Melanoma: Clinical Presentations

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Abstract

The malignant cell in melanoma is the melanocyte. Because melanocytes are located in the basal layer of the epidermis, melanoma is most commonly seen on the skin. However, melanoma can also arise on mucosal surfaces such as the oral cavity, the upper gastrointestinal mucosa, the genital mucosa, as well as the uveal tract of the eye and leptomeninges. Melanomas tend to be pigmented but can also present as pink or red lesions. They can mimic benign or other malignant skin lesions. This chapter presents the spectrum of typical and less typical presentations of melanoma, as well as patterns of spread. It is divided into (1) cutaneous lesions; (2) patterns of regional spread, (3) non-cutaneous lesions; and (4) distant metastases.

Keywords

Atypical pigmented cutaneous lesions · Non-cutaneous melanoma · Melanoma of unknown primary site

Contents

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1 Cutaneous Tumors

Cutaneous melanomas are classified on the growth pattern into superficial spreading, nodular, lentigo maligna, and acral. Growth is typically described in two planes: Radial (horizontal) growth refers to melanocytic proliferation limited to the epidermis or focally as single cells or small nests within the papillary dermis, whereas vertical growth describes deeper invasion of nests or nodules of atypical melanocytes that are often larger than their counterparts in the superficial skin [1]. In certain instances, it is useful to think of these as "phases" of growth, such that the radial growth phase (RGP) may sometimes precede a vertical growth phase (VGP). The typical lesion of cutaneous melanoma is an asymmetric macule or nodule with irregular borders, frequently with variations in color within the lesion. On histology, it reveals nests of melanocytes within the epidermis that varies in size, shape, spacing, and display pagetoid spread, or a pattern of focal confluence [2]. Architectural patterns and cytomorphological features have been studied and are reviewed extensively by [3].

Alternative ways of classification have been proposed based on rate of growth [4]. In this schema based on trends in melanoma epidemiology, there are three subtypes of lesions: (1) slow-growing, located on intermittently sun-exposed areas with a sharply rising incidence; (2) very slow-growing on sun-exposed skin with moderate increase in incidence; and (3) fast-growing, arising in any body part with stable incidence and high mortality. Any scheme can be adopted so long as it is helpful in stratifying risk, rationalizing therapy, and predicting prognosis.

1.1 Superficial Spreading Melanoma

Superficial spreading melanoma (SSM) is the most common subtype of cutaneous melanoma, particularly in individuals with Skin Phototypes I and II, accounting for 60–70 % of all melanomas. It is typically diagnosed between the ages of 40 and 60 (see Table 1). The association between the number of nevi and SSM has been established [5, 6]. This subtype typically arises on the trunk in men and on the

Table 1 Clinical subtypes and classical feature of cutaneous melanoma

Clinical subtype	Percentage[a] (%)	Median age (years)	Frequent location	Precursor lesion	Growth pattern	Dermoscopy	Histopathology
Superficial spreading melanoma	57.4	51	Trunk in men, lower legs in women [2]	Can arise de novo or in preexisting nevus [5, 6]	Begins as <5 mm macule with notched borders; slow RGP limited to epidermis or focally in papillary dermis; develops into papule or nodule with a rapid VGP [2]	Broad network of multiple brown dots with pseudopods, color variation (red and blue), a sharp cutoff, and possible depigmentation [7]	Asymmetric, poorly circumscribed, irregular nests of melanocytes within the epidermis; with pagetoid spread [2]
Nodular melanoma	21.4	56	Trunk, head, neck in men more than women [2]	De novo, less commonly in preexisting nevus [8]	Begins as a blue to black, or pink to red nodule which may ulcerate or bleed; rapid VGP [9]	Individual globules with color variation (blue-gray), white streaks and irregular vessels [7]	Similar to superficial spreading melanoma [9]
Lentigo maligna melanoma	8.8	68	Nose, cheek, or any sun-damaged skin (including neck, scalp, and ears in men) [2]	Lentigo maligna [10]	Begins as a brown-to-black macule with variegated color and irregular indented border [7, 11]	Asymmetric, hyperpigmented follicular openings slowly overgrown by irregular pigmented dots [7]	Solitary tumor cells within epidermis, epithelium of adnexal structures; epidermal atrophy and signs of elastosis [2]
Acral lentiginous melanoma	4	63	Soles, most commonly, also palms, within or around nail apparatus [12]		Brown-to-black macule with color variegation and irregular borders [2]	Irregular, gray-brown polygons, multiple hypopigmented areas [7]	Proliferating, atypical melanocytes within basal layer of hyperplastic dermis either arranged solitary or in irregular nests [13]

RGP radial growth phase; *VGP* vertical growth phase

[a]Percentages are based on all cases of cutaneous, ocular, and mucosal melanoma. Percentages do not add up to 100, because unclassified melanomas (3.5 %) and other (5 %) were not included in the table

lower extremities in women. Depending on the location, the differential diagnosis might include atypical nevus, common benign nevus, seborrheic keratosis, or basal cell carcinoma. Classically, SSM begins as an asymmetric, irregularly scalloped macule or papule, usually <5 mm with mottled variegated color, and a central elevation with some surface distortion [2]. Over time, the lesion can grow to be significantly larger (Fig. 1a, b). Initially, the lesion behaves indolently, proliferating within the epidermis or superficial papillary dermis. However, for unknown

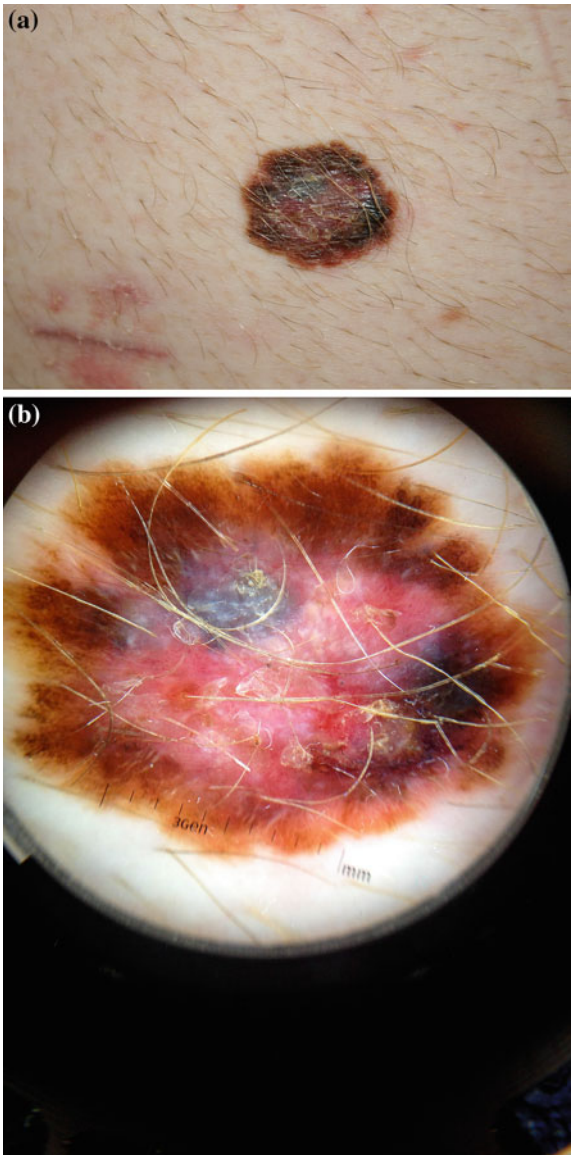

Fig. 1 **a** A superficial spreading melanoma presenting as a 1.9 × 1.7 cm *pink/brown/black* patch with a 7-mm *red* papule at the 5 o'clock location of the lesion. Histology revealed a 1.0 mm Breslow depth. **b** Dermoscopy showed prominent variegation in color and central haziness with pink, purplish, and gray discoloration

reasons, the malignant melanocytes invade the dermis and a more rapid VGP ensues, leading to a papule or nodule.

Although SSM is often associated with transformed nevi because of the association with nevi counts, it is estimated that approximately half of these lesions arise de novo. In fact, the likelihood that an individual nevus will progress to malignancy is low [14]: The risk of malignant transformation for common melanocytic nevi is one in thousands, while the risk for atypical melanocytic nevi is in the order of one in hundreds [15, 16]. Whereas the risk of SSM arising from common nevi increases with nevi counts [5, 6], for atypical nevi, the risk beyond five nevi does not accrue [17].

1.1.1 Melanoma In Situ

Melanoma in situ (MIS) is thought to precede more invasive melanoma. MIS refers to solitary melanocytes or nests of melanocytes found above the dermal–epidermal junction (DEJ) and extending into the uppermost layers of the epidermis. Melanocytes can involve the adnexal epithelium of pilosebaceous units and other structures. These nests do not mature as they cross into the dermis, but instead, retain the same size as their epidermal counterparts [2].

1.1.2 Host Immune Response in Melanoma

More so than any other malignant neoplasm, melanoma antigens are highly immunogenic [18]. To demonstrate the role of the immune system in melanoma, it was shown that melanoma incidence was higher in immunosuppressed individuals [19]. It is no surprise, therefore, that many melanomas display immune escape mechanisms: For instance, they may selectively lose or mutate known immunogenic antigens, down-regulate MHC class I molecules on antigen presenting cells, and change the cytokine milieu toward a tolerizing environment [20].

Up to two-thirds of patients show signs of partial regression, a phenomenon which may represent an immune response. Macroscopically, this is seen by focal areas in the lesion of gray, hypo-, or depigmented structures, which can be mistaken for vitiligo or halo nevi, while histopathological examinations reveal accumulated melanin-laden macrophages and infiltrating lymphocytes, often arranged in a bandlike pattern in the dermis [21, 22]. Spontaneous regression inversely correlates with tumor thickness; as such, up to two-thirds of the thinnest melanomas (0.75 mm or less in thickness) show partial regression [23, 24]. The mechanism of regression is unclear, though assumed to be immune-mediated, given the infiltrate of lymphocytes and plasma cells [25, 26]. Some have even proposed a contact sensitizer to be the cause for recruiting the adaptive immune system to the tumor environment [27].

The prognostic significance of regression is not well understood: A recent study demonstrated increased risk of metastases in 43 cases of melanoma with extensive but partial regression compared with matched controls [28]. To explain this, it is thought that regression signifies the presence of deeper invasion that may have already led “the horse out of the barn,” so to speak. Although some investigations have confirmed that partial regression is an adverse prognostic factor [29, 30],

others have failed to demonstrate this [31, 32]. To complicate matters further, melanoma of unknown primary (MUP), in which the primary lesion is assumed to be regressed, appears to have survival advantage as compared to patients with positive nodes and a known primary tumor [33, 34]. This would suggest that lymph node infiltration triggers the immune response against melanoma. The conflicting data may indicate the instances of success and failure of the immune system at attacking the tumor.

Besides spontaneous partial regression, which is common, complete regression is rare, and until 2005, only 38 cases were reported [35]. There is a marked predilection in males, with a male to female ratio of approximately 2:1, and an average age of onset of 48. Survival is variable, but poor, ranging from 6 weeks to 11 years. Among those that died of metastatic disease, the average survival was 13 months. Similar to partial regression, in complete regression, the patient often describes a change in a preexisting nevus: enlargement, friability, hypopigmentation, hyperpigmentation, bleeding, and eventual regression. Histology of the reviewed case reports by High et al. mostly showed epidermal attenuation, decreased epidermal melanocytes, papillary dermal fibrosis, a chronic inflammatory infiltrate, telangiectasia, and presence of dermal melanophages. The authors point out that requiring melanophages in the diagnostic criteria may exclude amelanotic melanoma lesions that have regressed, but without including this feature, the positive predictive value of diagnosis is too low, given that the prevalence of complete regression is low. One rare form of complete tumor regression is known as tumoral melanosis (TM). TM presents as a 1–5 cm blue-black nodule, suspicious for a primary invasive melanoma [22]. However, histology reveals dense dermal or dermal and subcutaneous melanophage infiltrates.

1.2 Nodular Melanoma

Nodular melanoma (NM) is the second most common type in fair-skinned individuals, representing approximately 15–20 % of melanomas. It commonly presents on the trunk, head, or neck, with a greater incidence in men (Fig. 2). This subtype is thought to arise de novo over a period of weeks to months as a vertically infiltrating tumor without much of a RGP. For this reason, they tend to be diagnosed at a thicker, more advanced stage [8]. Early on, the lesion is classically an asymmetric blue or black nodule with regular borders. Two to eight percent of such tumors, however, can be pink or red in coloration and in those instances are termed "amelanotic" [9]. Because they lack pigment and are often smaller in diameter, 70 % of the time, melanoma is not initially considered in the diagnosis [36]. Whether pink or pigmented, NM may ulcerate or bleed. Depending on the presence or absence of pigmentation, the differential diagnosis includes the following: (1) for pigmented lesions: blue nevi, pigmented basal cell carcinoma, common benign nevus, and pigmented Spitz nevus; and (2) for amelanotic lesions: basal cell carcinoma, pyogenic granuloma, and atypical fibroxanthoma.

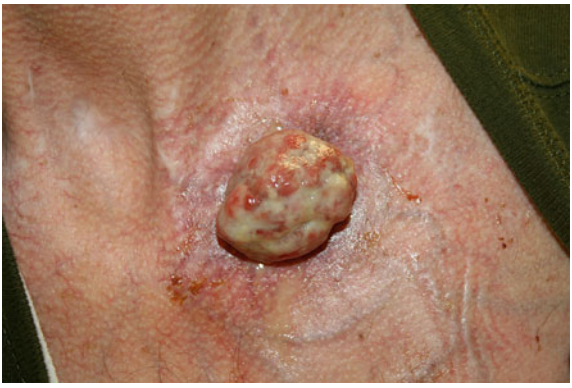

Fig. 2 A nodular melanoma presenting as a 4 cm fungating mass with purulent drainage. This nodule grew in size for over 2 years before the patient presented to the physician. Upon diagnosis, he was found to have lymph node involvement and died within 1 year from distant metastatic disease

1.2.1 Spitzoid Melanoma

Spitzoid melanoma can be mistaken early on for a Spitz nevus. On histology, both reveal a dermal nodule with overall symmetry of epithelioid melanocytes that do not mature with deeper extension. However, clues to the malignant nature of the lesion include arrangement into sheets of atypical melanocytes in the dermis and mitotic figures at the base of the lesion. Additional methods such as immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), and comparative genomic hybridization (CGH) have had variable rates of success in distinguishing melanoma from nevus [37]. For instance, melanomas, unlike benign nevi, show gains or losses of particular segments or whole chromosomes, while approximately 20 % of benign Spitz nevi show increase in copy number of chromosome 11p, not typically found in melanoma [38].

1.2.2 Atypical Fibroxanthoma-Like Melanoma

NM can also be mistaken for atypical fibroxanthoma (AFX), the former being a diagnosis more dangerous to miss. Sangueza and Zelger report 4 cases of melanoma in 3 patients whose diagnosis was mistaken initially due to the unusual clinical presentation and pathological correlation, as well as negative melanin staining on IHC [39]. However, others have reported that AFX can present as a pseudo-pigmented lesion that can be mistaken for melanoma on clinical and pathological evaluation [40]. To circumvent this, the authors recommend iron stains to diagnose AFX, because degraded erythrocytes following ulceration and hemorrhage are ingested and appear as accumulated hemosiderin in neoplastic cells.

1.2.3 Collision (Contiguous) Tumors

The skin, more than any other organ, is exposed to extensive DNA damage. In the right host, multiple contiguous tumors may arise. Clinical examination may reveal an atypical lesion, which on histology shows multiple etiologies. One such report involves 2 cases: one of a BCC, which ultimately revealed an underlying amelanotic melanoma, and another of an amelanotic melanoma that concealed an AFX [41]. Collision tumors can also arise in skin grafts [42]; however, the significance of that observation has not been found.

1.3 Lentigo Maligna Melanoma

Lentigo maligna melanoma (LMM) is a less common subtype, comprising approximately 9 % of all cutaneous melanomas. Typically, lesions occur in older, chronically sun-damaged individuals, with a predilection for the nose and cheek in women, and neck, scalp, and ears in men. Unlike other subtypes, it is thought that LMM arises from cumulative sun exposure rather than intermittent sun damage. Although LMM is associated with fair skin phototypes, unlike SSM, it is not correlated with nevus counts [5, 6]. The precursor lesion in LMM is a form of in situ melanoma, known as lentigo maligna (LM) (Fig. 3). There is a considerable risk—estimated at 5 %—for progression of LM into LMM [10]. Because it develops on a background of sun damage, the differential diagnosis for LMM includes lesions of sun damage (solar lentigo, pigmented actinic keratosis) as well as lentiginous nevus, macular seborrheic keratosis, and pigmented basal cell carcinoma. Of note, lentiginous junctional nevi are described in the elderly, especially on a background of poikilodermic skin, but they are located—unlike LM and LMM—on the trunk and limbs. Needless to say, they may transform into LM and small cell melanomas [43].

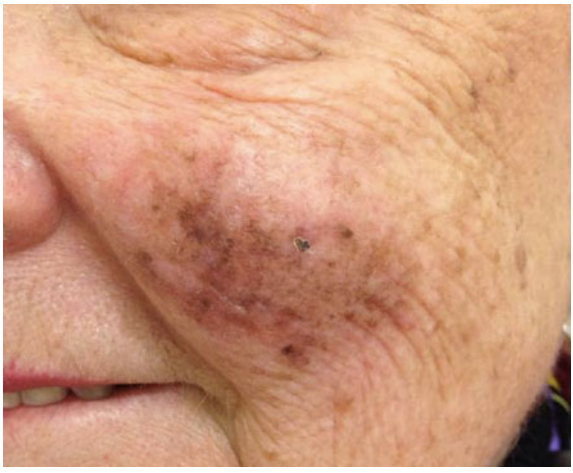

Fig. 3 Lentigo maligna (melanoma in situ) on the cheek of an elderly Caucasian woman. Site of hemorrhagic crust represents a recent biopsy site confirming the diagnosis. Full resection revealed no invasive component of melanoma

The lesion usually begins as an indolent, asymmetric brown-to-black macule with color variegation and an irregular indentation. On dermoscopy, these areas appear as hyperpigmented follicular openings that are overgrown by irregular pigmented dots arranged in an annular granular pattern [7, 11]. Stolz et al. estimated that 87 % of LMM presents with those features on dermoscopy. Others have tried to identify novel features, including increased density in the vascular network, and presence of rhomboidal structures and targetlike patterns [44]. Additionally, LMM may display subclinical levels of radial growth, resulting in incomplete excision, and high rates of recurrence. Later on, lesions may develop a nodular portion.

Microscopically, LMM exhibits lentiginous spread, in which solitary tumor cells, rather than tumor nests, extend into the epidermal and dermal layers [2]. Atypical melanocytes can be found in the epithelium of adnexal structures, particularly along the outer root sheath of hair follicles. An invasive component is often present and composed of spindle cells. Moreover, epidermal atrophy, signs of solar elastosis, and desmoplastic stromal change are not uncommon with LMM. Finally, work by King et al. suggests that atypical lentiginous proliferations may look similar to benign lentiginous junctional nevi in their retiform epidermal pattern; however, they also present with confluent growth of atypical melanocytes flanking the site of biopsy, which is more akin to atypical proliferative lesions (2005). Seeing as these lentiginous proliferations progress if left untreated, the authors suggest that they might be early LMM and therefore should be treated as such.

1.3.1 Desmoplastic Melanoma

LMM is associated with the highest rates of desmoplastic melanoma (DM). DM is a histological diagnosis that comprises 4 % of cutaneous melanomas and is found more commonly in older males and on sun-exposed skin [45, 46]. It can arise in LMM, acral melanoma (AM, see Sect. 1.4), or in the RGP of mucosal lymphoma [2]. The classic lesion is a skin-colored, red, or brown-black nodule or plaque in a sun-exposed site. Histologically, malignant melanocytes take on a spindle shape, separated by collagen fibers or fibrous stroma, which are present in foci or throughout the tumor. Cytologically, melanocytes appear bland, with visible atypia and stromal fibrosis [47]. The diagnosis requires deep tissue samples because superficial findings are nonspecific for scar or spindle cell neoplasms. The source of desmoplasia and increased collagen deposition is unknown. Some have postulated that the malignant melanocytes induce host responses leading to fibroblast proliferation and deposition of collagen [48, 49]. Others have argued that the melanocytes themselves undergo adaptive fibroplasia, allowing them to deposit collagen in the deeper dermal layers [50, 51].

DM is rarely metastatic but often highly infiltrative and locally aggressive, and approximately 30 % of cases display neurotropism. Of note, conventional staging has been shown to overestimate the likelihood of metastasis of these tumors [52, 53].

1.4 Acral Melanoma

AM is the least common subtype, comprising <5 % of cutaneous melanomas. It presents with equal incidence in all skin types and as such is the most common subtype in darker pigmented individuals. It constitutes 60–70 % of melanomas in black-skinned individuals [54] and 50 % in Asians [55–57]. Typically, AM occurs on the soles, but can also commonly occur on the palms and in or around the nail apparatus [12]. AM is difficult to diagnose because, especially when it is amelanotic, it can look like a benign lesion, such as a plantar wart or hematoma, or a squamous cell carcinoma.

Classically, AM begins as an asymmetric brown-to-black macule with variegated color and irregular borders. When involving the nail bed, it can present with longitudinal melanonychia extending onto the hyponychium or beyond the lateral or proximal nail fold, the latter referred to as Hutchinson's sign. Histologically, lesions begin as atypical single melanocytes or nests of melanocytes, sometimes displaying dendrites, and are present within all layers of a hyperplastic epidermis, in what is known as pagetoid scatter [13]. In the stratum corneum, numerous melanocytes and melanin granules are diffusely scattered.

The genetic markers of AM are different from the other subtypes of melanoma. Activating KIT mutations in exons 11, 13, and 17 is common, making the tumor susceptible to KIT inhibitors, such as imatinib [58, 59].

1.4.1 Subungual Melanoma

AM of the matrix is known as subungual melanoma (SUM) and represents 1–3 % of all cutaneous melanomas. Unlike any other melanoma type, SUM is not related to sun exposure. Because the nail plate is so dense, it is estimated that less than 2 % of UVA, and no UVB, is transmitted to the matrix [60].

SUM presents commonly with melanonychia striata, which are widening dark or irregularly pigmented longitudinal nail streaks with possible nail dystrophy and onycholysis [2]. Hyperpigmentation of the nail bed or matrix is concerning when it extends to the cuticle or hyponychium, and when the pigment is dark, irregular, or the width of the area involved is >3 mm. Nail pathologies to consider in that case are as follows: benign longitudinal melanonychia, subungual hematoma, pyogenic granuloma, onychomycosis with pigmentation, or hemorrhage.

SUM is misdiagnosed 85 % of the time, with the mean diagnostic delay being 30 months [61]. This is perhaps the case because approximately 23–44 % of patients with SUM reported local trauma to the nail [62]. It is unclear whether trauma draws attention to the area or whether post-traumatic inflammation induces carcinogenesis [63]. In favor of the latter, an analogous relationship exists between chronic skin wounds and the emergence of aggressive ulcerating forms of squamous cell carcinoma.

2 Regional Metastases

Regional metastases refer to the proximal spread of a melanoma within the skin and lymphatic vessels of the regional lymphatic system, including the regional lymph node. It is estimated that two-thirds of patients with clinical metastases following treatment of primary melanoma present initially with loco-regional metastases [64]. Regional metastases are classified into satellite, in-transit, and nodal based on the level of involvement within the lymphatic chain. As such, it relies on the premise that melanoma cells travel proximally in the lymphatic system. However, it is also known that melanoma can spread hematogenously and iatrogenically [65]. True hematogenous spread is confirmed by the development of metastases at the donor site of split thickness grafts and has been reported [66, 67]. That melanoma cells can spread in the blood vessels is no surprise, as tumor cells can express levels of tissue factor 1000-fold higher than normal tissue [68, 69]. The natural history of melanoma and patterns of spread can help guide treatment and set survival expectations.

2.1 Satellite and In-Transit Metastasis

Satellite metastases (SM) are metastatic nodules that appear within 2 cm of the primary tumor. In-transit metastasis (ITM) represent intralymphatic tumor invasion in the regional skin or subcutaneous tissue between the primary tumor site and the draining lymph node basin. Clinically, SM and ITM appear as cutaneous or subcutaneous tumors or, when present in the upper dermis, may present as dome-shaped papules or nodules, which may be brown, skin-colored, or pink (Fig. 4a, b). The reported 5-year survival rates of ITM are approximately 69 % without lymph node involvement and drop to 46 % with regional node involvement [70–72]. SM and ITM have been associated with thicker primary tumors, ulceration, primary lesions on the lower extremities, and regional lymph node metastasis [73–76]. In fact, second only to lymph node status, Weide et al. identified tumor thickness, not ulceration, as the greatest independent prognostic factor for melanoma patients with SM and ITM [71]. It is unclear whether the interval between primary diagnoses and emergence of regional disease is a prognostic factor, as studies report variable results [77–79].

The natural history and progression of melanoma to ITM is not understood. One theory postulates that melanoma cells enter the superficial and deep lymphatic vessels but, along the way, become lodged—as an embolus might—in the lymphatic channels, either due to obstructing nodal disease or due to impaired lymphatic drainage from the removal of lymph nodes [80]. This second explanation is based on a study in which patients with ITM who had undergone wide local excision (WLE) with elective lymph node dissection (ELND) were compared to those that underwent WLE only (and lymph node dissection if lymph nodes became clinically palpable) [75]. ITM incidence was 27 and 10 %, respectively, in those

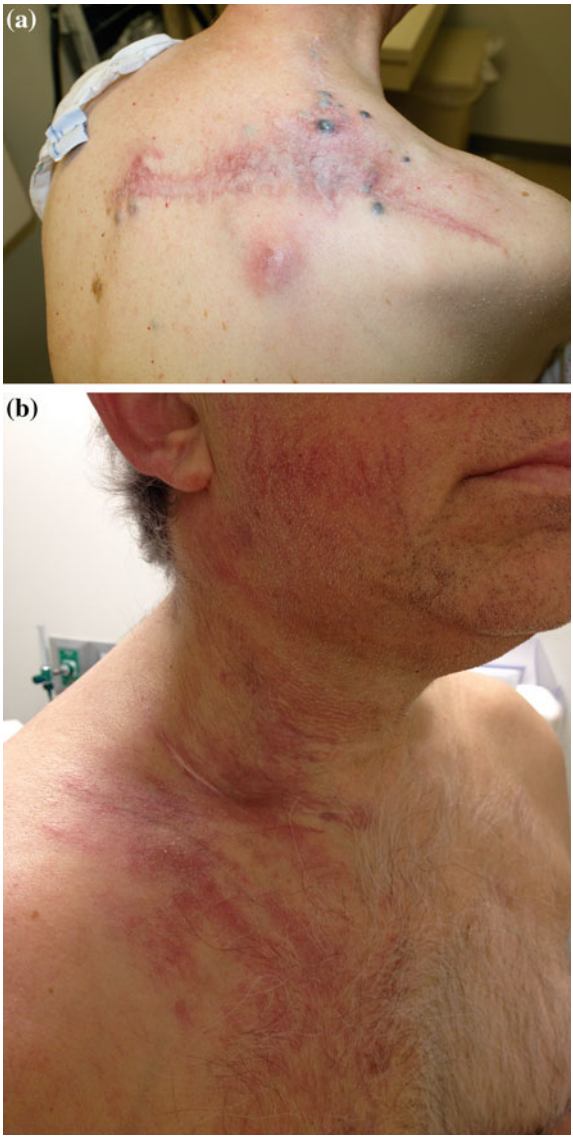

Fig. 4 **a** Numerous melanoma satellite metastases presenting as 0.3–1 cm subcutaneous blue-black nodules emanating from the original melanoma surgical site, in addition to a large 4-cm subcutaneous firm erythematous nodule inferior to the surgical site. **b** Satellite melanoma metastases presenting as streaklike erythematous plaques and nodules on the right neck and shoulder

groups, suggesting that surgical manipulation of regional nodes increased the risk of ITM. Other more recent studies have also suggested that ELND or SLND increases the risk of ITM [81, 82]. That being said, Pawlik et al. [83] are critical of these studies. They suggest that the comparison is unfair as most patients who undergo SLND or ELND have unfavorable tumor characteristics. In fact, a recent review of over 2000 patients with primary melanomas more accurately matched the two groups for tumor characteristics. The results showed that the rate of ITM in

patients treated with WLE alone was 4.9 % and not significant from those who underwent WLE and SLND, which was 3.6 % [84]. Another German study compared the 5-year overall ITM rate and showed no difference between the SLND and delayed lymphadenectomy groups [85].

2.2 Nodal Metastases

Before sentinel lymph nodes were introduced as part of the staging evaluation of solid tumors, the concept of "orderly progression of nodal metastases" was attractive in melanoma, since cutaneous lymphatic flow was better defined than any other solid organ. However, data suggest that 34–84 % of sentinel nodes are located in unexpected (discordant) sites [86]. Lymph node mapping is important as the presence of lymph node metastases, as well as the number of nodes involved, remains the single most important prognostic factor for patients with stages I, II, or III disease [71].

In a study of 466 patients with known primary cutaneous melanoma who developed metastases, 50 % metastasized to the regional lymph node, 22 % to loco-regional sites, and 28 % to distant sites [87]. The median latency period for nodal metastases, similar to loco-regional spread, was found to be approximately a year and a half.

MUP is a unique and not uncommon phenomenon, occurring in 10–20 % of patients presenting with palpable regional disease [33]. The clinical presentation of MUP with nodal metastases is characterized by palpable lymphadenopathy without evidence of further metastatic disease and without apparent primary melanoma. Prognostic significance is unclear compared with melanoma of known primary (MKP), largely due to studies with small sample sizes and lack of control for prognostic variables. In a large single institution study, Lee et al. found improved overall survival after appropriate lymphadenectomy in patients with MUP as compared to MKP [65], which suggests that, in the absence of distant metastases, surgical excision of the positive nodes may have been curative for some MUP patients.

Besides external factors, proposed causes of MUP include de novo transformation of ectopic nodal melanocytes or spontaneous regression of a primary lesion. In support of the first hypothesis, benign nevus cells have been found in lymph nodes [88, 89]. These melanocytes may originate from benign metastasis or differentiated neural crest cells [90]. The problem with this hypothesis, as Lee et al. point out, is that it does not explain the survival benefit in patients with MUP. The second explanation suggests immune-mediated regression of the primary tumor. Circulating factor has been found to be present in regressed melanomas and is important in mediating cytotoxic responses [91], and anti-melanoma antibodies are more prevalent in MUP than in MKP [92]. Moreover, the presence of tumor infiltrating lymphocytes has been associated with regression patterns [93]. These results suggest that a combination of humoral and cytotoxic responses is involved

in melanoma rejection. Finally, the most obvious explanation for improved survival in MUP is reduced disease burden, as patients with MUP undergo lymphadenectomy, which may also act to drive the activated immune system.

3 Non-cutaneous Melanomas

Normal melanocytes can be found in non-cutaneous sites, including the eye and mucosal tissues, such as the oral cavity, esophagus, nasal cavity and sinuses, genitals, and anus. Malignant transformation can occur in any of these sites. These subtypes of melanoma are less common than cutaneous melanoma and appear to be biologically distinct as well, given their patterns of spread and response to systemic therapy.

3.1 Uveal Melanomas

Two thousand new cases of uveal melanoma are diagnosed annually in the USA, an incidence that is much lower than cutaneous melanoma, and the incidence of uveal melanoma has been stable for the past decades, unlike cutaneous disease [94, 95]. This is the most common form of intraocular malignancy. The median age at presentation is in the 6th decade of life; however, it can also be diagnosed in young adults and children. The incidence does not differ between the genders, unlike cutaneous melanoma, which is more common in males. Familial cases of uveal melanoma are rarely reported. Only rare cases of uveal melanoma might have a heritable component, while family history is positive in 10 % of patients with cutaneous melanoma (Eagan et al. 1998). More recently, germline mutations in the BAP1 gene have been shown to be associated with uveal melanoma [96]. Approximately 50 % of patients with uveal melanoma will develop distant metastases, an incidence that is significantly higher than that of cutaneous melanoma [94].

Melanoma can arise in any of the three components of the uvea—the iris, the ciliary body, or the choroid. The latter is the most common site and represents the site of origin in 80 % of cases. The most common symptom at presentation is visual; patients typically report blurry vision or floaters when the disease is more advanced. However, uveal melanoma is often found on routine eye examination. Confirmation is accurately done by ultrasound and fluorescein angiography; fine needle aspiration biopsy is rarely needed and is no longer the standard of care to establish the diagnosis [97].

Staging of uveal melanoma is based on thickness and diameter, and these parameters correlate with survival. Given the lack of lymphatic drainage in the eye, dissemination to distant organs is hematogenous. Uveal melanomas appear to have a predilection to metastasizing to the liver more frequently than cutaneous

melanomas and tend to have different driver mutations than cutaneous melanomas [97]. Gene expression assays and cytogenetics play a role in determining the prognosis for non-metastatic uveal melanoma and are currently widely used in combination with measures of depth, location, and diameter to determine whether surveillance for distant disease is warranted [98].

Most frequently, metastatic uveal melanomas home to the liver and are diagnosed due to ascites, right upper quadrant pain or jaundice. Typically, at this point, the disease is very advanced and the prognosis is often poor, as the liver metastases are difficult to control with local or systemic therapy. Less frequently, the primary site of metastases is the lungs or skin. Under these circumstances, patients present either with lung nodules incidentally found on surveillance imaging or imaging done for other purposes or with respiratory symptoms, or cutaneous or subcutaneous nodules. Given that spread is hematogenous, metastatic uveal melanoma is typically not diagnosed by lymphadenopathy as the presenting sign.

In the era of targeted therapies, metastatic uveal melanoma is treated with different drugs than metastatic melanoma of cutaneous origin. Overall, the prognosis for metastatic uveal melanoma is worse than for metastatic cutaneous melanoma, as this disease is less responsive to immune therapy and currently available targeted therapies [99]. It similarly responds poorly to chemotherapy. A recent trial demonstrated superiority of an inhibitor of MEK over standard chemotherapy—dacarbazine or temozolomide—in progression-free survival [100]. Disease presentation is dependent on the location of metastases.

3.2 Mucosal Melanomas

Similar to uveal melanoma, mucosal melanomas are substantially less common than their cutaneous counterparts [101]. These tumors can arise from any mucosal surface, and their presentation depends largely on the site of origin. Just over half the cases originate in the head and neck region (oral, nasal, and sinus mucosa), while the other half originate in the anal/genital mucosal surfaces. Rare sites of origin of mucosal melanoma include the lower urinary tract, esophagus, small intestine, and gallbladder [102]. The presentation of mucosal melanomas depends on the site of origin. Clearly, mucosal melanoma originating in the oral cavity, anus, and vulva is less likely to go undetected for a prolonged period of time than that originating in internal sites.

Unlike cutaneous melanoma, mucosal melanomas are found with similar frequency in patients of Black, Hispanic, or Asian origin, compared to non-Hispanic Caucasians. The incidence of mucosal melanoma increases substantially with age, and the likelihood of developing metastatic disease is higher than for cutaneous melanoma. Specifically, the survival is particularly poor for melanomas that arise in the pharynx, gastrointestinal tract (including anus), urinary tract, and vagina. This appears to be independent of the stage at diagnosis [103].

Primary mucosal melanomas of the head and neck can be divided into two major categories: melanoma of the sino-nasal cavities and melanoma of the oropharynx. The majority of case series are fairly small, and the data on presentation are sparse. For example, in a series of patients with mucosal melanoma of the head and neck seen at Emory University during a 20-year period, only 30 cases were identified. Just over half the patients (53 %) presented with early-stage disease. Mucosal melanoma was more prevalent in men (60 % of patients), and the median age was in the late 60s [104]. In a series from the Royal Marsden Hospital, 89 patients were identified during a period of 50 years [105].

Data on the presentation of melanomas that arise in the genitalia are similarly sparse. In a review of gynecologic melanoma cases seen at Duke University, 43 cases were seen during a 25-year period. Most other published case series involve a similar or smaller number of patients [106]. Of the 43 cases identified at Duke, 70 % were vulvar in origin, 21 % vaginal, and 9 % cervical. Most of the patients were older (median age 61 years) and about two-thirds presented with localized disease only. Most of the patients were diagnosed upon routine gynecological examination and were treated with radical surgical procedures, which did not appear to improve the outcome. The prognosis was poor overall, with less than half the patients alive at 5 years. The prognosis, however, has been reported to be slightly superior in melanomas arising in the vulva than those arising in other sites [107]. Given the sparse data (110 cases in this series of mucosal melanomas from all origins), it is unclear whether the improved survival in vulvar melanomas is independent of thickness and other prognostic variables, as these melanomas are more likely to be seen on routine gynecologic examination.

Anal or anorectal mucosal melanomas are similarly rare, although the incidence appears to be increasing [108]. In a series from Memorial Sloan Kettering Cancer Center of 96 patients seen over a 17-year period, 43 % had anal melanoma, 33 % anorectal melanoma, and 24 % rectal melanoma. Overall, anal lesions tended to be thinner than lesions that were more proximal and tended to be of earlier stage with a lower likelihood of lymph node involvement. Interestingly, patterns of recurrence also differed based on anatomic location. However, the rates of recurrence and overall survival were not significantly different between the groups. The diagnosis of anal and anorectal melanoma is often delayed because these tumors can be amelanotic; 20–25 % of cases have no pigment and can be difficult to distinguish from benign masses [109].

4 Presentation of Metastatic Cutaneous Melanoma

4.1 Presentation of Metastatic Cutaneous Melanoma of Known Primary Site

The rate of metastatic relapse among patients with early-stage melanoma varies depending on key prognostic factors: Breslow depth, mitotic rate, presence of ulceration, and lymph node involvement. These factors make up the current

American Joint Committee on Cancer staging system. The likelihood of metastatic dissemination in patients with stage I–III melanoma is between 10 and 80 %, depending on these prognostic variables. For example, a patient with stage IA disease has a 10 % chance of developing metastatic disease over 15 years, a patient with stage IIA disease has a 40 % chance, and a patient with stage IIIC disease has approximately a 80 % chance of developing metastatic disease over a similar period [70, 72].

Patients with a history of primary melanoma are typically monitored for disease recurrence. Other than pathologic staging at diagnosis, blood tests and imaging are used to verify that a patient does not have stage IV disease. Patients are then followed with serial physical examinations, blood tests, and imaging. There is no consensus regarding which imaging studies to do and when to do them. The National Comprehensive Cancer Network (NCCN) recommends imaging for stage I patients only if they have symptoms. For stage II patients, a chest X-ray is optional; and for stage IIB and IIC and III, CT scans, PET scans, and MRI are recommended as clinically indicated (www.NCCN.org). Surveillance practices are therefore highly variable.

Presentation of metastatic cutaneous melanoma varies based on the location of metastases. Approximately half the patients have a single site of distant metastasis at initial presentation. Common sites of distant disease include cutaneous and subcutaneous tissues (approximately 20 %), lungs, liver, and brain (approximately 50 % each). Less common sites of metastatic dissemination include the bones, bowels, adrenal glands, and heart [110, 111].

The time to development of metastatic disease is highly variable. In a series of patients undergoing surveillance at Yale University, the majority of recurrences occurred by the end of the third year of follow-up, with 47 % recurring in the first year and 32 % in the second year. Median interval between the first visit and time to recurrence was 10.6 months, suggesting that follow-up should be more frequent and involve additional laboratory and imaging studies in the initial years after diagnosis [112].

4.2 Presentation of Metastatic Cutaneous Melanoma of Unknown Primary Site

Metastatic melanoma of unknown primary can present in lymph nodes alone or in distant organs as well as in lymph nodes. Nodal disease alone or limited dermal metastases alone are thought to be stage III melanoma of unknown primary, described in Sect. 3.2. This section focuses on stage IV metastatic melanoma of unknown primary.

Up to 20 % of metastatic melanomas are of unknown primary site, depending on the series [113]. Genotyping of metastatic melanomas of unknown primary indicates a mutational pattern similar to that of cutaneous melanoma, rather than other melanoma subtypes such as mucosal melanoma [114]. A number of potential

etiologies for melanoma of unknown primary site have been proposed; the most likely etiology is the regression of melanocytes at the primary site due to activity of tumor infiltrating lymphocytes, as reviewed by Lee et al. Other plausible explanations for melanoma of unknown primary site include malignant transformation of ectopic melanocytes, inability to differentiate a primary melanoma from benign nevi based on appearance, and resection of the primary lesion without pathologic examination of the biopsy site [33].

Presentation of stage IV melanoma of unknown primary is dependent on the site of metastasis. In a series of 398 cases from the John Wayne Cancer Center, over half had stage M1C disease at presentation (involvement of visceral organs other than the lungs and/or elevation of lactate dehydrogenase levels). Over half had more than one site of metastatic involvement, similar to the presentation of metastatic cutaneous MKP site. The prognosis in this series, as in other series of melanoma of unknown primary, appears to be superior to that of melanoma of known primary site, when adjusted for stage at presentation of metastatic disease [33] and [88, 115–118].

5 Summary

In this chapter, we summarized the clinical presentation of cutaneous, uveal, and mucosal melanomas. Each of these categories includes a mixed group of primary sites of origin, as melanoma can originate in pigmented cells at any physical location. The extent of disease at presentation influences the signs and symptoms with which patients will present. Overall, less extensive disease is associated with improved survival. Given the increasing incidence of this disease, heightened awareness is warranted, as it might lead to earlier detection.

References

1. Clemente C, Cook M, Ruiter D, Mihm M (2001) Histopathologic diagnosis of melanoma. World Health Organization melanoma programme publications, Milan, Trezzano SN
2. Bolognia JB, Jorizzo JL, Schaffer JV (2012) Dermatology. Saunders, Philadelphia
3. Ackerman A, Cerroni L, Kerl H (1994) Pitfalls in histopathologic diagnosis of malignant melanoma. Lea & Febiger, Philadelphia
4. Lipsker D, Engel F, Cribier B et al (2007) Trends in melanoma epidemiology suggest three different types of melanoma. Br J Dermatol 157(2):338–343
5. Swerdlow AJ, English J, Mackie RM et al (1986) Benign melanocytic naevi as a risk factor for malignant melanoma. Br Med J (Clin Res Ed) 292:1555–1559
6. Weiss J, Bertz J, Jung EG (1991) Malignant melanoma in southern Germany: different predictive value of risk factors for melanoma subtypes. Dermatologica 183:109–113
7. Argenziano G, Soyer HP, Chimenti S et al (2003) Dermoscopy of pigmented skin lesions: results of a consensus meeting via the internet. J Am Acad Dermatol 48:679–693
8. Demierre MF et al (2005) Early detection of thick melanomas in the United States: beware of the nodular subtype. Arch Dermatol 141(6):745–750
9. Koch SE, Lange JR (2000) Amelanotic melanoma: the great masquerader. J Am Acad Dermatol 42:731–734

10. Weinstock MA, Sober AJ (1987) The risk of progression of lentigo maligna to lentigo maligna melanoma. Br J Dermatol 116:303–310
11. Stolz W, Schiffner R, Burgdorf WH (2002) Dermatoscopy for facial pigmented skin lesions. Clin Dermatol 20:276–278
12. Shaw JH, Koea JB (1988) Acral (volar-subungual) melanoma in Auckland New Zealand. Br J Surg 75:69–72
13. Phan A, Touzet S, Dalle S et al (2007) Acral lentiginous melanoma: histopathological prognostic features of 121 cases. Br J Dermatol 157(2):311–318
14. Skender-Kalnenas TM, English DR, Heenan PJ (1995) Benign melanocytic lesions: risk markers or precursors of cutaneous melanoma? J Am Acad Dermatol 33:1000–1007
15. Bauer J, Garbe C (2004) Risk estimation for malignant transformation of melanocytic nevi. Arch Dermatol 140:127
16. Tsao H, Bevona C, Goggins W, Quinn T (2003) The transformation rate of moles (melanocytic nevi) into cutaneous melanoma. A population based estimate. Arch Dermatol 139:282–288
17. Garbe C, Buttner P, Weiss J et al (1994) Risk factors for developing cutaneous melanoma and criteria for identifying persons at risk: multicenter case-control study of the central malignant melanoma registry of the German Dermatological Society. J Invest Dermatol 102:695–699
18. Caballos P, Barnhill R (1993) Spontaneous regression of cutaneous tumors. Adv Dermatol 8:229–261
19. Nestle FO, Burg G, Dummer R (1999) New perspectives on immunobiology and immunotherapy of melanoma. Immunol Today 20:5–7
20. Marincola FM, Jaffee EM, Hicklin DJ, Ferrone S (2000) Escape of human solid tumors from T-cell recognition: molecular mechanisms and functional significance. Adv Immunol 74:181–273
21. Barr RJ (1994) The many faces of completely regressed malignant melanoma. Pathology (Phila) 2(2):359–370
22. Hayes PJ, Malone JC, Brown TC (2014) New blue-black nodule in a patient with a history of melanoma. JAMA Dermatol 150:767–768
23. McGovern VJ, Shaw HM, Milton GW (1983) Prognosis in patients with thin malignant melanoma: influence of regression. Histopathology 7:673–680
24. Abramova L, Slingluff CLJR, Patterson JW (2002) Problems in the interpretation of apparent "radial growth phase" malignant melanomas that metastasize. J Cutan Pathol 29:407–414
25. Ceballos PI, Barnhill RL (1993) Spontaneous regression of cutaneous tumors. Adv Dermatol 8:229–261
26. Boon T, Cerottini JC, Van den Eynde B et al (1994) Tumor antigens recognized by T lymphocytes. Annu Rev Immunol 12:337–365
27. Menzies SW, McCarthy WH (1997) Complete regression of primary cutaneous malignant melanoma. Arch Surg 132:553–556
28. Guitart J, Lowe L, Piepkorn M et al (2002) Histological characteristics of metastasizing thin melanomas. Arch Dermatol 138:603–608
29. Clark WH, Elder DE, Guerry D et al (1989) Model predicting survival in stage I melanoma based on tumor progression. J Natl Cancer Inst 81:1893–1904
30. Ronan SG, Eng AM, Briele HA et al (1987) Thin malignant melanomas with regression and metastases. Arch Dermatol 123:1326–1330
31. Fontaine D, Parkhill W, Greer W et al (2003) Partial regression of primary cutaneous melanoma. Am J Dermatopathol 25:371–373
32. Shaw HM, McCarthy WH, McCarthy SW et al (1987) Thin malignant melanomas and recurrence potential. Arch Surg 122:1147–1150
33. Lee CC, Faries MB, Wanek LA, Morton DL (2008) Improved survival after lymphadenectomy for nodal metastasis from an unknown primary melanoma. J Clin Oncol 26:535–541

34. Prens SP, van der Ploeg AP, van Akkooi AC, van Montfort CA, van Geel AN et al (2011) Outcome after therapeutic lymph node dissection in patients with unknown primary melanoma site. Ann Surg Oncol 13:3586–3592
35. High WA, Steward D, Wilbers CRH et al (2005) Completely regressed primary cutaneous malignant melanoma with nodal and/or visceral metastases: a report of 5 cases and assessment of the literature and diagnostic criteria. J Am Acad Dermatol 53(1):89–100
36. McClain SE, Mayo KB, Shada AL et al (2012) Amelanotic melanomas presenting as red skin lesions: a diagnostic challenge with potentially lethal consequences. Int J Dermatol 51 (4):420–426
37. Bastian BC (2002) Molecular cytogenetics as a diagnostic tool for typing melanocytic tumors. Recent Results Cancer Res 160:92–99
38. Bauer J, Bastian BC (2006) Distinguishing melanocytic nevi from melanoma by DNA copy number changes: comparative genomic hybridization as a research and diagnostic tool. Dermatol Ther 19:40–49
39. Sangüeza M, Zelger B (2007) Melanoma simulating atypical fibroxanthoma. Am J Dermatopathol 29(6):551–554
40. Diaz-Cascajo C, Weyers W, Borghi S (2003) Pigmented atypical fibroxanthoma: a tumor that may be easily mistaken for malignant melanoma. Am J Dermatopathol 25:1–5
41. McGregor DH, Cherian R, Romanas MM et al (2008) Amelanotic malignant melanoma: two collision tumors presenting as basal cell carcinoma and atypical fibroxanthoma. Ann Clin Lab Sci 38(2):157–162
42. Hiscutt EL, Adams JR, Ryan JM, Langtry JA et al (2009) Atypical fibroxanthoma, lentigo maligna melanoma and squamous cell carcinoma arising in the site of a thermal burn treated with skin grafts. Br J Oral Maxillofac Surg 47(2):157–158
43. Kossard S (2002) Atypical lentiginous junctional naevi of the elderly and melanoma. Aust J Dermatol 43(2):93–101
44. Pralong P, Bathelier E, Dalle S et al (2012) Dermoscopy of lentigo maligna melanoma: report of 125 cases. Br J Dermatol 167(2):280–287
45. Quinn MJ, Crotty KA, Thompson JF, et al (1998) Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 patients. Cancer 83:1128–35
46. Jaimes N, Chen L, Dusza SW, Carrera C et al (2013) Clinical and dermoscopic characteristics of desmoplastic melanomas. JAMA Dermatol 149(4):413–421
47. McCarthy SW, Scolyer RA, Palmer AA (2004) Desmoplastic melanoma: a diagnostic trap for the unwary. Pathology 36(5):445–451
48. Gartner MF, Fearns C, Wilson EL, et al (1992) Unusual growth characteristics of human melanoma xenografts in the nude mouse: a model for desmoplasia, dormancy and progression. Br J Cancer 65:487–90
49. Fearns C, Dowdle EB The desmoplastic response: induction of collagen synthesis by melanoma cells in vitro. Int J Cancer 50:621–7
50. Bryant E, Ronan SG, Felix EL, Manaligod JR (1982) Desmoplastic malignant melanoma: a study by conventional and electron micro-scopy. Am J Dermatopathol 4:467–474
51. From L, Hanna W, Kahn HJ, Gruss J, Marks A, Baumal R (1983) Origin of the desmoplasia in desmoplastic malignant melanoma. Hum Pathol 14:1072–1080
52. De Almeida LS, Requena L, Rutten A et al (2008) Desmoplastic malignant melanoma: a clinicopathologic analysis of 113 cases. Am J Dermatopathol 30:207–215
53. Zettersten E, Sagebiel RW, Miller III Jr et al (2002) Prognostic factors in patients with thick cutaneous melanoma (>4 mm). Cancer 94:1049–1056
54. Hudson DA, Krige JE (1995) Melanoma in black South Africans. J Am Coll Surg 180:65–71
55. Chang JW, Yeh KY, Wang CH et al (2004) Malignant melanoma in Taiwan: a prognostic study of 181 cases. Melanoma Res 14:537–541
56. Cress RD, Holly EA (1997) Incidence of cutaneous melanoma among non-Hispanic whites, Hispanics, Asians, and blacks: an analysis of California cancer registry data, 1988–93. Cancer Causes Control 8:246–252

57. Cress RD, Holly EA (1997) Incidence of cutaneous melanoma among non-Hispanic whites, Hispanics, Asians and blacks: an analysis of California cancer registry data, 1988–93. Cancer Causes Control 8:246
58. Curtin JA, Fridlyand J, Kageshita T et al (2005) Distinct sets of genetic alterations in melanoma. N Engl J Med 353:2135–2147
59. Torres-Cabala CA, Wang WL, Trent J et al (2009) Correlation between KIT expression and KIT mutation in melanoma: a study of 173 cases with emphasis on the acral-lentiginous/mucosal type. Mod Pathol 22:1446–1456
60. Stern DK, Creasey AA, Quijije J et al (2011) UVA and UVB penetration of normal human cadaveric fingernail plate. Arch Dermatol 147(4):439–441
61. Gosselink CP, Sindone JL, Meadows BJ et al (2009) Amelanotic subungual melanoma: a case report. J Foot Ankle Surg 48(2):220–224
62. Mohrle M, Hafner HM (2002) Is subungual melanoma related to trauma? Dermatology 204 (4):259–261
63. Bormann G, Marsch WC, Haerting J et al (2006) Concomitant traumas influence prognosis in melanomas of the nail apparatus. Br J Dermatol 155(1):76–80
64. Reintgen DS, Cox C, Slingluff CLJ, Seigler HF (1992) Recurrent malignant melanoma: the identification of prognostic factors to predict survival. Ann Plast Surg 28:45–49
65. Mathes SJ and Hentz VR (2006) Malignant melanoma. Saunders, Philadelphia
66. Erol B, Ufuk U, Husamettin T et al (2008) True hematogenous metastases of melanoma on contralateral skin graft donor site: a case report. Melanoma Res 18(6):443–446
67. Hall JG, Herman C, Cook JL et al (2005) Melanoma arising in a skin graft. Ann Plast Surg 54:92–96
68. Mueller BM, Reisfeld RA, Edgington TS et al (1992) Expression of tissue factor by melanoma cells promotes efficient hematogenous metastasis. Proc Natl Acad Sci USA 89:11832–11836
69. Bromberg ME, Konigsberg WH, Madison JF et al (1995) Tissue factor promotes melanoma metastasis by a pathway independent of blood coagulation. Proc Natl Acad Sci USA 92:8205–8209
70. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB et al (2009) Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 27:6199–6206
71. Weide B, Faller C, Büttner P, Pflugfelder A et al (2013) Prognostic factors of melanoma patients with satellite or in-transit metastasis at the time of stage III diagnosis. PLoS One 8 (4):e63137
72. Balch CM, Gershenwald JE, Soong SJ, Thompson JF, Atkins MB, Byrd DR, Buzaid AC, Cochran AJ, Coit DG, Ding S, Eggermont AM, Flaherty KT, Gimotty PA, Kirkwood JM, McMasters KM, Mihm MC Jr, Morton DL, Ross MI, Sober AJ, Sondak VK (2009) Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 27(36):6199–6206. doi:10.1200/JCO.2009.23.4799 Epub 2009 Nov 16
73. Wong JH, Cagle LA, Kopald KH et al (1990) Natural history and selective management of in transit melanoma. J Surg Oncol 44:146–150
74. Cascinelli N, Bufalino R, Marolda R et al (1986) Regional non-nodal metastases of cutaneous melanoma. Eur J Surg Oncol 12:175–180
75. Calabro A, Singletary SE, Balch CM (1989) Patterns of relapse in 1001 consecutive patients with melanoma nodal metastases. Arch Surg 124:1051–1055
76. Zogakis TG, Bartlett DL, Libutti SK et al (2001) Factors affecting survival after complete response to isolated limb perfusion in patients with in-transit melanoma. Ann Surg Oncol 8:771–778
77. Francken AB, Accortt NA, Shaw HM, Wiener M, Soong SJ et al (2008) Prognosis and determinants of outcome following locoregional or distant recurrence in patients with cutaneous melanoma. Ann Surg Oncol 15:1476–1484
78. Roses DF, Karp NS, Oratz R, Dubin N, Harris MN et al (1991) Survival with regional and distant metastases from cutaneous malignant melanoma. Surg Gynecol Obstet 172:262–268

79. Kretschmer L, Preusser KP, Marsch WC, Neumann C (2000) Prognostic factors of overall survival in patients with delayed lymph node dissection for cutaneous malignant melanoma. Melanoma Res 10:483–489
80. Karakousis CP, Choe KJ, Holyoke ED (1980) Biologic behavior and treatment of intransit metastasis of melanoma. Surg Gynecol Obstet 150:29–32
81. Estourgie SH, Nieweg OE, Valdes Olmos RA et al (2003) Review and evaluation of sentinel node procedures in 250 melanoma patients with a median follow-up of 6 years. Ann Surg Oncol 10:681–688
82. Estourgie SH, Nieweg OE, Kroon BB (2004) High incidence of in-transit metastases after sentinel node biopsy in patients with melanoma. Br J Surg 91:1370–1371
83. Pawlik TM, Ross MI, Thompson JF et al (2005) The risk of in-transit melanoma metastasis depends on tumor biology and not the surgical approach to regional lymph nodes. J Clin Oncol 23(21):4588–4590
84. Van Poll D, Thompson JF, McKinnon JG et al (2005) A sentinel node biopsy does not increase the incidence of in-transit metastasis in patients with primary cutaneous melanoma. Ann Surg Oncol 12(8):597–608
85. Kretschmer L, Beckmann I, Thoms KM et al (2005) Sentinel lymphonodectomy does not increase the risk of loco-regional cutaneous metastases of malignant melanomas. Eur J Cancer 41:531–538
86. Thompson JF, Uren RF, Shaw HM et al (1999) Location of sentinel lymph nodes in patients with cutaneous melanoma: new insights into lymphatic anatomy. J Am Coll Surg 189:195–204
87. Meier F, Will S, Ellwanger U et al (2002) Metastatic pathways and time courses in the orderly progression of cutaneous melanoma. Br J Dermatol 147:62–70
88. Das Gupta T, Bowden L, Berg JW (1963) Malignant melanoma of unknown primary origin. Surg Gynecol Obstet 117:341–345
89. Ridolfi RL, Rosen PP, Thaler H (1977) Nevus cell aggregates associated with lymph nodes: Estimated frequency and clinical significance. Cancer 39:164–171
90. Shenoy BV, Fort L 3rd, Benjamin SP (1987) Malignant melanoma primary in lymph node: the case of the missing link. Am J Surg Pathol 11:140–146
91. Maurer H, McIntyre OR, Rueckert F (1974) Spontaneous regression of malignant melanoma: pathologic and immunologic study in a ten year survivor. Am J Surg 127:397–403
92. Giuliano AE, Moseley HS, Irie RF et al (1980) Immunologic aspects of unknown primary melanoma. Surgery 87:101–105
93. Tefany FJ, Barnetson RS, Halliday GM et al (1991) Immunocytochemical analysis of the cellular infiltrate in primary regressing and non-regressing malignant melanoma. J Invest Dermatol 97:197–202
94. Singh AD, Topham A (2003) Incidence of uveal melanoma in the United States: 1973–1997. Ophthalmology 110:956–961
95. Jemal A, Siegel R, Xu J, Ward E (2010) Cancer statistics, 2010. CA Cancer J Clin 60:277–300
96. Battaglia A (2014) The importance of multidisciplinary approach in early detection of BAP1 tumor predisposition syndrome: clinical management and risk assessment. Clin Med Insights Oncol 28(8):37–47
97. Materin MA, Faries M, Kluger HM (2011) Molecular alternations in uveal melanoma. Curr Probl Cancer 35(4):211–224
98. Field MG, Harbor JW (2014) Recent developments in prognostic and predictive testing in uveal melanoma. Curr Opin Ophthalmol 25(3):234–239
99. Luke JJ, Triozzi PL, McKenna KC, Van Meir EG, Gershenwald JE, Bastian BC, Gutkind JS, Bowcock AM, Streicher HZ, Patel PM, Sato T, Sossman JA, Sznol M, Welch J, Thurin M, Selig S, Flaherty KT, Carvajal RD (2014) Biology of advanced uveal melanoma and next steps for clinical therapeutics. Pigment Cell Melanoma Res 28:135–147

100. Carvajal RD, Sosman JA, Quevedo JF, Milhem MM, Joshua AM, Kudchadkar RR, Linette GP, Gajewski TF, Lutzky J, Lawson DH, Lao CD, Flynn PJ, Albertini MR, Sato T, Lewis K, Doyle A, Ancell K, Panageas KS, Bluth M, Hedvat C, Erinjeri J, Ambrosini G, Marr B, Abramson DH, Dickson MA, Wolchok JD, Chapman PB, Schwartz GK (2014) Effect of **selumetinib** vs chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. JAMA 311(23):2397–2405
101. Chang AE, Karnell LH, Menck HR (1998) The national cancer data base report on cutaneous and noncutaneous melanoma: a summary of 84,836 cases from the past decade. The American College of surgeons commission on cancer and the American Cancer Society. Cancer 83:1664
102. Patrick RJ, Fenske NA, Messina JL (2007) Primary mucosal melanoma. J Am Acad Dermatol 56(5):828–834
103. Bishop KD, Olszewski AJ (2014) Epidemiology and survival outcomes of ocular and mucosal melanomas: a population-based analysis. Int J Cancer 134(12):2961–2971
104. McLean N, Tighiouart M, Muller S (2008) Primary **mucosal melanoma** of the head and neck. Comparison of clinical **presentation** and histopathologic features of oral and sinonasal **melanoma**. Oral Oncol 44(11):1039–1046. doi:10.1016/j.oraloncology.2008.01.014
105. Yii NW, Eisen T, Nicolson M, A'Hern R, Rhys-Evans P, Archer D, Henk JM, Gore ME (2003) **Mucosal** malignant **melanoma** of the head and neck: the Marsden experience over half a century. Clin Oncol (R Coll Radiol) 15(4):199–204
106. DeMatos P, Tyler D, Seigler HF (1998) Mucosal melanoma of the female genitalia: a clinicopathologic study of forty-three cases at Duke University Medical Center. Surgery 124 (1):38–48
107. Mehra T, Grözinger G, Mann S, Guenova E, Moos R, Röcken M, Claussen CD, Dummer R, Clasen S, Naumann A, Garbe C (2014) Primary localization and tumor thickness as prognostic factors of survival in patients with mucosal melanoma. PLoS One 9(11):e112535
108. Cagir B, Whiteford MH, Topham A, Rakinic J, Fry RD (1999) Changing epidemiology of anorectal melanoma. Dis Colon Rectum 42:1203–1208
109. Brady MS, Kavolius JP, Quan SH (1995) Anorectal melanoma: a 64-year experience at Memorial Sloan-Kettering Cancer Center. Dis Colon Rectum 38:146–151
110. Tas F (2012) Metastatic behavior in melanoma: timing, pattern, survival, and influencing factors. J Oncol 2012(647684)
111. Flanigan JC, Jilaveanu LB, Faries M, Sznol M, Ariyan S, Yu JB, Knisely JP, Chiang VL, Kluger HM (2011) Melanoma brain metastases: is it time to reassess the bias? Curr Probl Cancer 35(4):200–210
112. Poo-Hwu WJ, Ariyan S, Lamb L, Papac R, Zelterman D, Hu GL, Brown J, Fischer D, Bolognia J, Buzaid AC (1999) Follow-up recommendations for patients with American Joint Committee on cancer stages I-III malignant melanoma. Cancer 86:2252–2258
113. Lee CC, Faries MB, Wanek LA et al (2009) Improved survival for stage IV melanoma from an unknown primary site. J Clin Oncol 27:3489–3495
114. Egberts F, Bergner I, Krüger S, Haag J, Behrens HM, Hauschild A, Röcken C (2014) Metastatic melanoma of unknown primary resembles the genotype of cutaneous melanomas. Ann Oncol 25(1):246–250
115. King R, Page RN, Googe PB et al (2005) Lentiginous melanoma: a histologic pattern of melanoma to be distinguished from lentiginous nevus. Mod Pathol 18(10):1397–1401
116. Satzger I, Völker B, Kapp A, Gutzmer R (2007) Tumoral melanosis involving the sentinel lymph nodes: a case report. J Cutan Pathol 34(3):284–286
117. Essner R, Lee JH, Wanek LA, Itakura H, Morton DL (2004) Contemporary surgical treatment of advanced-stage melanoma. Arch Surg 139:961–966
118. Egan KM, Seddon JM, Glynn RJ, Gragoudas ES, Albert DM (1988) Epidemiologic aspects of uveal melanoma. Surv Ophthalmol 32:239–251