic features of dark-skinned ethnic groups and Caucasians.
• Chronic scarring processes and areas of chronic inflammation are the most important risk factors for the development of SCC in Blacks.

References

Howles JK (1936) Cancer of the skin in the Negro race. JAMA 89:143–145


Core Messages

Primary prevention

› Skin Cancer is one of the most preventable cancers and there is strong evidence that UV radiation is the main environmental factor.
› The best interventional target for primary prevention is children.
› Adequate photoprotection may be achieved by wearing protective clothes and by using a broad-spectrum sunscreen.
› Actinic keratosis and squamous cell carcinoma have shown a direct protective effect on sunscreen use in human beings. More time will be needed to prove the efficiency of the preventive effect on melanoma and basal cell carcinoma.
› Sunbeds use is a major concern since it has been confirmed a positive association between melanoma and sunbed use.

Secondary prevention

› Skin cancers are perfect targets for secondary prevention since it is visible on the skin’s surface and can be detected at an early, curable stage.
› Early detection can be enhanced by different educational procedures.
› Early detection requires skin inspection which can be done by dermatologists, primary care physicians, nurses, patients and their family. The self skin examination’s effectiveness in reducing mortality has been demonstrated.
12.1 Introduction

Skin cancer is the most common cancer and it is also one of the most preventable. There is strong epidemiological evidence that UV radiation is the main environmental risk factor for the induction of NonMelanoma Skin Cancer (NMSC) and Melanoma. The pattern of sun exposure for different types of skin cancer differs, with cumulative sun exposure most detrimental for NMSC, particularly squamous cell carcinoma, and intermittent sun exposure more relevant for melanoma.

12.2 Sun Exposure

Sun exposure is a difficult variable to measure. One type of sun exposure is incidental sun exposure, which is acquired outdoors on sunny days for the purpose of travel and for routine activities of daily living. Another type is recreational sun exposure, which occurs when people are enjoying recreational or sports activities outdoor in the sun. The third type of sun exposure is occupational sun exposure, which occurs when working outdoor. An increasingly important type of sun exposure in Western societies is intentional sun exposure taken for the purpose of sunbathing and getting a suntan. Over the last four decades, acquiring a suntan has also become possible by the use of indoor tanning devices, which have become increasingly popular and widespread in the United States and Europe.

These different types of sun exposure differ in terms of their associations with skin cancer risk, the populations most affected, and therefore lead to different approaches for skin cancer prevention.

12.3 Skin Cancer Primary Prevention: Behaviors, Strategies

The main recommendation for the primary prevention of skin cancer is minimizing exposure to ultraviolet radiation, both natural and artificial. The targets for primary prevention are changes in behavior which will lead to a decrease in risk of developing skin cancer.

12.3.1 Primary Prevention Behaviors: Type, Evaluation

Sun protection behaviors are described in three main categories:

– Sunscreen use
– Covering up (wearing hats and protective clothing)
– Seeking shade

Successful skin cancer prevention should include strategies for changing several different behaviors in relation to sun exposure, clothing, seeking shade, and using sunscreens. Behaviors in the sun vary considerably between countries as these are affected by a number of factors, for example, latitude, climate, and geography, but also cultural and religious factors as well as skin type.

Measurement of behaviors in the sun typically involves self-report, parental report, and direct observation of the behaviors [1]. Most studies rely on self-report of habitual sun protection practice and there is no gold standard questionnaire for evaluation [2, 3], but direct observation is known to be the most effective approach to assess wearing hats, shirts, and sunglasses. The evaluation of sunscreen use is even more challenging and needs more objective methods. Monitoring sunburn prevalence with population-based surveys also allows an estimation of compliance regarding sun protection behaviors, assessment of risk of skin cancer, and evaluation of the success of prevention programs. A report on sunburn prevalence among US adults from the Behavioral Risk Factor Surveillance System Surveys failed to show a decrease in sunburn prevalence over time with 31.8% in 1999 compared to 33.7% in 2004 [4]. This shows that despite increased knowledge about the risk of skin cancers, changes in behavior in the sun are not yet occurring.
12.3.2 Primary Prevention Targets: Location, Age, Period, Environment

Different targets in different settings can be used. Targets include child care centers, primary schools, secondary schools, recreational or tourism settings, occupational settings, and health care settings. Different types of interventions have been tried with outcomes published regarding interventions to prevent skin cancer by reducing exposure to ultraviolet light. This latter task force found sufficient evidence that two sites of intervention appeared effective: primary schools and tourism sites [1, 5]. They were based on encouraging sun-protective behavior such as wearing protective clothing including long sleeves and hats. Children and young people are ideal targets for prevention, mainly because it has been estimated that 80% of a person’s lifetime exposure to UVR occurs before 21 years of age [6]. Recently, it has also been evaluated that sun protection education for young children is worthwhile from a cost benefit, cost effectiveness perspective and even a small to modest behavioral impact may result in a significant reduction in skin cancer incidence and mortality [7]. Furthermore, lifestyle habits are often established during childhood, particularly before adolescence [8]. Health habits established in childhood may be sustained through life, more so than those acquired during any other periods during the lifespan. The length of the intervention in skin cancer education is also associated with the duration of the effect.

Health intervention education is most likely to succeed if it is supported by strategies in the school environment, particularly primary schools [9, 10]. The period in which the education program is scheduled has to be adapted to latitude: if in sunny places, UV prevention has to be a permanent theme, in less exposed places the education has to be adapted to a seasonal period. A “sun-safe” study performed in a primary school where an improvement in knowledge, attitude and behavioral intentions from the participants was observed suggests that this is most usefully put into effect a week before the summer holiday [11].

The supportive environment for sun protection in school settings has to be adapted in relation to climate, geography, and UVR levels. In young children, any exposure in the sun is likely to be unintentional; thus in sunny climates, combining well-planned and designed shades with favored play areas will attract children’s playtime where the risks associated with UVR are minimized and where there will be lesser need to wear hats, clothing, and sunscreen. For older students (teenagers), the shaded area also has to be adapted to their age group by creating attractive places for them. Good physical outdoor environment at school may contribute to the development of sun protective habits during childhood which are likely to be kept in adult life. This is a challenge because this will need the early mobilization of local authorities like school leaders, city architects, and planners in charge of school playgrounds and school outdoor environments.

Special attention should be given to teenagers as their sun exposure usually becomes intentional. Most studies indicate that intentional tanning peaks are in late adolescence [12]. However, interventions performed in secondary schools and colleges did not appear to be as effective in decreasing sunburns or improving sun protective behaviors [10].

The prevalence of summer sunburns among US youths from 11 to 18 years of age [13] demonstrates that sunburn is the norm: 72% reported having at least one summer sunburn and 12% reported at least five sunburns during the summer. Wearing protective clothing, a wide-brimmed hat, or staying in the shade were infrequent behaviors. The most serious sunburn of the summer tended to occur when youths engaged in water sports. Another study showed that adolescents with a family history of skin cancer were not more likely to use sunscreens than other teenagers [6]. At that age, the attractiveness of a tan is the major motivation for frequent intentional exposure. Consequently, the educational strategies that stress cancer prevention only may be less effective than those that also stress photo-ageing [14].

A recent study performed on a young adult population to evaluate the effects of UV with photographs, photo-aging information, and use of self tanning lotion on their preventive attitude showed promises as an approach to motivate sun exposure practices in teenagers [15]. Effectively, this intervention resulted in a significantly stronger sun protection intentions and greater sun protection behaviors relative to the controls. Furthermore, the group that also used self tanning lotion tended to engage in greater sun protection behavior than the group that received the intervention alone.

Recreational and tourism settings are also ideal targets where education to promote sun protective
behaviors among adults and children with their parents can occur. These interventions include at least one of the following:

1. Providing information to children and adults (i.e., through leaflets and posters and small media education or both).
2. Activities intended to change the knowledge attitudes, beliefs, or intentions of children and adults.
3. Additional activities to influence the behavior of children and adults such as modelling, demonstration, or role-playing
4. Environmental or policy approaches including provision of sunscreen or shade or scheduling of outdoor activities to avoid hours of peak sunlight.

Evidence of interventions in recreational or tourism settings appears effective regarding the increase in adult sun-protective behaviors. However, there is insufficient evidence to prove the effectiveness of these interventions in reducing the prevalence of sunburns in adults and children because the results were inconsistent (adult sunburns) or too few in numbers (children sunburns). However, enough reports demonstrate evidence of effectiveness of the intervention based on children’s protective behaviours, including sunscreen use and sun-protective behaviours and appear to have improved following interventions [10].

Behaviors limiting or minimizing sun exposure such as avoiding exposure during UV peak hours, seeking shade, and wearing protective clothing are essential, but sun exposure is associated with “pleasure” and it is very difficult to suppress something so related to wellness and relaxation particularly for people living in northern latitudes where sunny days are rare. It is also very likely that seeking sunshine in northern latitudes occurs because of health benefits associated with this behavior such as enhancing mood and production of vitamin D. It is, therefore, clear that limiting sun exposure has to be carefully adapted and tailored to various parts of the world as one primary prevention program may not fit all may even be detrimental.

### 12.3.3 Sun Protection

Adequate protection may be achieved by wearing protective clothes and by using a broad-spectrum sunscreen.

#### 12.3.3.1 Sun Protection Clothes

The protection from clothing can be estimated with the ultraviolet protection factor (UPF), which is analogous to the ubiquitous sun protection factor (SPF) seen on sunscreens. The common method to determine the UPF of a cloth is to measure the UV intensity before and after passing through the fabric sample. The ratio is numerically equal to the UPF [16]. A fabric whose UPF is 15 really provides this level of sun protection which is not the same for sunscreens which depends on the method and frequency of application. Different laboratories in the UK and Australia have shown that almost 90% of summer clothing have an UPF above ten, and in practice, provides equivalent protection to an SPF 30 sunscreen or higher [16]. A number of factors affect the protection offered by fabrics against solar UV radiation and these include weave, color, weight, stretch, and wetness. In general, polyesters fibres are more protective than nylon or polyacrylics, bleached cotton or viscose rayon. More than 90% of summer clothing is made out of cotton. Dark colors provide better protection than light colors and a textile that is wet by perspiration or water significantly increases the UV transmission through the fabric [17–20].

Recently, products have been developed to increase UVR protection through a washing process which significantly improves the UPF value of, for example, cotton fabrics. UV absorber compounds are colorless compounds that absorb in the wavelength range of 280–400 nm and are available in selected detergents and in dedicated laundry products (Rit Sunguard®, manufactured by Phoenix Brands, Indianapolis). These compounds are composed from UV chromophore where titanium dioxide is frequently used as a blocking substance (like Tinosorb® produced by Ciba) [21].

#### 12.3.3.2 Sunscreens

Sunscreens appeared on the market in the late 1920s, originally to prevent sunburn. Sunscreens were also used during the Second World War by the US Military. The sun tanning fashion appeared among light-skinned population in the 30s ([22–24]. During the second half of the twentieth century, with the explosion of holidays in sunny resorts, sunscreens were used as a tanning aid to acquire a safe tan while avoiding sunburns. The first sunscreens used quinine in lotion, while the most
successful sunscreens of the early twentieth century contained benzyl salicylate (Ambre Solaire®) and benzylimidazole sulfonic acid (Delial®) [25]. The list of chemicals useful for sunscreen formulations is extensive and a list of approved sunscreens is regularly updated in the European Union ([26] 28 products listed), in the US by the FDA ([27] 16 products listed) and in Australia ([28] 28 products listed). The number of sunscreens approved between the three continents is regulated, but sunscreens are approved as cosmetics in Europe or Australia, while they are classified as drugs in the USA resulting in stricter regulations. Today topical sunscreens are divided into two broad categories: organic (chemical) and inorganic (physical agent). Sunscreens containing inorganic agents tend to be less acceptable cosmetically because of their opaque quality. They are generally recommended for children because of their lack of penetration in the skin and subsequent degradation, the absence of photo-related effects, and no evidence of photo-genotoxicity in vivo. Organic sunscreens, on the other hand, act by penetrating the epidermis and absorbing ultraviolet radiation. These agents are broadly divided into UVB, UVA, or broadband absorbers. Since a sunscreen should protect from the entire ultraviolet spectrum, different filters have to be combined in the same product.

In terms of efficacy, actinic keratosis and squamous cell carcinoma studies have shown a direct protective effect of sunscreen use in human beings [29].

Transplant recipients are particularly susceptible to develop cutaneous neoplasms (squamous and basal cell carcinoma) [30]. Unfortunately, in spite of this risk, transplant patient recipients are poorly compliant with the use of sunscreens and even worse in the group at higher risk of NMSC [31]. Interestingly, a recent controlled study using a highly protective liposomal sunscreen (daylong actinica®) studying the development of NMSC (AK, SCC, BCC) in the organ transplant population showed a significant decrease in the number of new AK and protection against newly developed squamous cell carcinoma after 24 months. The use of a sunscreen which acts all day probably influences positively the compliance observed in the former study [32].

A recent systematic review failed to show a beneficial effect of sunscreen in the prevention of malignant melanoma and basal cell carcinoma, and this may be due to the long latent period between exposure and onset of disease as the follow up period was very short [33]. Different factors must be taken into account to explain the actual lack of preventive effects [34].

- First the median SPF of commonly used sunscreen before the early 1990s was between 4 and 10, and these sunscreens incorporated active ultraviolet filters that were limited largely to the UVB waveband. Only by the late 1990s had median SPF risen to about 15.
- There is, however, a concern that higher protection factors induce longer sun exposure by postponing warning signs such as sunburn, or by providing a false impression of safety in the sun. In this regard, two randomized trials in students during their holidays have shown that application of a high SPF prompted them to increase duration [35, 36] of their sun exposure. However, the first observation on students was not confirmed in a randomized controlled study in a adult population on which the use of high SPF did not influence the duration of sun exposure [37].
- Third, the failure to apply sunscreens properly must be emphasized: sunscreens are frequently not applied before exposure or early enough after onset of exposure. Additionally, the SPF of a sunscreen is assessed after photo-testing in vivo at an international agreed application thickness of 2 mg/cm$^2$. Several studies have shown that consumers apply much less than this, achieving only 10–25% of the protection expected from the product label. Uniformity of sunscreen application, failure to apply to all exposed skin, resistance to water immersion, and number of applications per day are known to influence protection.

Considering these factors, Diffey [38] concluded that it is not surprising that case control studies have failed to find any association between the use of sunscreen and the risk of melanoma. Therefore, the benefit proffered by more effective broad spectrum sunscreens might not be apparent for several decades.

### 12.3.4 The Role of Tanning Beds

The indoor tanning industry began to develop in the 1960s, and created a demand and a market following promotional campaigns that were essentially based on the promises that it provided safe tanning with some
unproven promises of improvement in public health. Nowadays, millions of individuals expose themselves to artificial UVR with a clear gradient from North to South (decreasing at lower latitudes). Nearly two million Americans tan indoors each day, with the number of individual users in the United States having doubled to nearly 30 million in the past decade (international tanning association site [39]). Even now, and certainly after the impact of publications on the beneficial effect of Vitamin D, it is still encouraged to use sunbeds for improving health and not just to promote tanning [40].

A recent study involving university students shows that the indoor tanners belong to different demographic, psychosocial, and behavioral groups ([41]. The subtypes varies from event-tanners (50% of the group), spontaneous mood-tanners (6%), the mixed- and regular-tanners (30%, around 25 times a year), and finally the regular-tanners. This latest group means a 70 times-per-year habit where tanning is an integral part of their lifestyle and social group. Different intervention techniques may, therefore, be needed to be effective on their habits considering such different behaviors.

Sunbeds use is also changing since it is observed that not only teenagers [42], but also children are regularly exposed [43]. An Australian study [44] showed that even with the industrial voluntary code established since 2002 (which recommends guidelines to ensure that customers are correctly informed of the risk associated with sunbed use), informed consent is rarely obtained from solarium outlets. High-risk groups such as fair skin (phototype 1) or those less than 18 years of age should have barred or limited access. Studies have shown that 52% of solarium outlets give access to sunbeds to children without oral or written parental consent.

Since the 1980s, scientists, doctors, charities, and health authorities have attempted with little success to draw attention to the uncontrolled growth of the fashion for tanning. After the worldwide recognition of the increase in skin cancers and particularly melanoma, the World Health Organisation (WHO) launched its INTERSUN program. There was a general recommendation to reduce unnecessary UVR exposure, i.e., reduction in artificial tanning. The WHO’s latest publication on this subject “Artificial Tanning Sunbeds: Risk and Guidance” is intended for governmental health authorities to assist them in the development of public health policies in relation to sunbeds. The WHO does not recommend the use of tanning devices for tanning purposes [45–47].

Over the past 20 years, there have been several studies assessing the risk of melanoma and NMSC in relation to sunbeds exposure and the results are conflicting [48]. However, recently, two metaanalyses [49, 50] have confirmed a positive association between sunbeds use and melanoma risk. The odds ratios for melanoma were between 1.57 and 1.71. These odds ratios are much lower than those associated with an excess of naevi (Odds between 4 and 20), and furthermore, there was no dose response relationship. However, even if the odd ratios can be seen as relatively small, it is consistent in its magnitude, despite differences in measurement of exposure, methodologies, and locations [51]. Different bias can influence risk estimates of sunbeds use in relation to melanoma [52]. The time interval between the exposure and the development of melanoma is quite large and may explain underestimation ([53], but the first exposure to sunbeds before 35 years of age appears to increase the risk of melanoma (relative risk 1.75; 95% CI 1.35–2.26) [50, 54]).

Few studies have considered the association between tanning devices and basal and squamous cell carcinoma. The sex difference of sunbed practice was also used to study the incidence of new diagnosed basal and squamous carcinoma by Fauruschou et al. [55]. In this latest study, sunbed use was associated with basal carcinoma, but no sufficient data exist for SCC. In two earlier studies, the first study showed no association between NMSC and past exposure with sunbeds [56]. A study by Karagas et al. [57] found a positive association between sunbed use and both basal and squamous carcinoma with a relative risk of 2.5 (95% CI: 1.7–3.8) and 1.5 (CI: 1.1–2.1) for SCC and BCC, respectively. These findings are more in line with data showing new squamous cell carcinoma in patients affected by severe psoriasis and treated with PUVA therapy [58]. However, psoriasis patients received many courses of phototherapy often involving PUVA, which is not entirely comparable to commercially available sunbeds.

A recent analysis by Oliver et al. 2007 [59] showed that the number of sunbeds provided commercially to private use is increasing and many of the privately operated sunbeds did not attempt to impose a limit on the number of sessions. Additionally, the majority of sunbeds do not comply with the British and European standard for cosmetic tanning units by producing UVB irradiances that exceeded the limit specified in the standard.
12.4 Secondary Prevention: Who, Where, and How?

Skin cancers are amenable to secondary prevention as these tumors are usually visible on the skin surface and can be detected at an early curable stage. This is especially relevant for melanoma where early diagnosis is crucial. Secondary prevention includes all early detection programs [60].

Admittedly, there is no reliable and precise measure of the magnitude of survival benefit that can be achieved by early detection; no randomized trials have reported on its effectiveness as this would be unethical, but the potential is huge. However, a trend in improved survival in melanoma in recent decades is observed and can presumably be due in part to early detection efforts.

Early detection can be enhanced by different educational procedures issued from screening campaigns (community wide dermatology led or not) or by diffusing information via the media or healthcare workers concerning early signs. Different recognition patterns are established. Since 1985 [61], the well-known “ABCD”-parameters of Asymmetry, Border irregularity, Color variegation, and Diameter greater than 6 mm are used globally in medical education and as self-screening criteria [62]. It provides simple parameters for appraisal of pigmented lesions that may need to be further examined by a specialist. Specialist evaluation may result in a further work-up of pigmented lesions via dermoscopy, biopsy, or both [63].

These criteria (ABCD) have been criticized by different authors because they are often shared with benign lesions such as seborrheic keratoses or may be absent in lesions like nodular melanoma [64]. In patients with the Atypical Mole Syndrome (AMS), atypical lesions are often large with asymmetry so the ABCD rules are also difficult to use in these patients. Also, the D criterion regarding size needs to be revised because of a growing body of literature documenting the existence of small diameter melanoma. Finally, the history of recent evolution or “changing” in a nevus has been documented as a key to the diagnosis of melanoma, especially for small, early and in situ tumors [65–67]. In this regard the expansion of the ABCD to include “E” for “evolving” has been suggested by [68], which may improve and enhance the ability of physician and laypersons to recognize melanomas at an earlier stage [68].

Nevertheless, the ABCD criteria have been verified in studies documenting their diagnostic accuracy in clinical practice [69, 70].

Grob and Bonerandi [71] proposed another useful indicator: the sign of the “ugly duckling” nevus that does not resemble its “brother nevi” and does not show common features. In this way an ugly duckling nevus can, thus, be easily detected, even though it is not atypical according to ABCD criteria.

In order to investigate the recognition processes by dermatologists examining pigmented lesions, Gachon et al. [72] studied 135 volunteer dermatologists in their daily practices. The analysis of this study showed that the recognition separates different processes: morphologic criteria such as ABCD, assessment of overall pattern, the ugly duckling sign, and finally the knowledge of a recent change. It concludes that individuals most skilled at the clinical detection of melanoma such as dermatologists seem to unconsciously rely on cognitive (overall pattern) and comparative (ugly duckling sign) processes, rather than an algorithm of morphologic criteria using the ABCD.

Gachon et al. [72] proposed, thus, to use this method in the medical training of general practitioners as well as education of the general population, where they might be more efficient than the algorithm used in the ABCD criteria. More recently, Scope et al. [73] confirmed the ugly duckling sign as a useful parameter for the detection of melanoma in pigmented lesion clinics, but were more skeptical regarding its use for self-examination.

Early detection of melanoma requires skin inspection which can be done by dermatologists, primary care physicians, nurses and patients (self skin examination:SSE), and their families.

The effectiveness of the skin self examination (SSE) in reducing mortality from melanoma has been demonstrated by Berwick et al. [74] who showed a reduction of by 63% provided by SSE. More recently, SSE was found to be a key predictor for melanoma of <1 mm in thickness [75]. It follows that SSE should be widely taught to people at risk for melanoma.

Besides, it has been demonstrated that it is often the patient who first notices their melanomas: around 50% by patients, while clinicians found approximately 15–25% of the tumors. The remainders were divided between spouses and others [75–78]. Women are more likely to perform skin self examination, are more knowledgeable about the disease, and are more likely
to discover their own lesions as well as those of their husband ([74, 76–81]).

Even if awareness (family history of skin cancer, past physician skin examination, previous biopsy, or an abnormal mole) increases the practice of SSE [125–127], only a minority of individuals practice regular SSEs, even if they are high-risk patients [81, 82]. Despite the fact that patients are often first in the detection of their lesions, the clinicians tend to identify earlier lesions (thinner) than lesions either self-detected or spouse detected [76–78, 81]. Primary care physicians are also in a unique position to perform skin cancer screening and provide education about the early signs of skin cancer as well as giving advice about sun safe behaviors [83–85]. The help of a non-physician health care provider with expertise in skin lesion recognition (physician assistant) may improve the level of skin cancer screening performed by family physicians [86].

Dermatologists, with an appropriate training, are certainly the most skilled for providing cutaneous examinations because of the volume of lesions examined in their career and the likelihood of diagnosing many melanomas a year, which improves their diagnostic skills over time [81, 85]. Dermatologists benefit from an intense training, but also use technical help such as demoscopy and cutaneous photography [63, 87]. This latest technique, performed on high-risk patients, helps in the early detection of melanoma especially in patients with the AMS [88–91]. The sensitivity and specificity of the procedure can also be enhanced with dermoscopy [92].

12.5 Population at High-Risk

The design of efficient preventive programs for skin cancer requires the identification of high-risk groups of individuals appropriate for participation in preventive interventions.

12.5.1 Melanoma

High-risk groups for developing melanoma are middle age or older man, family members of melanoma patients, lower socioeconomic status, many moles/atypical moles, fair skin, and blue/green eyes or blond/red hair. However, the presence of many of these phenotypic risks are too common in many Caucasian populations to offer regular screening if these features are present. The presence of a family history of melanoma and multiple atypical nevi should justify long-term screening. The presence of multiple atypical nevi in the context of a strong family history of cancers (other than melanoma) may also lead to long-term screening. Men aged 50 years or older have a higher incidence and mortality for melanoma [93, 94], thus special efforts have been focused on this subgroup which can sometimes be combined with screening for other cancers [95, 96].

Fair skin type, blond/red hair, and freckling are associated with a 2–4 fold increase in the risk of melanoma [97–103]. Numerous case control studies have shown that total nevus counts are to date the most powerful and significant risk factor for melanoma. Thus, individuals with more than 50 nevi have 5–17-fold increased risk of CMM [104–106]. Dysplastic nevi (DN) or atypical nevi (AN) are melanocytic lesions which were initially described in members of families with familial melanoma, but have shown to be relatively frequent in the general population: the proportion reported varying between 1 and 18% in different populations [106–108]. The term atypical nevus (AN) is preferred to dysplastic nevus (DN) as the latter means that the lesion has been excised to confirm dysplasia, while the histological confirmation of dysplastic features in an atypical nevus is not necessary and is not recommended. Many studies confirm a significant and elevated risk of melanoma risk in individuals with AN, but estimates of relative risks vary considerably between different studies with odds ratios varying between 5 and 20 [108, 109]. AN are more likely to be a marker of an increased risk of melanoma, rather than a very unstable precursor lesion as the rate of transformation of AN is very low as these lesions are very prevalent in the general population [108–114].

However, there is no doubt that some of these lesions will proceed to melanoma as studies have shown that histologically melanomas had an underlying nevus present, and of these, 38% were histologically classified as DN [115].

It is estimated that 5–10% of all cases of CMM occur in kindred with hereditary predisposition to CMM [116]. In population-based studies, 1–13% of melanoma cases report melanoma in at least one first-degree relative [117–119]. Whereas individuals with a single first
degree relative with CMM have a 2.2-fold increase of developing the disease themselves, members of families with multiple CMM cases have a much higher risk. The number of melanomas in the family is therefore helpful to determine the risk of melanoma in any related individuals [117]. Future research is hoping to discover better genetic predictors of increased melanoma risk in the general population as using the nevus phenotype may not be selective enough to design long-term screening programs. The identification of common low penetrance genes involved in nevus formation and melanoma susceptibility via worldwide consortium such as Genomel may provide useful candidates in the future.

12.5.2 Nonmelanoma Skin Cancer

Fair skin, longstanding sun-exposure, advanced age and immunosuppression are the most important risk factors for the development of NMSC and are referred to in Chaps. 4, 5, and 9 in more details.

12.5.3 Screening

Melanoma appears to have many characteristics which make it suitable to screening as it is identifiable at early stages when treatment results in survival figures approaching 100%. The screening examination is sensitive and specific, noninvasive, inexpensive, generally acceptable, and does not pose a risk to patients.

Mass, population-wide screening programs first initiated in United States and Australia are now extended to many European countries, sometimes following an isolated initiative (Italy, Austria, etc.) or associating countries like the Euromelanoma [60].

Because of low melanoma mortality and the high costs for mounting such a study in the general population, no community-based randomized trial has provided definitive information to determine whether screening asymptomatic persons with whole body exams by physicians reduces mortality from skin cancer. The only controlled study conducted in Australia was disbanded because of the lack of government funding [119, 120]. However, recently, the first screening program showing a reduced melanoma mortality has been published. This study, not randomized or controlled, was designed to promote self-examination and targeted screening at the Lawrence Livermore National Laboratory, and shows that the increasing community awareness as associated with a progressive decreasing incidence of thicker melanoma, which reduced melanoma-related mortality to zero [121].

As the efficiency of screening is debated, it is clear that targeting high-risk population should improve the screening efficiency. High-risk population is defined by light-skinned population as those with a personal or familial history of melanoma, high number of nevi (>50) and numerous dysplastic nevi, a history of an excessive sun exposure, men older than 50, and a low socioeconomic status [122]. During the AAD screening program, the yield of melanoma (number of confirmed cases per number of screenees) was 1.5/1,000 in contrast to 2.6 among men greater or equal to 50 years. The yield was further improved for men greater or equal to 50 years who reported either a changing mole (4.6/1,000) or skin type I and II (3.8/1,000) [122].

Screening programs have been performed by dermatologists, by regular physicians, or even by nurses. The efficacy to diagnose melanoma varies greatly between professionals, and it has been clearly shown that a dermatologist skin examination has a relatively high sensitivity [123].

However, as suggested by Geller [122], it is difficult to really make a distinction between screening and education. Education is not only promoted by the contact with professionals who explain the risk of having a melanoma, but also by the material disseminated in different places (folder, posters, etc.) and by the media who support the event. Interestingly, it has been pointed out that in the strategies using the media, the association of a celebrity has a real impact on public awareness and preventive action [124].

12.6 Conclusion

The control of the rising incidence of skin cancer worldwide is still challenging. Children and young people are ideal targets for primary prevention. Different means are actually available for sun protection such as sunscreens, clothing, or change in behavior with a reduction in sun exposure. A supportive environment in schools, nurseries, and touristic settings has to be present for the primary prevention messages to be implemented. Strict
regulations concerning indoor tanning beds in relation to fair-skinned individuals and those below the age of 18 years have also to be implemented and policed.

However, primary prevention is a significant challenge as change of knowledge does not always lead to change in behavior. Secondary prevention, however, is more likely to make an impact in the shorter term.

Skin tumors are visible, and early diagnosis, especially for melanoma, will save lives. The focus should, therefore, be not only on early diagnosis of melanoma, but also on invasive NMSC and its precursors, which can be promoted by education. Education regarding the early detection can be offered to health professionals, and also the public by prompting skin self examination (SSE). Mass screening is neither feasible nor cost effective. The yield of melanoma in population screening is usually very low and so high-risk groups need to be targeted. These may include men over 50 and individuals with high number of nevi with or without family history of melanoma. It is anticipated that genetic research looking at low penetrance genes may lead to important genetic markers, which may help to target those most at risk of skin cancers. For NMSCs, representing the most frequent malignancies in mankind, primary prevention through training of adequate sun protection behavior, the widespread use of medically evaluated sunscreens, as well as early and field directed therapy of preinvasive malignancies is required. In order to ensure a diagnosis at the earliest time point possible, a basic knowledge about diagnosis of skin malignancies should be reinforced in all medical disciplines. Dermatologists as much as other health-care providers worldwide should become aware of the challenge and chances of the global skin cancer epidemic.

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