Chapter 1
Pathology of Melanoma and Skin Carcinomas

Anna Szumera-Ciećkiewicz and Daniela Massi

Melanoma

The fourth edition of the WHO Classification of Skin Tumors concerns two basic types of melanoma with a radial phase and those that develop vertically [1]. The first group includes superficial spreading melanoma (SMM) and lentigo maligna melanoma (LMM). In contrast, nodular melanoma (NM) has only a vertical growth phase, and also naevoid melanoma usually does not have a radial phase. Both types of melanoma growth differ in the clinical picture, genetic profile, and mechanism of oncogenesis, in which the most critical role is played by ultraviolet radiation, both naturally associated with sun exposure and artificial [2]. In the latest WHO classification of skin tumors, it is proposed to divide skin melanomas into the following categories: those with a high degree of solar damage resulting from high cumulative skin damage (high-CSD)/superficial spreading melanoma (SMM)—and those that develop in skin exposed to low UV exposure (low-CSD)—lentigo maligna melanoma (LMM) and desmoplastic melanoma (DM) [1, 3]. The high-CSD melanoma group outlines many point mutations, including the *NF1, NRAS, BRAF* (other than *p.V600E*), *KIT* (*MAPK* activation pathway), and *TP53* genes. In low-CSD melanomas, the dominant molecular signature is the mutation in codon 600 of the *BRAF*

A. Szumera-Ciećkiewicz (✉)
Department of Pathology and Laboratory Diagnostics, Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland

Department of Diagnostic Hematology, Institute of Hematology and Transfusion Medicine, Warsaw, Poland
e-mail: Anna.Szumera-Cieckiewicz@pib-nio.pl

D. Massi
Department of Health Sciences, Section of Pathological Anatomy, University of Florence, Florence, Italy
e-mail: daniela.massi@unifi.it

P. Rutkowski, M. Mandalà (eds.), *New Therapies in Advanced Cutaneous Malignancies*, https://doi.org/10.1007/978-3-030-64009-5_1

gene (*BRAF p.V600E*) [4–8]. A group of melanomas that are not associated with UV radiation exposure was also distinguished and included acral melanoma (AM), malignant Spitz tumor/Spitz melanoma, mucosal melanoma (genital, oral, sinonasal), and uveal melanoma. In all the above types, different genetic change profiles are detected, for example, mutations in the *HRAS* (Spitz melanoma), *KIT, NRAS, BRAF, HRAS, KRAS, ALK, NTRK3* (acral melanoma), *KIT, NRAS, KRAS* (mucosal melanoma); *GNAQ, GNA11, CYSLTR2* (uveal melanoma) [9]. The classification based on the nine molecular pathways is presented later in the chapter.

The differentiation of melanocytic lesions into benign or malignant is clear, but, still, some of them manifest uncertain malignant potential. In these cases, morphological features, immunohistochemical profile, and the status of genetic changes cannot determine the clinical prognosis. The fourth edition of the WHO classification provides definitions of terms used to describe atypical melanocytic proliferation, that is, Melanocytic Tumors of Uncertain Malignant Potential (MELTUMP) —atypical melanocytic proliferation in the dermis, which means that it has a "tumorigenic" phase in the absence of specific criteria needed to distinguish benign from a malignant lesion. Furthermore, the superficial atypical melanocytic proliferation of uncertain significance (SAMPUS) was also defined as atypical melanocytic proliferation located only in the epidermis and upper layer of the skin with insufficient features for a conclusive diagnosis, lacking the vertical growth phase but without the possibility of radial growth exclusion [1, 10–12]. Practically, the therapeutic procedure is identical and consists of widening the surgical margin (so-called scar cutting) and observing the patient. Differential diagnosis of SAMPUS is challenging and subjective, especially if the only available material is biopsy or regression is severe. The concept of "uncertain significance" in SAMPUS means the possibility of recurrence or progression, while "uncertain malignant potential" in MELTUMP strengthens the risk of malignant progression. Differential diagnosis of MELTUMP always includes melanoma, and the histopathological report must contain a detailed description and so-called "provisional" diagnosis. The pathologist should always try to determine the most precise and unambiguous result of the histopathological examination, and the borderline results should not exceed 1% of all diagnoses.

The melanocytic neoplasm of low malignant potential (provisional category) and melanocytoma were introduced to WHO classification as well. Both changes are included in the evolution pathway from benign naevus to melanoma [13–15]. Melanocytic neoplasm of low malignant potential is the proliferation that fulfills the traditional criteria of invasive melanoma. However, clinically, it is not associated with melanoma-related deaths (lesions thinner than 1 mm, without vertical growth, mitotic activity, and regression, diagnosed among patients >55 years of age). Melanocytoma was provided for tumorigenic lesions with increased cellularity and/or atypia and an increased risk of progression [1]. The above "intermediate" lesions still require further investigation and long-term clinical observation.

Pathology of Melanoma According to Molecular Pathways

Pathway I. Low-CSD Melanoma/Superficial Spreading Melanoma (SMM)

Low-CSD melanoma is characterized by the absence of marked solar elastosis and frequent *BRAF V600E* mutation (>50% of cases) [16]. According to the fourth ed. of the WHO classification, SMM is included in that category. It comprises approximately 60% of all melanoma types among people with lighter skinned people. Usually, it is found in locations with intermittent sun exposure with a predilection to legs in females and back or shoulders in males.

Macroscopically, low-CSD/SMM begins with a radial growth phase, and lesions in situ present as patches of pigmentation on the skin that progress into elevated plaques. Initially, the borders are sharply delimited and that lesions are indistinguishable from benign junctional nevi. The pigmentation is variable, from tan to black with white areas that represent regression areas. Some tumors are amelanocytic and may be misdiagnosed with keratinocytic neoplasms. The dermal invasion may present as a papule, usually without ulceration. As the lesion gradually develops, the distinctive "ABCDE" clinical characteristics are seen [17].

Microscopically, the pagetoid pattern of growth is seen in in situ lesions. The intraepidermal melanoma cells may form nests that can be prominent (buck-shot pagetoid spread). The extension along epidermal adnexes may be found. There is also a lentiginous pattern of low-CSD/SMM with the reduced pagetoid spread. The invasive usually starts with the single, scattered cells within the papillary dermis (invasive RGP) and may progress into large, expansive nests with brisk mitotic activity (VGP) (Fig. 1.1a). In the dermis, the diffuse fibroplasia and areas of regression may be found. The differentiation between low- vs. high-CSD requires evaluation of solar elastosis. The grading system includes mild (grade 1) single elastic fibers in the dermis visible at ×20 magnification; moderate (grade 2) altered fibers in bunches or fascicles; severe (grade 3) homogeneous clumps of elastotic material without that texture of individual fibrils [18]. Usually, most cases of SSM/low-CSD melanoma show some degree of mild-to-moderate solar elastosis. Melanomas on non-glabrous skin with no, mild, or moderate solar elastosis should be classified as low CSD. Lesions with histological features of SMM (pagetoid scatter, a predominance of large epithelioid melanocytes with powdery melanin pigmentation, or a contiguous melanocytic nevus as a precursor) despite severe solar elastosis should also be described as low-CSD/SSM.

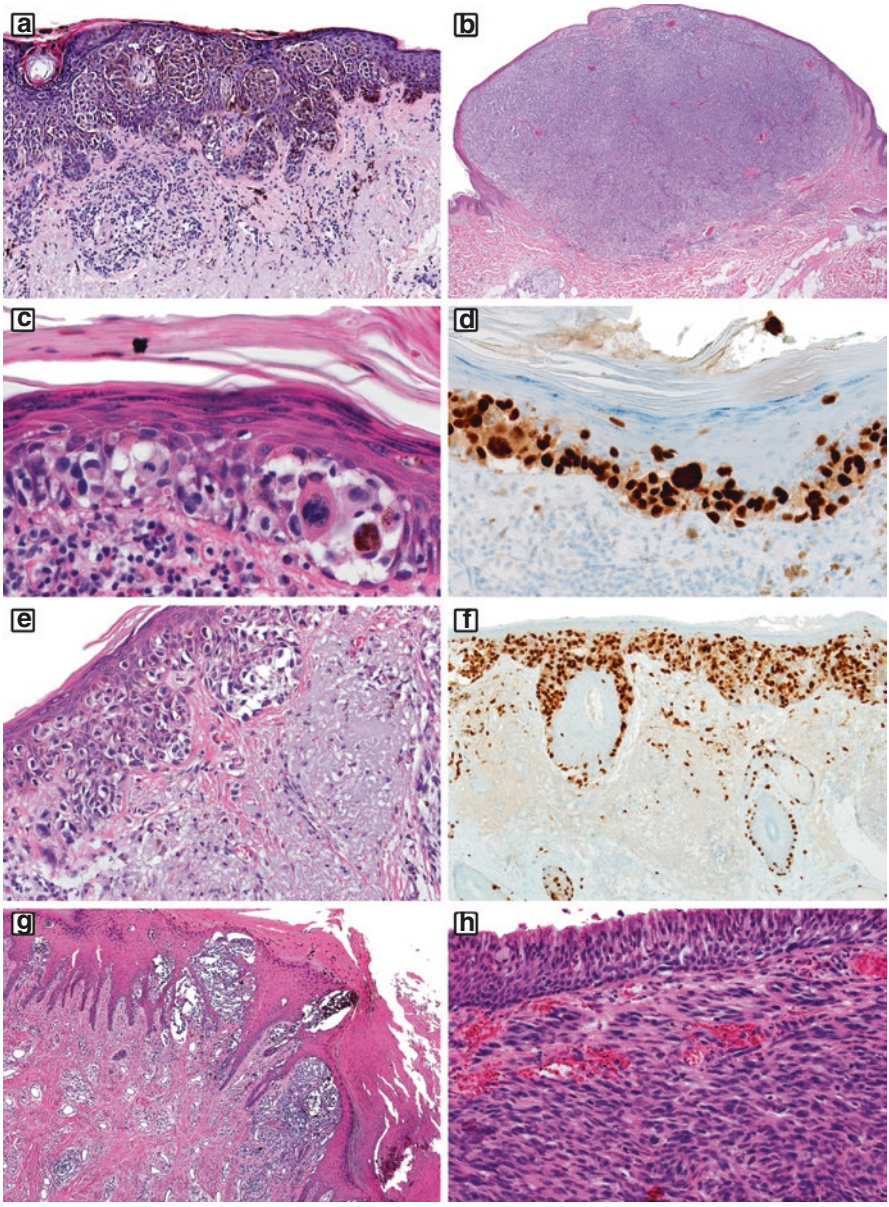

Fig. 1.1 (**a**) Low CSD/superficial spreading melanoma (200×), melanoma cells and nests present at all levels of the epidermis; (**b**) Nodular melanoma (HE, 10×), epidermis adjacent to melanoma lacks RGP component; (**c**, **d**) Lentigo maligna (HE, 600×) and in SOX10 immunostaining (400×), respectively; (**e**, **f**) Lentigo maligna melanoma (HE, 200×) and in SOX10 immunostaining (100×), respectively, severe solar elastosis is seen as an extension of melanoma along skin adnexes; (**g**) Acral melanoma (HE, 20×), atypical melanocytes present as nests and pagetoid spread; (**h**) Mucosal melanoma (HE, 200×), infiltration of the sinonasal tract

Pathway II: High-CSD Melanoma/Lentigo Maligna Melanoma (LMM)

High-CSD melanomas are less common than low-CSD/SMM and occur more frequently among older people who were chronically exposed to the sun [18]. That population includes particular outdoor professions as well as high daily exposure related to recreation.

Macroscopically, LMM presents as a patch or plaque, usually with a less circumscribed border. The lesions may extend a marked distance beyond the clinically visible border; thus, the local recurrence is found more frequently. The LMM evolve from RGP to VGP and subsequently fulfill the ABCDE criteria. The VGP progression (region of thickening, palpable or visible nodule, plaque-like area, desmoplastic) seems to be slower than in SMM [19]. Pigmentation is less expressed than in SSM; some lesions are amelanotic, and primarily may be diagnosed as an inflammatory skin disorder.

Microscopically, high-CSD melanomas/LMMs demonstrate severe (grade 3) solar elastosis. The RGP presents two types of growth: classic lentigo maligna (continuous proliferation of atypical naevoid to epithelioid melanocytes along dermoepidermal junction) and dysplastic naevus-like lentigo maligna (nest formation tendency, with bridging adjacent elongated rete ridges) (Fig. 1.1c, d). The differentiation with dysplastic naevus can be challenging; LMM shows asymmetry and continuous growth [20]. On the contrary to solar and other lentigines, in LMM the rete ridges tend to be effaced rather than elongated, the epidermis is thinned, and the proliferation is at least focally continuous rather than intermittent. The so-called "skipped" regions with evident fibroplasia are the regression evidence. High-CSD melanomas are not derived from a precursor nevus (unlike low-CSD melanomas) [21]. The VGP of LMM is constituted from small-to-moderate, atypical ovoid melanocytes, which may resemble naevoid or spindle to desmoplastic melanocytes (Fig. 1.1e, f).

Pathway III: Desmoplastic Melanoma

Desmoplastic melanoma is a variant of spindle cell melanoma, which accounts for 1–4% of all cases. There is a slight predilection to females and older patients (median age at diagnosis approximately 65 years). Desmoplastic melanoma involves severely sun-damaged skin with a high mutation load.

Macroscopically, desmoplastic melanoma usually presents as a firm, painless scar-like tumor. The lesions are commonly localized at the head and neck region (nose, lip, ears, scalp) and are amelanotic or sparsely pigmented. The clinical differential diagnosis is difficult; only a few tumors rise below a preexisting pigmented patch. The lesions are typically endophytic and rarely form a nodule [22].

Microscopically, in most cases, there is an in situ/invasive RGP component, with general characteristics of LMM. Pigmentation is usually sparse or absent. In some cases, there is an inconspicuous junctional proliferation that does not meet the melanoma in situ criteria; limited cases present no junctional component. The VGP is composed of spindle cells that resemble schwannian differentiation pattern [23]. Melanoma cells are separated by delicate collagen fibers, which are synthesized by the tumor (Fig. 1.2a, b). A distinctive feature is the presence of lymphocytes aggregated into nodular clusters. The desmoplastic component is highly infiltrative and extend into the subcutis (diffusely or in fibrous bands) and may involve fascia and interlobular septa. The cytological atypia is generally mild, but typically a few larger cells with hyperchromatic nuclei are seen [24]. In the majority of cases, desmoplastic melanoma lacks HMB-45 and Melan A immunohistochemical expression; spindle cells are usually at least focally positive for SOX10 and pS100 [25, 26]. The differential diagnosis includes not only lesions with melanocytic origin (desmoplastic naevus, desmoplastic Spitz naevus, sclerosing blue naevus) but also immature scars and other spindle cell neoplasms (dermatofibroma, atypical fibroxantoma/pleomorphic dermal sarcoma, sarcomatoid carcinoma, leiomyosarcoma).

Pathway IV: Spitz Melanoma

Malignant Spitz tumor/Spitz melanoma is a rare variant of melanoma derived from Spitz naevus. The diagnosis criteria are based on clinical features, histopathological and cytological image, immunohistochemical pattern, genetic alterations profile, and clinical evolution [27]. The spectrum from Spitz naevus to Spitz melanoma is morphologically characterized by the distinctive large spindle and/or epithelioid melanocytes and genetically by a different set of driver mutations and fusion kinases. Lesions "in-between" are categorized as atypical Spitz tumors.

Macroscopically, Spitz melanoma presents as enlarging, asymmetrical, and changing plaque or nodule, which occurs in any age but more often among patients over 40 years of age, usually located on extremities and trunk. The features suggesting melanoma include larger size (>6 mm), irregular borders, color variegation, ulceration, or bleeding [28].

Microscopically, Spitz melanoma is defined by the presence of large spindle and/or epithelioid melanocytes with high-grade cytological atypia (Fig. 1.2c, d). The features supporting histopathological diagnosis in the epidermal component are size (often >10 mm), asymmetry, poor circumscription, ulceration, irregular and confluent nesting, extensive pagetoid spread, effacement of the epidermis, lack of maturation, high mitotic index (>6 and >3 mitoses/mm^2 in the dermal component in children and adults, respectively), deep or atypical mitoses and necrosis. Immunohistochemically, Spitz melanoma shows HMB-45 and Ki-67 expression in

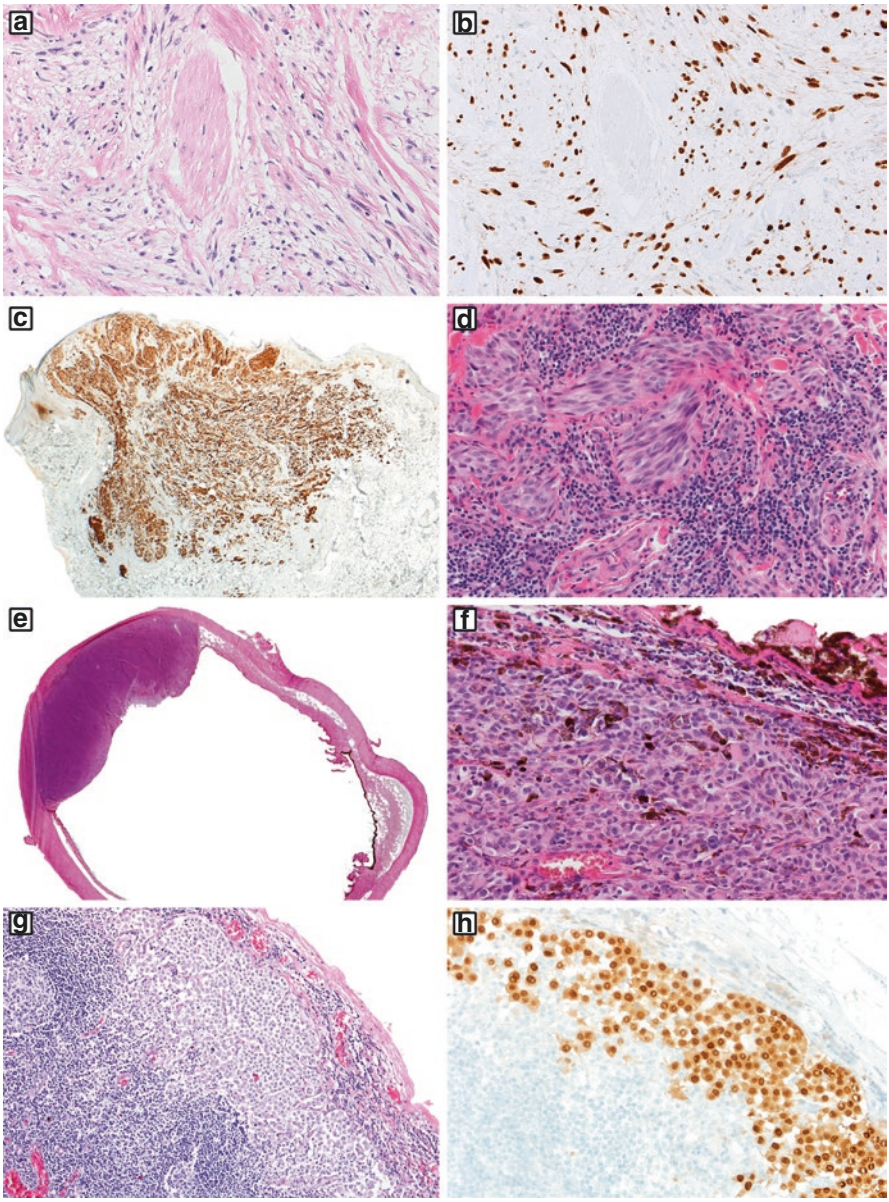

Fig. 1.2 (**a**, **b**) Desmoplastic melanoma (HE, 200×) and in SOX10 immunostaining (200×), respectively, malignant melanoma cells with elongated nuclei and cytological atypia are found within abundant collagen fibers; (**c**, **d**) Spitz melanoma in S100 immunostaining (20×) and HE (400×), respectively, asymmetrical, poorly circumscribed lesion with effacement of the epidermis and lack of maturation; (**e**, **f**) Uveal melanoma (10× and 400×); (**g**, **h**) lymph node metastasis of melanoma (HE and SOX10, 200× respectively)

more profound parts of a lesion; elevated Ki-67 (in a hot-spots >20%) and p16 staining loss are common findings [29–31]. The genomic landscape is also specific, but comprehensive molecular testing is not always accessible [32].

Pathway V: Acral Melanoma

Acral melanoma refers to melanoma occurring in the glabrous acral skin, including palms, soles, and nail beds. The non-hair-bearing volar surface of the skin has a thick stratum corneum, which is a natural barrier against UV radiation. The risk factors may be associated with mechanical or physical stress. The total incidence rate of acral melanomas is similar, but in some populations (Asian, Hispanic, African), it is the most frequent melanoma subtype [33, 34].

Macroscopically, acral melanoma begins with a patch lesion that enlarges into asymmetrical, black, pigmented irregular plaque. The RGP may be prolonged (several months to years) before progression to VGP. Advanced lesions usually become ulcerated nodules. Subungual melanoma often presents as longitudinal melanonychia, and Hutchinson's sign (pigmented patch spreads over the nail plate, beyond the proximal nail fold and hyponychium). Rare amelanocytic acral melanomas can be misdiagnosed with other, nonmalignant conditions. The dermoscopy is very supportive in making the diagnosis, while many features differentiating naevus and melanoma can be easily found [33].

Microscopically, acral melanomas most commonly present with a lentiginous pattern of proliferation (acral lentiginous melanomas). The pagetoid growth is less conventional, and both histologically and genetically resembles low-CSD/SSM (Fig. 1.1g). The VGP may be composed of spindle cells with or without a desmoplastic pattern of growth, which corresponds with increased neurotropism. The subungual melanomas show frequent bone invasion due to its superficial location. The differential diagnosis with acral naevi may be challenging also because of problems with proper biopsy of the nail [35, 36].

Pathway VI: Mucosal Melanoma

Melanoma occurring in a mucous membrane is most commonly found in genital sites, oral and nasal cavities, and conjunctiva. These lesions are not specific epidemiologically, and risk factors are largely unknown. Mucosal melanomas are not associated with UV exposure or other factors (chemical substances, viruses, or trauma) [37, 38].

Macroscopically, the pigmentation change is seen in the majority of cases. The difficulties in visualizing lesions located in nasal sinuses and visceral organs result in a bulky tumor presentation. These advanced tumors sometimes present with pain, bleeding, epistaxis, nasal stuffiness, proptosis, and diplopia [39, 40].

Microscopically, mucosal melanomas mostly show a lentiginous or nodular pattern of growth. Both epithelioid and spindle cell morphology is seen (Fig. 1.1h). The ulceration and lymphovascular invasion are typical.

Pathway VII: Melanoma Arising in a Congenital Nevus

Melanomas occur in giant congenital nevi; a lifetime incidence of melanoma is estimated at 2–5%. Most melanomas are located on the scalp or back and occur during childhood (first 5 years of life) within the epicenter of the intradermal or subcutaneous lesion [41, 42].

Macroscopically, rapidly growing nodules or plaques with ulceration are found. The differences in color and texture between melanoma and surrounding nevus are apparent. At the time of initial diagnosis, the lymph node metastatic spread is often found [43–45].

Microscopically, three main histological subtypes are epithelioid, spindled, or "small round blue" cells; rarely melanoma arising in congenital nevus may exhibit malignant schwannoma, rhabdomyosarcoma, or liposarcoma morphology. The developing melanoma may be clinically masked by the heavily pigmented nevus. Moreover, cellular and proliferative nodules in congenital nevi, which are benign lesions, need to be excluded [41, 45–47].

Pathway VIII: Melanoma Arising in Blue Nevus

That type of melanoma is rare and usually occurs on the scalp among adult individuals (usually >45 years). The risk factors remain unknown.

Macroscopically, it presents as a rapidly growing nodule; the residual cellular blue nevus may be found [48].

Microscopically, melanoma arising in a blue nevus is a tumorigenic proliferation. The diagnosis is usually late due to overlay with the presence of the precursor lesions. Ulceration may occur; however, some melanomas are deeply growing lesions, which are recognized only because of an increase in the size of the preexisting nevus. Melanoma consists of large, anaplastic cells with brisk mitotic activity. Loss of nuclear BAP1 expression favors the melanoma diagnosis as well [49, 50].

IX Uveal melanoma

Uveal melanoma is a malignant ocular melanocytic tumor that originates in the iris, ciliary body, or choroid (the most frequent localization constituting 90% of all cases). It occurs mainly within adults (median age 60 years) with an estimated incidence of 2–8 million cases per year.

Clinically, patients have visual problems. Large necrotic melanomas may manifest as painful uveitis or glaucoma.

Macroscopically, uveal melanomas grow like a dome- or mushroom-shaped tumors. The typical changes related to choroidal melanoma are retinal pigment epithelium disruption, lipofuscin accumulation, and serous retinal detachment. The invasive spread of melanoma along nerves (small nerves into orbit and optic nerve) and blood and lymphatic vessels is described [51, 52].

Microscopically, uveal melanomas may be epithelioid or spindle cells. The typical melanoma features such as mitotic figures, necrosis, lymphocytic infiltration, and melanophages are seen (Fig. 1.2e, f). In differential diagnosis, the panel of melanocytic markers should be used. Genetically, uveal melanomas show frequent loss-of-function mutations in *GNA11*, *GNAQ*, *BAP1*, *EIF11AX*, *SF3B11*, *PLCB4,* and *CYSLTR2* [46].

The conjunctival melanomas are included in ocular melanomas but genetically do not belong to the IX pathway (harbor *BRAF p.V600* mutations/low-CSD melanoma vs. *NRAS* or *KIT* mutations/high-CSD melanoma). Histologically, conjunctival melanoma is *the novo* malignancy; in the majority of cases, it can be associated with a precursor naevus or primary melanosis. The microscopical features are the same as in cutaneous melanoma, and all morphological variants can be found [53].

Nodular Melanoma

Nodular melanomas can occur in any of the pathways discussed above, and therefore the epidemiologic and genomic features are likely to be heterogeneous.

Macroscopically, nodular melanomas present as a rapidly growing papular or nodular lesion with a wide range of pigmentation. Typically, nodular melanomas are elevated above the epidermis, demonstrating the growth in an upward direction. They can be heavily melanized (dark nodules), but also amelanotic (pink papulonodular lesions) cases are seen. Nodular melanomas have a worse prognosis on average than other melanomas, but this difference diminishes in multivariable analyses [54].

Microscopically, nodular melanoma shows tumorigenic, vertical growth phase with generally high Breslow thickness. The lesions are usually ulcerated. The surrounding epidermis is normal (Fig. 1.1b). The melanoma cells are mostly epithelioid, but also spindle cell or a mixture of cells can be found (patchwork or clonal pattern). The pseudo-maturation (superficial cells are larger than cells located

deeply) may lead to misdiagnosis with nevi of naevoid melanomas. The differential diagnosis includes metastatic melanoma and a wide range of non-melanocytic tumors (i.e., carcinomas, sarcomas, and lymphomas). Nodular melanomas are typically devoid of melanin, and additional immunohistochemistry needs to support the diagnosis [54, 55].

Reporting of Melanoma

The eighth edition of the American Joint Committee on Cancer (AJCC) staging system keeps microscopic infiltration depth of melanoma and ulceration as the most important prognostic parameters [56, 57]. Currently, the mitotic activity has not been included in the stratification of pT1 and does not change influence categorization from pT1a to pT1b. However, it remains an important prognostic factor and should be a component of histopathological diagnosis. Thin melanomas are lesions with a depth of up to 0.8 mm without ulceration. Clinically, these changes are treated as locally advanced and do not require a sentinel lymph node removal procedure. However, pT1 melanomas are characterized by the variable risk of recurrence (from 1% to 12%) [58, 59]. Still, there is a strong need for the identification of additional robust prognostic factors to support decision-making processes.

Moreover, the combination of the T and N categories led to the redefinition of stage III (Fig. 1.2g, h). Long-term observation under the AJCC database proved that the 10-year survival among patients with T1, T2, T3, and T4 melanomas were 92%, 80%, 63%, and 50%, respectively [67]. The most important prognostic factors in patients with extra-regional metastases are the localization of metastases and LDH activity. Patients with central nervous system metastases have the worst prognosis in this group. The detailed definitions, according to the eighth edition of the AJCC melanoma staging, are depicted in Table 1.1 [64].

Histopathological Prognostic Markers

Breslow Thickness

Breslow thickness is the most reproducible measurement (in millimeters) of the melanoma vertical growth phase. It should be assessed from the granular layer or, in ulcerated lesions, from the bottom of ulceration, up to the deepest part of infiltration [3, 65]. Adnexal involvement by melanoma is currently considered as in situ disease [66]. However, the classification and measurement of periadnexal extension melanoma remain ambiguous. If it is the only focus of invasion, it is recommended to measure Breslow thickness from the inner layer of the outer root sheath epithelium or inner luminal surface of sweat glands, to the furthest extent of infiltration into the

Table 1.1 pTNM for melanoma, according to the eighth edition of the AJCC staging [64]

T category		
	Breslow thickness (mm)	Ulceration
TX: primary tumor thickness cannot be assessed (e.g., fragmented biopsy)		
T0: no evidence of primary tumor (e.g., unknown primary or completely regressed primary melanoma		
T is (melanoma in situ)		
T1	***≤1.0***	Unknown or unspecified
T1a	<0.8	Without
T1b	<0.8	With
	0.8–1.0	Without or With
T2	***>1.0–2.0***	Unknown or unspecified
T2a		Without
T2b		With
T3	***>2.0–4.0***	Unknown or unspecified
T3a		Without
T3b		With
T4	***>4.0***	Unknown or unspecified
T4a		Without
T4b		With
N category		
	Extent of regional lymph node and/or lymphatic metastasis	Presence of in-transit, satellite, and/or microsatellite metastases
NX: Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) Exception: pathological N category is not required for T1 melanomas, use cN, if regional lymph nodes not assessed for patient with T1 melanoma		
N0	0	No
N1	One tumor-involved node or any number of in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	Clinically occult (i.e., detected by SLN biopsy)	No
N1b	Clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Clinically occult (i.e., detected by SLN biopsy)	No
N2b	At least one clinically detected	No
N2c	One clinically occult or clinically detected	Yes

Table 1.1 (continued)

N3	Four or more tumor-involved nodes or any number of in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Clinically occult (i.e., detected by SLN biopsy)	No
N3b	At least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes
M category		
	Anatomic site	LDH level
M0 No evidence of distant metastasis Not applicable		
M1	Evidence of distant metastasis	
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

periadnexal dermis [66]. The interpretation problems of Breslow thickness include cases with a preexisting nevus, severe regression, or exophytic melanoma with verruciform architecture.

Nevertheless, Breslow's thickness is a highly reliable and accepted prognostic factor that shows an excellent correlation with mortality. The prognosis is worsening logarithmically with increasing thickness to 8 mm, then it achieves a plateau, but 100% mortality is never accomplished [56]. Long-term observation in the AJCC database proved that the 10-year survivals among patients with T1, T2, T3, and T4 melanomas were 92%, 80%,63%, and 50%, respectively [67].

Ulceration

Microscopical assessment of the presence of ulceration must be performed in each primary melanoma. The criteria of ulceration are well established and include full-thickness epidermal defect (including the absence of stratum corneum and basement membrane), evidence of reactive changes (fibrin deposition and neutrophils), thinning, effacement, or reactive hyperplasia of the surrounding epidermis in the absence of trauma or a recent surgical procedure. Recently, the extension of ulceration has shown substantial prognostic value; it may be reported as a diameter or percentage of tumor width [68]. Increasing melanoma thickness is correlated with more frequent ulceration (for thin vs. thick melanomas, ulceration is found in 6% vs. 63% of cases, respectively), but those two factors are independent prognostic factors [67]. The analysis of the eighth edition of the AJCC staging system showed that patients with ulcerated melanomas had a twofold higher estimated risk of dying due to melanoma in comparison to non-ulcerated tumors. Moreover, the presence of ulceration is reducing survival rates—these cases may be matched to the one level thicker non-ulcerated melanomas —5-year survival for T2b ulcerated vs. T3a non-ulcerated melanomas was 82% vs. 79%, T3b ulcerated vs. T4a non-ulcerated melanomas was 68% vs. 71%, respectively [56].

Mitotic Rate

In the previous AJCC staging system, the mitotic count was crucial in the pathological separation pT1a from pT1b melanoma [56]. The multivariate analysis presented the mitotic count as the strong prognostic factor, especially for thin melanomas. Currently, the number of mitoses per 1 mm^2 in the invasive dermal component, including "hot spots," should be reported [59]. Measurement of mitoses per mm^2 instead of per high-power field (HPF) is recommended because the HPF diameters vary between microscopes. Moreover, the reproducibility is high only when the scaling per 1 mm^2 and hot-spot method are used [69].

Tumor-Infiltrating Lymphocytes

The cross-talk between melanoma and microenvironment cells is still not fully understood. A significantly better prognosis among patients with a marked lymphocytic infiltrate within primary cutaneous melanoma than among those with absent TILs was found [70]. The TILs were classified according to their distribution and intensity as brisk (the lymphocytes present throughout the substance of the vertical

growth phase or present and infiltrating across the entire base of the vertical growth phase), non-brisk (the lymphocytes in one focus or more foci of the vertical growth phase, either dispersed throughout or situated focally in the periphery), and absent (no lymphocytes or if the lymphocytes present but did not infiltrate the melanoma) [71]. The conflicting results of several studies under the role of TILs as prognostic factors were presented as well as modifications of TILs classification [72–74]. Regardless, the authors of the current AJCC system support the "classical" methods of TILs evaluation [59].

Clark's Level

Clark's level is based on the histopathological evaluation of the melanoma invasion related to the anatomical level of the skin [75]. Melanoma limited to the epidermis (in situ) is described as level I and characterizes excellent prognosis with low risk of distant metastases. Level II (superficial extension to the papillary dermis), III (infiltration of the papillary dermis up to the reticular dermis), IV (invasion of the reticular dermis), and V (invasion of subcutaneous fat) should be additionally reported, but they cannot replace Breslow thickness anymore [56].

Tumor Growth Phase

The radial (the proliferation of melanocytes in the epidermis and/or in the papillary dermis, without the formation of tumor nodule) and vertical phases (presence of an expansive nodule larger than the intraepidermal aggregates and/or by the presence of mitotic figures in the invasive melanoma component) are described. The evolution from radial to vertical growth is correlated with increased metastatic potential.

Tumor Regression

Regression is defined as a replacement of the melanoma by fibrosis. The increased vascularity, presence of scattered melanophages, and lymphocytes are also seen. The residual epidermal component can be identified. Regression is classified as partial (early to the intermediate stage; <75% of the melanoma) or extensive (late-stage; ≥75% of the melanoma) [76]. In the majority of studies, regression is indicated as an inferior prognostic factor. Lack of standardized diagnostic criteria and reduced interobserver reproducibility place regression among features that are assessed electively [77].

Lymphovascular Invasion

Melanoma cells within the blood vessels or lymphatics lumina are called lymphovascular invasion. Surprisingly, it is found in less than 10% of primary cutaneous melanoma [78]. The detectability rises when the immunohistochemical staining is applied. However, in routine diagnostics, it is not recommended. The presence of lymphovascular invasion is related to a worse prognosis [79, 80].

Microsatellites

Microsatellites are described as microscopic and discontinuous cutaneous and/or subcutaneous metastases >0.05 mm in diameter found adjacent to a primary melanoma (but separated from the main invasive component by a distance of at least 0.3 mm). Microsatellites are cutaneous or subcutaneous deposits of melanoma trapped within the lymphatics between the primary tumor and the regional lymph node basin. Microsatellitosis defines a subgroup of patients with a higher risk for regional and systemic recurrence [59, 64].

Melanoma Histotype

The melanoma histotypes (according to the fourth ed. of the WHO classification) have minor independent prognostic significance [1]. The interpretation is not objective, and the interobserver variability rate is high. Currently, the correlation of melanoma histotype with molecular signatures is emphasized [24, 81, 82].

The synoptic report for primary cutaneous melanoma, including the histopathological prognostic factors, is shown in Table 1.2 [3].

Keratinocytic/Epidermal Tumors

Keratinocytic neoplasms are the most frequent cancers from all other human malignancies. The spectrum of epidermal tumors includes benign lesions (i.e., verrucae, acanthomas, and seborrhoeic keratoses), premalignant lesions (i.e., actinic, arsenical and PUVA keratoses), and malignant lesions (squamous cell carcinoma and basal cell carcinoma). Merkel cell carcinoma, which originates from neuroendocrine skin cells, is incorporated into epidermal tumors according to the fourth edition of the World Health Organization (WHO) classification. Another significant change concerns keratoacanthoma, which should now be categorized as a variant of squamous cell carcinoma. High-risk variants of basal cell carcinoma were revised, and the pathological criteria were specified [1].

Table 1.2 Histopathological synoptic report for primary cutaneous melanoma [3]

Pathologic feature	
Site/localization	Right, left/anatomic site
Diagnosis	According to fourth ed. of the WHO classification
Breslow thickness	Value in mm
Clark level	I–V
Ulceration	Present/Absent
Dermal mitotic rate	Value per mm^2
Melanoma subtype	According to 4th ed. of the WHO classification
Vascular or lymphatic invasion	Present/Absent
Neurotropism	Present/Absent
TILs	Present [brisk/non-brisk]/ Absent
Microsatellites	Present/Absent
Regression	Present/Absent
Predominant cell type	Epithelioid/
Associated nevus	Description
Solar elastosis	Present/Absent
Margins of excision for invasive and in situ components (in mm)	Description
Comments	Description

Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common skin cancer, accounting for about 75% of all skin cancers. It is characterized by slow growth and local malignancy, and distant metastases are extremely rare. BCC occurs in sun-exposed skin, primarily in the face (skin above the line connecting the corners of the mouth with external auditory ducts), especially nose, forehead, cheeks, eyelids, corner of the eye, and auricle. The superficial variant of BCC is located more frequently on the trunk [83–86]. The risk factors of BCC are similar to those of the squamous cell carcinoma. Gorlin syndrome or nevoid basal cell carcinoma syndrome is defined by numerous basal cell carcinomas occurring in young adults (below 30 years old), cysts within the jaw, and skeletal abnormalities. The disease is inherited autosomally dominant and is characterized by the loss of function PTCH1 suppressor gene mutation (9q22.1-q31) [87–89].

Macroscopically, basal cell carcinoma presents with one of the three most common appearances: nodular, ulcerative, or superficial.

The most common histological types of basal cell carcinoma, along with their characteristics, are presented in Table 1.3.

Microscopically, cell aggregates are derived from the basal layer of the epidermis. Cancer cells have scant cytoplasm and hyperchromatic nuclei. Fibromyxoid

Table 1.3 Morphological variants of basal cell carcinoma, including recurrence risk stratification grouping [1, 90]

BCC variant	Macroscopic presentation and the most important characteristics
Nodular	The most common variant (45–60%) Usually located on head and neck A slowly growing pearly flesh-colored flesh Well demarcated from the skin With numerous telangiectasias In the late phase, ulcers often have well-delimited, cylindrical margins ("nonhealing ulcer") It can grow as a primary ulcerative (previously called "rodent ulcer"): particularly dangerous in the medial corner of the eye, characterized by significant tissue destruction and high bone infiltration potential
Superficial	10–30% of all BCC The least aggressive, often numerous It is more common on the trunk and arms Slow course for months or years Flatly elevated lesions surrounded by an embankment, well-demarcated, pink to erythematous and scaly patches, non-ulcerative
Micronodular	The flat or slightly elevated lesion, not clearly defined Cancer cells appear as small, discrete nests or cysts that can deeply infiltrate and exhibit neuroinvasive features More aggressive course
Infiltrating	It resembles a scar Frequent recurrences after surgical treatment Usually infiltrates perineural spaces In later stages, stromal fibrosis occurs, and the image may overlap with the sclerosing/morpheic variant
Sclerosing/ morpheic	A flat, not clearly defined change resembles a scar Stroma highly collagenized Often, nerve invasion Frequent recurrences after surgical treatment
Pigmented	Contains melanin deposits Dermoscopic specific features: large blue-gray ovoid nests, blue-gray globules, leaf-like areas Nodular or superficial morphological variant It may resemble melanoma
Other morphological variants	
Basosquamous carcinoma Basal cell carcinoma with sarcomatoid differentiation Basal cell carcinoma with adnexal differentiation Fibroepithelial BCC (Pinkus tumor)	
BCC grouping according to recurrence risk stratification	
Higher risk	Location: nose, nasolabial fold, inner corner of the eye, lip, ear ≥20 mm Variants: Basosquamous carcinoma, Sclerosing/morpheic BCC, Infiltrating BCC, BCC with sarcomatoid differentiation, Micronodular BCC
Lower risk	Location: other than those listed for the higher risk type <20 mm Variants: Nodular BCC, Superficial BCC, Pigmented BCC, Infundibulocystic BCC, Fibroepithelial BCC

stromal change impacts on tumor retraction from the stroma. The different patterns, including solid, trabecular, cystic, adenoid, cribriform, are described. Additionally, within the BCC infiltrate, focal keratinization, desmoplasia, and scarring may be seen (Fig. 1.3b–d). A common feature is the peripheral palisading of neoplastic cells arranged as nests. On the contrary to squamous cell carcinoma, no intercellular bridges are visible; however, high mitotic activity and apoptosis can be found. BCC containing large amounts of melanin must be differentiated with melanoma. In the differential diagnosis, immunohistochemistry is used rarely. Combination of

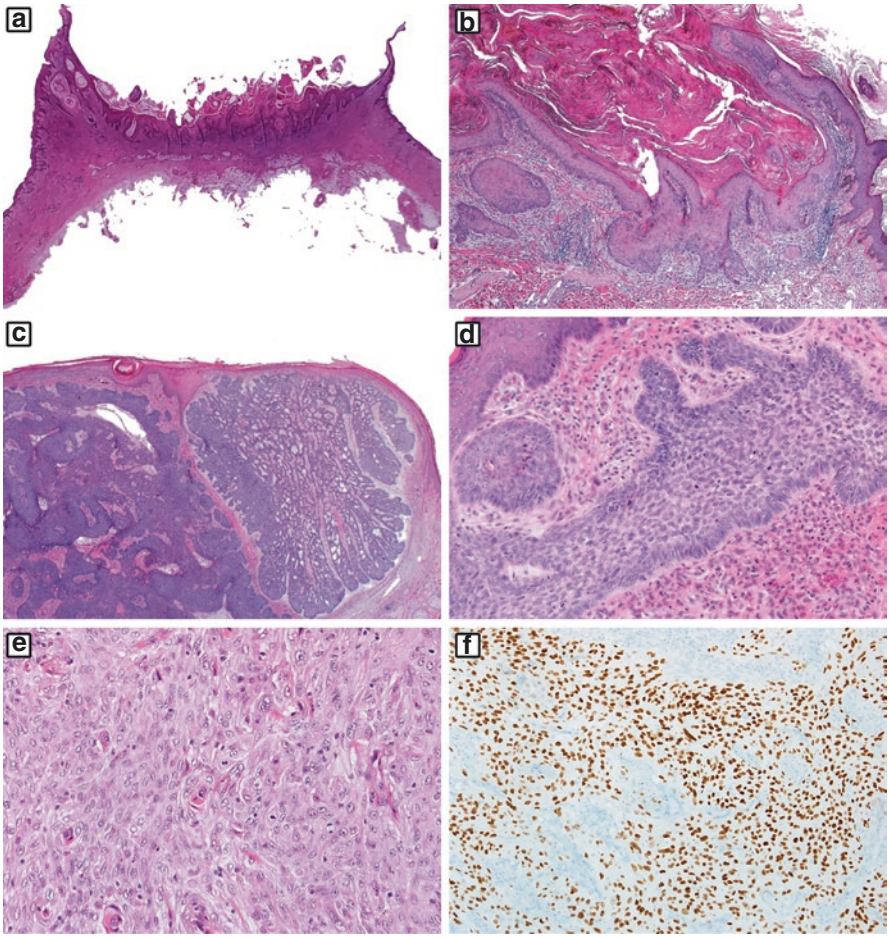

Fig. 1.3 Keratoacanthoma. (**a**) Mature stage of keratoacanthoma, characteristic crateriform architecture with central keratin masses (HE, 10×), peripheral epidermal lipping is seen; (**b**) keratin debris and proliferative squamous cells (HE, 40×). Basal cell carcinoma. (**c**) The nodular type of basal cell carcinoma (HE, 20×); (**d**) Characteristic peripheral palisading (HE, 200×); Squamous cell carcinoma. (**e**) Moderately differentiated squamous cell carcinoma with prominent cytological atypia, mitotic figures, and intercellular bridges (HE, 200×); (**f**) Squamous cell carcinoma is typically positive for p40 (200×)

BerEP4 and EMA is useful in distinguishing BCC from squamous cell carcinoma [BCC: BerEP4(+)/EMA(−); SCC: BerEP4(−)/EMA(+)] [1].

The TNM classification is not routinely used to determine the prognosis of BCC. The histopathological variant and the largest dimension of cancer infiltration, together with the depth of infiltration, and location are of significant importance for patient follow-up and risk stratification of local recurrence (see Table 1.3) [90]. The histopathological report requires the status of surgical margins [91].

Squamous Cell Carcinoma

Squamous cell carcinoma (SCC) is the second most common type of skin cancer. It usually occurs in elderly individuals on the skin exposed to sunlight (head and neck, auricles, dorsal parts of hands). Risk factors that are associated with SCC also include immunosuppressive treatment, human papillomavirus infection, burn scars, chronic inflammation, arsenic, and coal tar [92–95].

Macroscopically, SCC in situ may present as roughened hyperkeratotic lesions similar to benign keratoses, dermatoses, or lichen simplex chronicus. An invasive SCC can be described as exo- or endophytic lesion. The first occurs mainly on the face, auricles, and lips, and the second one develops on both sun-exposed skin and skin covered from UV radiation. The keratoacanthoma, which is a well-differentiated variant of SCC, shows a crateriform lesion with central keratin plugs (see also below).

Microscopically, the following variants of SCC are distinguished: acantholytic, spindle cell, verrucous, adenosquamous carcinoma, clear cell, and other (uncommon) rare variants, that is, SCS with sarcomatoid differentiation, lymphoepithelioma-like carcinoma, pseudovascular SCC, SCC with osteoclast-like giant cells. Regardless of the histological variant, the assessment of the histological grade is based on the establishment of the shape of cells with cellular atypia, mitotic activity, presence of necrosis, intercellular bridges, and keratin pearls (Fig. 1.3e, f). The well- (G1), medium- (G2), and low-differentiated (G3) SCC are distinguished. The histological grading system refers to the least differentiated part of SCC; even it is only a small part of the entire tumor. Well-differentiated SCC is characterized by the presence of large, polygonal cells with abundant acidophilic cytoplasm, with clearly visible intercellular bridges and the presence of keratin pearls, while the mitotic index is low. In low-differentiated SCC, the cells are often spindle-like or round with a medium abundant or scant cytoplasm; high atypia and brisk mitotic activity are found. Keratinization may be visible only in single cells. These lesions often present no apparent features of squamous cell differentiation and require immunohistochemical confirmation of the diagnosis. Positive reactions with p40, p63, and CK5/6 antibodies are typical for SCC. The SCC, G2, is characterized by an intermediate differentiation between G1 and G3 [1, 96, 97].

The histopathological report of SCC should include macroscopic description: location of the lesion; type of diagnostic material (biopsy, surgical excision); dimensions of the material, and examined lesion; type of tumor growth; and margins of resection. A microscopic evaluation obligatorily present diagnosis with a morphological variant

of SCC; histological grading; the largest dimension of carcinoma and the depth of the infiltrate (measured from the granular layer of the epidermis; does not apply to the "in situ" lesions); clinical staging (pTNM) [98, 99]; assessment of vessels and nerves infiltration; margins assessment [100]. Besides, in advanced SCC, bone and bone marrow infiltration may need to be described. In the case of SCC metastases to the lymph node/nodes, reporting of the number of lymph nodes, the largest dimension of the metastasis and extranodal metastasis extension is required [101, 102]. It is worth noting that the TNM classification of SCC is distinct for the following locations: conjunctiva, head and neck, perianal region, vagina, and penis [103].

Keratoacanthoma

Keratoacanthoma (KA) is a frequent change characterized by rapid growth and spontaneous regression. Histologically, it has a morphology that corresponds to well-differentiated SCC with a benign clinical course. Most often, these changes occur on sun-exposed skin on the face, dorsal part of hands, forearms, and legs among people over 50 years of age [104]. Multiple lesions are found in rare disease syndromes, that is, multiple familial keratoacanthomas or the Ferguson–Smith type or Muir–Torre syndrome. Exposure to UV radiation, effect of HPV, point mutations in the *TP53* gene, and *MAP 3K8* (*TPL2*) oncogene changes play a crucial role in pathogenesis [105, 106].

Macroscopically, it is a well-limited dome-shaped lesion with raised edges and a central "crater"—an ulcerative depression. Lesions are usually single, and their size does not exceed 3 cm.

Microscopically, the keratoacanthoma is symmetrical: in the central part (crater), keratin masses predominate, the lateral parts are composed of squamous epithelium forming nests and elongated bands (Fig. 1.3a). A characteristic feature is epidermal lipping on both sides of the keratin core. At the base of the lesion, usually dense, mixed inflammatory infiltrates and fibrosis are visible. Due to the macroscopic presentation in the fourth edition of the WHO classification, the following KA subtypes were distinguished: solitary KA, multiple KA, multiple familial KA of Ferguson–Smith type, centrifugum marginatum KA, generalized eruptive KA of Grzybowski, subungual KA. KAs undergo spontaneous regression and rarely recur, especially central facial giant KA and subungual KA [1, 107]. The clinical picture of KA may overlap with other SCC variants as well. The recent recommendations indicate that KA should be qualified for total surgical excision.

Merkel Cell Carcinoma

Merkel cell carcinoma (MCC) is a rare primary skin neuroendocrine tumor that occurs mainly in elderly patients (over the age of 70), usually in the scalp and neck (especially the eyelids and orbital area) and limbs [108]. It is characterized by an

aggressive course with the presence of lymph node metastases in about 50% of cases at the time of diagnosis; local and distant metastases are found in 35–40% of patients [109–111].

Macroscopically, MCC presents itself as a hard, painless tumor with a smooth surface, usually covered with intact epidermis.

Microscopically, MCC is composed of small, oval cells with characteristic cell nuclei with granular chromatin described as "salt with pepper" (Fig. 1.4a, b). Cancer cells form solid infiltrates or alveolar, trabecular, or rosette-like structures. Merkel

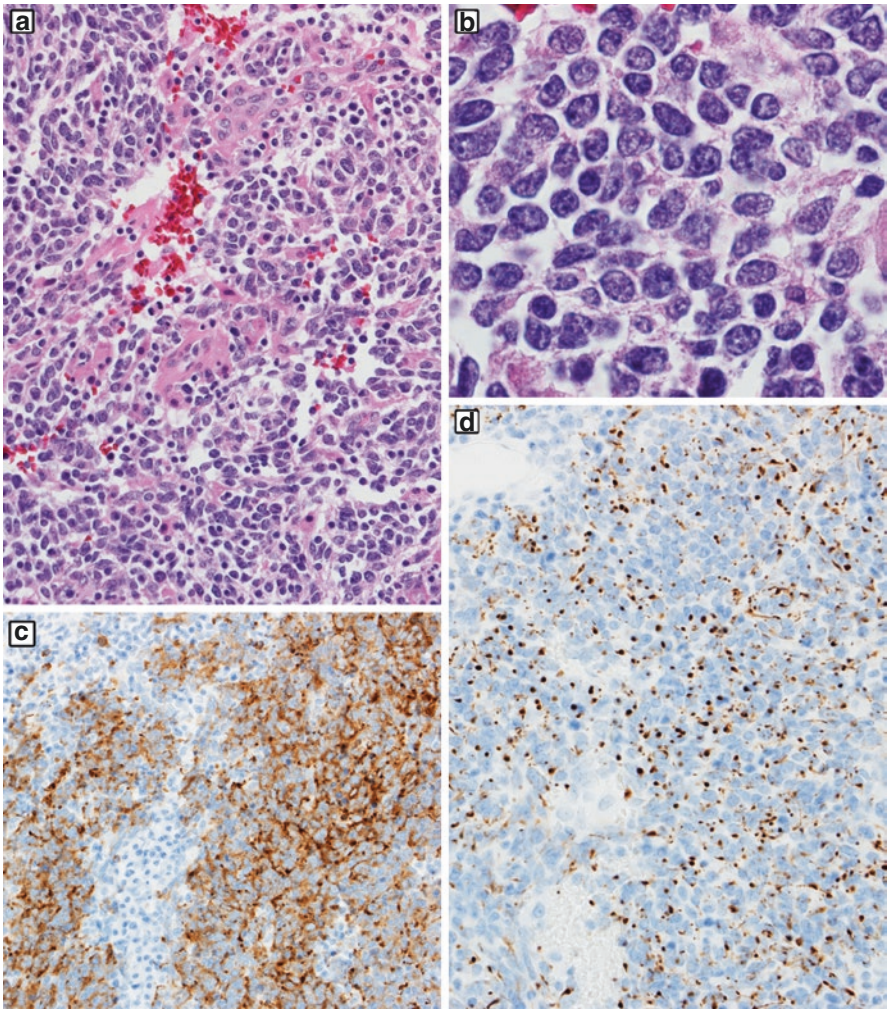

Fig. 1.4 Merkel cell carcinoma. (**a**, **b**) The intermediate cell type with nuclear salt-and-pepper chromatin pattern (200×, 600×); (**c**) Neuroendocrine markers include positive reaction with chromogranin (200×); (**d**) CK20 immunoreaction presents characteristic) perinuclear dot-like pattern (200×)

cell carcinoma resembles low-differentiated round cell neoplasm, which must be differentiated with small cell lung cancer (SCLC), melanoma, lymphoma, and Ewing's sarcoma [112–114]. The final diagnosis requires confirmation in immunohistochemistry. The characteristic immunoprofile includes positive reactions with neuroendocrine markers, that is, synaptophysin, chromogranin A and CD56 and dot-like, perinuclear reaction with CK20 (Fig. 1.4c, d). Lack of S100, HMB-45, SOX-10, LCA/CD45, TTF-1 expression supports the exclusion of melanoma, lymphoma, and SCLC [115].

MCC high-risk factors in the adverse clinical course include lymph node metastases at the time of diagnosis, tumor size >2 cm, primary lesion location on the limbs, and male gender [110, 111, 114, 116]. The histopathological report additionally should include information about lymph node and in-transit metastases. The pTNM for MCC has been separated in the WHO classification [117, 118].

References

1. Elder DE, Massi D, Scolyer RA, Willemze R, editors. WHO classification of skin tumours. 4th ed. Lyon: International Agency for Research on Cancer (IARC); 2018.
2. World Health Organization. Skin cancers. 2013. http://www.who.int/uv/faq/skincancer/en/index1.html. Accessed 28 June 2013.
3. Scolyer RA, Rawson RV, Gershenwald JE, Ferguson PM, Prieto VG. Melanoma pathology reporting and staging. Mod Pathol. 2020;33(1):15–24.
4. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature. 2002;417:949–54.
5. Edlundh-Rose E, Egyházi S, Omholt K, Månsson-Brahme E, Platz A, Hansson J, et al. BRAF mutations in melanoma tumours in relation to clinical characteristics: a study based on mutation screening by pyrosequencing. Melanoma Res. 2006;16(6):471–8.
6. Ellerhorst JA, Greene VR, Ekmekcioglu S, Warneke CL, Johnson MM, Cooke CP, et al. Clinical correlates of NRAS and BRAF mutations in primary human melanoma. Clin Cancer Res. 2011;17:229–35.
7. Long GV, Menzies AM, Nagrial AM, Haydu LE, Hamilton AL, Mann GJ, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol. 2011;29:1239–46.
8. Mann GJ, Pupo GM, Campain AE, Carter CD, Schramm SJ, Pianova S, et al. BRAF mutation, NRAS mutation, and the absence of an immune-related expressed gene profile predict poor outcome in patients with stage III melanoma. J Invest Dermatol. 2013;133:509–17.
9. Elder DE, Bastian BC, Cree IA, Massi D, Scolyer RA. The 2018 World Health Organization Classification of cutaneous, mucosal, and uveal melanoma: detailed analysis of 9 distinct subtypes defined by their evolutionary pathway. Arch Pathol Lab Med. 2020;144(4):500–22.
10. Roncati L, Piscioli F, Pusiol T. SAMPUS, MELTUMP and THIMUMP - diagnostic categories characterized by uncertain biological behavior. Klin Onkol. 2017;30(3):221–3.
11. Pusiol T, Morichetti D, Piscioli F, Zorzi MG. Theory and practical application of superficial atypical melanocytic proliferations of uncertain significance (SAMPUS) and melanocytic tumours of uncertain malignant potential (MELTUMP) terminology: experience with second opinion consultation. Pathologica. 2012;104(2):70–7.
12. Pusiol T, Piscioli F, Speziali L, Zorzi MG, Morichetti D, Roncati L. Clinical features, dermoscopic patterns, and histological diagnostic model for melanocytic tumors of uncertain malignant potential (MELTUMP). Acta Dermatovenerol Croat. 2015;23(3):185–94.

13. Zembowicz A, Scolyer RA. Nevus/Melanocytoma/Melanoma: an emerging paradigm for classification of melanocytic neoplasms? Arch Pathol Lab Med. 2011;135(3):300–6.
14. Yeh I. New and evolving concepts of melanocytic nevi and melanocytomas. Mod Pathol. 2020;33(Suppl 1):1–14.
15. Urso C. Melanocytic skin neoplasms: what lesson from genomic aberrations? Am J Dermatopathol. 2019;41(9):623–9.
16. Maldonado JL, Fridlyand J, Patel H, Jain AN, Busam K, Kageshita T, et al. Determinants of BRAF mutations in primary melanomas. J Natl Cancer Inst. 2003;95(24):1878–90.
17. Rigel DS, Friedman RJ, Kopf AW, Polsky D. ABCDE--an evolving concept in the early detection of melanoma. Arch Dermatol. 2005;141(8):1032–4.
18. Lee EY, Williamson R, Watt P, Hughes MC, Green AC, Whiteman DC. Sun exposure and host phenotype as predictors of cutaneous melanoma associated with neval remnants or dermal elastosis. Int J Cancer. 2006;119(3):636–42.
19. Viros A, Fridlyand J, Bauer J, Lasithiotakis K, Garbe C, Pinkel D, et al. Improving melanoma classification by integrating genetic and morphologic features. PLoS Med. 2008;5(6):e120.
20. Farrahi F, Egbert BM, Swetter SM. Histologic similarities between lentigo maligna and dysplastic nevus: importance of clinicopathologic distinction. J Cutan Pathol. 2005;32(6):405–12.
21. King R, Page RN, Googe PB, Mihm MC Jr. Lentiginous melanoma: a histologic pattern of melanoma to be distinguished from lentiginous nevus. Mod Pathol. 2005;18(10):1397–401.
22. Lens MB, Newton-Bishop JA, Boon AP. Desmoplastic malignant melanoma: a systematic review. Br J Dermatol. 2005;152(4):673–8.
23. Chen JY, Hruby G, Scolyer RA, Murali R, Hong A, Fitzgerald P. Desmoplastic neurotropic melanoma: a clinicopathologic analysis of 128 cases. Cancer. 2008;113:2770–8.
24. Busam KJ, Mujumdar U, Hummer AJ, Nobrega J, Hawkins WG, Coit DG. Cutaneous desmoplastic melanoma: reappraisal of morphologic heterogeneity and prognostic factors. Am J Surg Pathol. 2004;28:1518–25.
25. Plaza JA, Bonneau P, Prieto V, Sangueza M, Mackinnon A, Suster D, et al. Desmoplastic melanoma: an updated immunohistochemical analysis of 40 cases with a proposal for an additional panel of stains for diagnosis. J Cutan Pathol. 2016;43(4):313–23.
26. Kooper-Johnson S, Mahalingam M, Loo DS. SOX-10 and S100 negative desmoplastic melanoma: apropos a diagnostically challenging case. Am J Dermatopathol. 2020;42(9):697–9.
27. Newman S, Fan L, Pribnow A, Silkov A, Rice SV, Lee S, et al. Clinical genome sequencing uncovers potentially targetable truncations and fusions of MAP3K8 in spitzoid and other melanomas. Nat Med. 2019;25(4):597–602.
28. Cerrato F, Wallins JS, Webb ML, McCarty ER, Schmidt BA, Labow BI. Outcomes in pediatric atypical spitz tumors treated without sentinel lymph node biopsy. Pediatr Dermatol. 2012;29(4):448–53.
29. Requena C, Botella R, Nagore E, Sanmartín O, Llombart B, Serra-Guillén C, et al. Characteristics of spitzoid melanoma and clues for differential diagnosis with spitz nevus. Am J Dermatopathol. 2012;34(5):478–86.
30. Garrido-Ruiz MC, Requena L, Ortiz P, Pérez-Gómez B, Alonso SR, Peralto JL. The immunohistochemical profile of Spitz nevi and conventional (non-Spitzoid) melanomas: a baseline study. Mod Pathol. 2010;23(9):1215–24.
31. Crotty KA, Scolyer RA, Li L, Palmer AA, Wang L, McCarthy SW. Spitz naevus versus Spitzoid melanoma: when and how can they be distinguished? Pathology. 2002;34(1):6–12.
32. Indsto JO, Kumar S, Wang L, Crotty KA, Arbuckle SM, Mann GJ. Low prevalence of RAS-RAF-activating mutations in Spitz melanocytic nevi compared with other melanocytic lesions. J Cutan Pathol. 2007;34(6):448–55.
33. Durbec F, Martin L, Derancourt C, Grange F. Melanoma of the hand and foot: epidemiological, prognostic and genetic features. A systematic review. Br J Dermatol. 2012;166(4):727–39.
34. Basurto-Lozada P, Molina-Aguilar C, Castaneda-Garcia C, Vázquez-Cruz ME, Garcia-Salinas OI, Álvarez-Cano A, et al. Acral lentiginous melanoma: basic facts, biological characteristics and research perspectives of an understudied disease. Pigment Cell Melanoma Res. 2020; https://doi.org/10.1111/pcmr.12885.

35. Nakamura Y, Fujisawa Y. Diagnosis and management of acral lentiginous melanoma. Curr Treat Options in Oncol. 2018;19(8):42.
36. Darmawan CC, Jo G, Montenegro SE, Kwak Y, Cheol L, Cho KH, et al. Early detection of acral melanoma: A review of clinical, dermoscopic, histopathologic, and molecular characteristics. J Am Acad Dermatol. 2019;81(3):805–12.
37. Chen F, Zhang Q, Wang Y, Wang S, Feng S, Qi L, et al. KIT, NRAS, BRAF and FMNL2 mutations in oral mucosal melanoma and a systematic review of the literature. Oncol Lett. 2018;15(6):9786–92.
38. Lazarev S, Gupta V, Hu K, Harrison LB, Bakst R. Mucosal melanoma of the head and neck: a systematic review of the literature. Int J Radiat Oncol Biol Phys. 2014;90(5):1108–18.
39. Jarrom D, Paleri V, Kerawala C, Roques T, Bhide S, Newman L, et al. Mucosal melanoma of the upper airways tract mucosal melanoma: a systematic review with meta-analyses of treatment. Head Neck. 2017;39(4):819–25.
40. Kottschade LA, Grotz TE, Dronca RS, Salomao DR, Pulido JS, Wasif N, et al. Rare presentations of primary melanoma and special populations: a systematic review. Am J Clin Oncol. 2014;37(6):635–41.
41. Lim Y, Shin HT, Choi Y, Lee DY. Evolutionary processes of melanomas from giant congenital melanocytic nevi. Pigment Cell Melanoma Res. 2020;33(2):318–25.
42. Chopra A, Sharma R, Rao UNM. Pathology of melanoma. Surg Clin North Am. 2020;100(1):43–59.
43. Kiuru M, Tartar DM, Qi L, Chen D, Yu L, Konia T, et al. Improving classification of melanocytic nevi: association of BRAF V600E expression with distinct histomorphologic features. J Am Acad Dermatol. 2018;79(2):221–9.
44. Alendar T, Kittler H. Morphologic characteristics of nevi associated with melanoma: a clinical, dermatoscopic and histopathologic analysis. Dermatol Pract Concept. 2018;8(2):104–8.
45. Vergier B, Laharanne E, Prochazkova-Carlotti M, de la Fouchardière A, Merlio JP, Kadlub N, et al. Proliferative nodules vs melanoma arising in giant congenital melanocytic nevi during childhood. JAMA Dermatol. 2016;152(10):1147–51.
46. Toomey CB, Fraser K, Thorson JA, Goldbaum MH, Lin JH. GNAQ and PMS1 mutations associated with uveal melanoma, ocular surface melanosis, and nevus of ota. Ocular Oncol Pathol. 2019;5(4):267–72.
47. Oaxaca G, Billings SD, Ko JS. p16 Range of expression in dermal predominant benign epithelioid and spindled nevi and melanoma. J Cutan Pathol. 2020;47(9):815–23.
48. Borgenvik TL, Karlsvik TM, Ray S, Fawzy M, James N. Blue nevus-like and blue nevus-associated melanoma: a comprehensive review of the literature. ANZ J Surg. 2017;87(5):345–9.
49. Murali R, McCarthy SW, Scolyer RA. Blue nevi and related lesions: a review highlighting atypical and newly described variants, distinguishing features and diagnostic pitfalls. Adv Anat Pathol. 2009;16(6):365–82.
50. Loghavi S, Curry JL, Torres-Cabala CA, Ivan D, Patel KP, Mehrotra M, et al. Melanoma arising in association with blue nevus: a clinical and pathologic study of 24 cases and comprehensive review of the literature. Mod Pathol. 2014;27(11):1468–78.
51. Zhao M, Mu Y, Dang Y, Zhu Y. Secondary glaucoma as initial manifestation of ring melanoma: a case report and review of literature. Int J Clin Exp Pathol. 2014;7(11):8163–9.
52. Nayman T, Bostan C, Logan P, Burnier MN Jr. Uveal melanoma risk factors: a systematic review of meta-analyses. Curr Eye Res. 2017;42(8):1085–93.
53. Zhang HG, Moser JC, Dalvin LA. Characterization of uveal melanoma clinical trial design: a systematic review to establish an elusive standard of care. Acta Oncol (Stockholm, Sweden). 2020;59(11):1401–8.
54. Corneli P, Zalaudek I, Magaton Rizzi G, di Meo N. Improving the early diagnosis of early nodular melanoma: can we do better? Expert Rev Anticancer Ther. 2018;18(10):1007–12.
55. Greenwald HS, Friedman EB, Osman I. Superficial spreading and nodular melanoma are distinct biological entities: a challenge to the linear progression model. Melanoma Res. 2012;22(1):1–8.

56. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009;27(36):6199–206.
57. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. In: Amin MB, Edge SB, Greene FL, Carducci MA, Compton CA, editors. AJCC cancer staging manual. 8th ed. Springer International Publishing: New York; 2017. p. 563–85.
58. Gimotty PA, Guerry D, Ming ME, Elenitsas R, Xu X, Czerniecki B, et al. Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. J Clin Oncol. 2004;22(18):3668–76.
59. Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67:472–92.
60. Eggermont AMM, Blank CU, Mandala M, Long GV, Atkinson V, Dalle S. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med. 2018;378:1789–801.
61. Weber J, Mandala M, Vecchio M, Gogas HJ, Arance AM, Cowey CL. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med. 2017;377:1824–35.
62. Long GV, Hauschild A, Santinami M, Atkinson V, Mandala M, Chiarion-Sileni V. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med. 2017;377:1813–23.
63. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Ding S, Byrd DR, et al. Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. J Clin Oncol. 2010;28:2452–9.
64. Gershenwald JE, Scolyer RA. Melanoma staging: American Joint Committee on Cancer (AJCC) 8th Edition and beyond. Ann Surg Oncol. 2018;25:2105–10.
65. Breslow A. Thickness, cross-sectional areas and depth of invasion in the prognosis of cutaneous melanoma. Ann Surg. 1970;172:902–8.
66. Dodds TJ, Lo S, Jackett L, Nieweg O, Thompson JF, Scolyer RA. Prognostic significance of periadnexal extension in cutaneous melanoma and its implications for pathologic reporting and staging. Am J Surg Pathol. 2018;42:359–66.
67. Barnhill RL, Fine JA, Roush GC, Berwick M. Predicting five-year outcome for patients with cutaneous melanoma in a population-based study. Cancer. 1996;78:427–32.
68. In 't Hout FE, Haydu LE, Murali R, Bonenkamp JJ, Thompson JF, Scolyer RA. Prognostic importance of the extent of ulceration in patients with clinically localized cutaneous melanoma. Ann Surg. 2012;255:1165–70.
69. Scolyer RA, Shaw HM, Thompson JF, Li LX, Colman MH, Lo SK. Interobserver reproducibility of histopathologic prognostic variables in primary cutaneous melanomas. Am J Surg Pathol. 2003;27:1571–6.
70. Klein G, Klein E. Surveillance against tumors: Is it mainly immunological? Immunol Lett. 2005;100:29–33.
71. Clark WH, Elder DE, Guerry D, Braitman LE, Trock BJ, Schultz D, et al. Model predicting survival in stage I melanoma based on progression. J Natl Cancer Inst. 1989;81:1893–904.
72. Taylor RC, Patel A, Panageas KS, Busam KJ, Brady MS. Tumor-infiltrating lymphocytes predict sentinel lymph node positivity in patients with cutaneous melanoma. J Clin Oncol. 2007;25:869–75.
73. Mandalà M, Imberti GL, Piazzalunga D, Belfiglio M, Labianca R, Barberis M, et al. Clinical and histopathological risk factors to predict sentinel lymph node positivity, disease-free and overall survival in clinical stages I–II AJCC skin melanoma: outcome analysis from a single-institution prospectively collected database. Eur J Cancer. 2009;45:2537–45.
74. Azimi F, Scolyer RA, Rumcheva P, Moncrieff M, Murali R, McCarthy SW. Tumor-infiltrating lymphocyte grade is an independent predictor of sentinel lymph node status and survival in patients with cutaneous melanoma. J Clin Oncol. 2012;30:2678–83.
75. Clark WH, From L, Bernardino EA, Mihm MC. The histogenesis and biologic behavior of primary human malignant melanomas of the skin. Cancer Res. 1969;29:705–27.
76. Morris KT, Busam KJ, Bero S, Patel A, Brady MS. Primary cutaneous melanoma with regression does not require a lower threshold for sentinel lymph node biopsy. Ann Surg Oncol. 2008;15:316–22.

77. Gualano MR, Osella-Abate S, Scaioli G, Marra E, Bert F, Faure E, et al. Prognostic role of histological regression in primary cutaneous melanoma: a systematic review and meta-analysis. Br J Dermatol. 2018;178(2):357–62.
78. Storr SJ, Safuan S, Mitra A, Elliott F, Walker C, Vasko MJ, et al. Objective assessment of blood and lymphatic vessel invasion and association with macrophage infiltration in cutaneous melanoma. Mod Pathol. 2012;25:493–504.
79. Massi D, Puig S, Franchi A, Malvehy J, Vidal-Sicart S, González-Cao M, et al. Tumour lymphangiogenesis is a possible predictor of sentinel lymph node status in cutaneous melanoma: a case–control study. J Clin Pathol. 2006;59:166–73.
80. Xu X, Chen L, Guerry D, Dawson PR, Hwang WT, VanBelle P, et al. Lymphatic invasion is independently prognostic of metastasis in primary cutaneous melanoma. Clin Cancer Res. 2012;18:229–37.
81. Murali R, Shaw HM, Lai K, McCarthy SW, Quinn MJ, Stretch JR. Prognostic factors in cutaneous desmoplastic melanoma: a study of 252 patients. Cancer. 2010;116:4130–8.
82. Eroglu Z, Zaretsky JM, Hu-Lieskovan S, Kim DW, Algazi A, Johnson DB, et al. High response rate to PD-1 blockade in desmoplastic melanomas. Nature. 2018;553:347–50.
83. Cives M, Mannavola F, Lospalluti L, Sergi MC, Cazzato G, Filoni E, et al. Non-melanoma skin cancers: biological and clinical features. Int J Mol Sci. 2020;21(15):5394.
84. Dika E, Scarfì F, Ferracin M, Broseghini E, Marcelli E, Bortolani B, et al. Basal cell carcinoma: a comprehensive review. Int J Mol Sci. 2020;21(15):5572.
85. McDaniel B, Badri T. Basal cell carcinoma. StatPearls. Treasure Island FL: © 2020, StatPearls Publishing LLC; 2020.
86. Nikolouzakis TK, Falzone L, Lasithiotakis K, Krüger-Krasagakis S, Kalogeraki A, Sifaki M, et al. Current and future trends in molecular biomarkers for diagnostic, prognostic, and predictive purposes in non-melanoma skin cancer. J Clin Med. 2020;9(9):2868.
87. Campione E, Di Prete M, Lozzi F, Lanna C, Spallone G, Mazzeo M, et al. High-risk recurrence basal cell carcinoma: focus on hedgehog pathway inhibitors and review of the literature. Chemotherapy. 2020;65:2–10.
88. Spiker AM, Troxell T, Ramsey ML. Gorlin syndrome (Basal Cell Nevus). StatPearls. Treasure Island FL: © 2020, StatPearls Publishing LLC; 2020.
89. Evans DG, Farndon PA. Nevoid basal cell carcinoma syndrome. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, et al., editors. GeneReviews(®). Seattle WA: © 1993-2020, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle; 1993.
90. Bichakjian CK, Olencki T, Aasi SZ, Alam M, Andersen JS, Berg D, et al. Basal cell skin cancer, version 1.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2016;14(5):574–97.
91. Quazi SJ, Aslam N, Saleem H, Rahman J, Khan S. Surgical margin of excision in basal cell carcinoma: a systematic review of literature. Cureus. 2020;12(7):e9211.
92. Azimi A, Kaufman KL, Kim J, Ali M, Mann GJ, Fernandez-Penas P. Proteomics: an emerging approach for the diagnosis and classification of cutaneous squamous cell carcinoma and its precursors. J Dermatol Sci. 2020;99(1):9–16.
93. Campos MA, Lopes JM, Soares P. The genetics of cutaneous squamous cell carcinogenesis. Eur J Dermatol. 2018;28(5):597–605.
94. Collins L, Quinn A, Stasko T. Skin cancer and immunosuppression. Dermatol Clin. 2019;37(1):83–94.
95. Wang J, Aldabagh B, Yu J, Arron ST. Role of human papillomavirus in cutaneous squamous cell carcinoma: a meta-analysis. J Am Acad Dermatol. 2014;70(4):621–9.
96. Alferraly IT, Munir D, Putra IB, Sembiring RJ. Correlation of Ki-67 expression as tumor cell proliferation activity marker with cutaneous squamous cell carcinoma grading. Open Access Maced J Med Sci. 2019;7(20):3384–6.
97. Yantsos VA, Conrad N, Zabawski E, Cockerell CJ. Incipient intraepidermal cutaneous squamous cell carcinoma: a proposal for reclassifying and grading solar (actinic) keratoses. Semin Cutan Med Surg. 1999;18(1):3–14.

98. Keohane SG, Proby CM, Newlands C, Motley RJ, Nasr I, Mohd Mustapa MF, et al. New 8th edition of TNM staging and implications for skin cancer. Br J Dermatol. 2018;179(4):824–8.
99. Brierley JD, Gospodarowicz MK, Wittekind CH. TNM classification of malignant tumours, Eighth Edition. Oxford: WILEY Blackwell; 2017. Union for International Cancer Control.
100. Heppt MV, Steeb T, Berking C, Nast A. Comparison of guidelines for the management of patients with high-risk and advanced cutaneous squamous cell carcinoma - a systematic review. J Eur Acad Dermatol Venereol. 2019;33(Suppl 8):25–32.
101. Claveau J, Archambault J, Ernst DS, Giacomantonio C, Limacher JJ, Murray C, et al. Multidisciplinary management of locally advanced and metastatic cutaneous squamous cell carcinoma. Curr Oncol (Toronto, Ont). 2020;27(4):e399–407.
102. Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk factors for cutaneous squamous cell carcinoma recurrence, metastasis, and disease-specific death: a systematic review and meta-analysis. JAMA Dermatol. 2016;152(4):419–28.
103. Nägeli MC, Ramelyte E, Dummer R. Cutaneous squamous cell carcinomas on special locations: perioral, periocular and genital area. J Eur Acad Dermatol Venereol. 2019;33(Suppl 8):21–4.
104. Savage JA, Maize JC Sr. Keratoacanthoma clinical behavior: a systematic review. Am J Dermatopathol. 2014;36(5):422–9.
105. Le S, Ansari U, Mumtaz A, Malik K, Patel P, Doyle A, et al. Lynch Syndrome and Muir-Torre Syndrome: an update and review on the genetics, epidemiology, and management of two related disorders. Dermatol Online J. 2017;23(11)
106. Lai V, Cranwell W, Sinclair R. Epidemiology of skin cancer in the mature patient. Clin Dermatol. 2018;36(2):167–76.
107. Paolino G, Donati M, Didona D, Mercuri SR, Cantisani C. Histology of non-melanoma skin cancers: an update. Biomedicines. 2017;5(4):71.
108. Calder KB, Smoller BR. New insights into merkel cell carcinoma. Adv Anat Pathol. 2010;17(3):155–61.
109. Cornejo C, Miller CJ. Merkel cell carcinoma: updates on staging and management. Dermatol Clin. 2019;37(3):269–77.
110. Keohane SG, Proby CM, Newlands C, Motley RJ, Nasr I, Mohd Mustapa MF, et al. The new 8th edition of TNM staging and its implications for skin cancer: a review by the British Association of Dermatologists and the Royal College of Pathologists, U.K. Br J Dermatol. 2018;179(4):824–8.
111. Portilla N, Alzate JP, Sierra FA, Parra-Medina R. A systematic review and meta-analysis of the survival and clinicopathological features of p63 expression in Merkel cell carcinoma. Australas J Dermatol. 2020;61(3):e276–e82.
112. Barksdale SK. Advances in Merkel cell carcinoma from a pathologist's perspective. Pathology. 2017;49(6):568–74.
113. Kervarrec T, Samimi M, Guyétant S, Sarma B, Chéret J, Blanchard E, et al. Histogenesis of Merkel cell carcinoma: a comprehensive review. Front Oncol. 2019;9:451.
114. Pulitzer M. Merkel cell carcinoma. Surg Pathol Clin. 2017;10(2):399–408.
115. Pasternak S, Carter MD, Ly TY, Doucette S, Walsh NM. Immunohistochemical profiles of different subsets of Merkel cell carcinoma. Hum Pathol. 2018;82:232–8.
116. Karunaratne YG, Gunaratne DA, Veness MJ. Systematic review of sentinel lymph node biopsy in Merkel cell carcinoma of the head and neck. Head Neck. 2018;40(12):2704–13.
117. Amin MB, Edge SB, Greene FL. AJCC cancer staging manual. 8th edn. Merkel cell carcinoma (Chapter 46). Springer; 2017.
118. Trinidad CM, Torres-Cabala CA, Prieto VG, Aung PP. Update on eighth edition American Joint Committee on Cancer classification for Merkel cell carcinoma and histopathological parameters that determine prognosis. J Clin Pathol. 2019;72(5):337.