Chapter 6
Melanoma

Jennifer Divine and Anna S. Clayton

Abstract Melanoma most commonly presents as a new or changing pigmented lesion on sun exposed skin. The skin cancer can be categorized into varying subtypes based on its clinical appearance and anatomical location. The prognosis is similar amongst the subtypes with tumor thickness as the most important factor for survival. Melanoma staging depends upon the patient's symptoms, clinical exam and clinician's index of suspicion. Surgery is the first line treatment for localized melanoma. Advances in tumor genetics and immunology have led to the development of targeted therapies for metastatic disease.

Keywords Invasive · Melanoma · Nevi · Genetic mutations · *BRAF* · *MAPK* · *MEK* · *NRAS* · *Kit CDKN2A* · Risk factors · UV radiation · Dysplastic nevi · ABCD · Dermoscopy · Melanoma in situ · Nodular melanoma · Metastatic melanoma · Histology · Immunohistochemistry · Breslow depth · Staging · TNM · Prognosis · Survival · Sentinel lymph node · Wide local excision · Margins · Radiation therapy · Chemotherapy · Adjuvant therapy · Immunotherapy · Cytokines · Cancer vaccine · Oncolytic viral therapy · Targeted therapy

Introduction

Melanoma is the most lethal skin cancer. Melanoma most commonly presents on the skin but can arise in any location where melanocytes are present, including mucosa, uvea, and leptomeninges. Melanoma can present as a new or changing nevus. The prognosis depends upon how deeply the tumor invades the underlying dermis and subcutaneous structures. Invasive lesions carry the risk of metastasis and increased morbidity and mortality.

J. Divine (✉)
Divine Dermatology and Surgical Institute, Fort Collins, CO, USA

A. S. Clayton
Dermatology, Vanderbilt University of Medicine, Nashville, TN, USA

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Epidemiology

Global incidence rates of melanoma are rising. In the United States, non-Hispanic whites account for over 95% of disease occurrences, but minority groups are more likely to present with advanced-stage disease [1]. Melanoma is more common in men than women. In patients less than 40 years old, women have a greater melanoma incidence than men likely due to differences in UV exposure and hormonal factors [1, 2]. Melanoma is one of the most common cancers in young adults and has an average age of onset nearly a decade before most solid organ malignancies [3]. With improved screening, incidence rates of thin melanomas <1 mm are increasing faster than thick lesions. Despite earlier detection, death rates from melanoma are increasing for white men, those aged >65 years, and for thin lesions. Death rates have stabilized for younger age groups and thick lesions [4].

Pathogenesis

Melanoma pathogenesis is traced to changes in copies of DNA and several distinct genomic aberrations based upon body location and variations in intensity and duration of UV exposure [5]. The mitogen-activated protein kinase (*MAPK)* pathway plays a key role in normal melanocyte function and melanoma transformation. The most common genetic alteration, present in 40–60% of all melanomas, is a single-codon substitution: V600E of the *BRAF* gene. This results in subsequent dysregulation of *MAPK* signaling pathway leading to cellular proliferation, growth, and migration [6]. *NRAS* lies just upstream of *BRAF* in the *MAPK* pathway and is the second most common mutation. *NRAS* and *BRAF* are predominant mutations in intermittently sun-exposed skin [5]. *CDKN2A* gene encodes downstream p16 tumor suppressor protein which plays an inhibitory role in the *MAPK* pathway. Mutation in the *CDKN2A* gene is the cause of rare cases of inherited familial melanoma but may also be acquired [7]. *KIT* gene encodes tyrosine kinase receptors which is the first step in *MAPK* and *P13K* signaling and plays a critical role in melanoma of chronically sun-exposed skin, mucosa, and uvea [8]. Other key mutations identified lie in the *GNAQ* and *ERBB4* gene [9]. These discoveries led to the development of molecular targeted therapies such as the BRAF kinase inhibitors dabrafenib and vemurafenib.

Risk Factors

Risk factors for melanoma are environmental and genetic. UV radiation is a known carcinogen responsible for over 85% of melanomas. Having more than five sunburns at any period in life doubles the risk of melanoma, while daily use of SPF 15

or above decreases the risk of invasive melanoma by 73% [10–12]. Intermittent intense UV exposure, often associated with shirtless recreational activities, increases the risk of melanoma on the trunk. Chronic lower level and continuous occupational UV exposure increases risk on the head and neck [1]. The risk of melanoma increases with the number of indoor tanning sessions and younger age when indoor tanning behavior starts [13].

The tendency to burn, light skin, light eyes, and light hair (especially red hair) are all phenotypic traits that increase susceptibility to UV radiation and therefore increase the risk of melanoma. Freckling and a large number of nevi indicate past UV exposure. Personal history of melanoma is a strong predictor for subsequent melanoma. Family history of melanoma has a twofold effect correlating with similar skin phenotype as well as an inborn genetic tendency for melanoma. Patients with dysplastic nevus syndrome (aka familial atypical multiple mole-melanoma syndrome) exemplify the strong impact of genetics. Inheritance may be autosomal dominant or sporadic. Two melanoma susceptibility genes are identified in melanoma-prone families: *CDKN2A* and more rarely *CDK4*. There are numerous remaining melanoma families without either of these mutations, so more research is needed [14, 15]. Melanoma in children, people with darker skin tones, and the existence of non-cutaneous melanomas (in the eye, mouth, nasal cavity, vagina, and anogenital locations) point to further unidentified genetic and possible environmental causes that require more research.

The immune system plays an important role in melanoma development and treatment. Immunosuppressed patients have an increased risk of developing melanoma, especially iatrogenically immunosuppressed solid organ transplant recipients and leukemia patients. Appropriately activated $CD8^+$ cytotoxic T cells recognize melanoma antigens and kill tumor cells resulting in complete or incomplete tumor regression. $CD4^+$ helper cells and antibodies also play key roles in host immunity to melanoma. Exploiting these host immune responses is the basis for immunotherapy [16, 17].

Clinical Presentation

Melanoma has a broad clinical presentation. Most commonly, melanoma presents on sun-exposed skin as a changing nevus or a new, changing pigmented lesion. First introduced in 1985, the ABCD acronym represented clinical features for melanoma diagnosis. Asymmetry (A), border irregularity (B), color variability (C), and diameter greater than 6 mm (D) are associated with worrisome clinical features for melanoma [18]. Diameter is a controversial parameter as melanomas can be smaller than 6 mm. Later, E was added to the acronym for evolution as a changing lesion is concerning [19]. The ABCDE of melanoma helped remind the public of melanoma's features but is not inclusive of all pigmented tumors. The acronym was expanded further to include elevated, firm (F), and growing(G) to encompass clinical features for nodular and amelanotic melanomas. Grob et al. observed that an

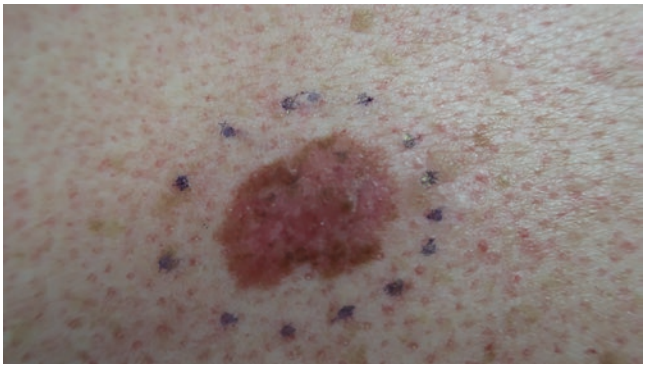

Fig. 6.1 Superficial spreading melanoma (Photo courtesy of Anna Dewan, MD)

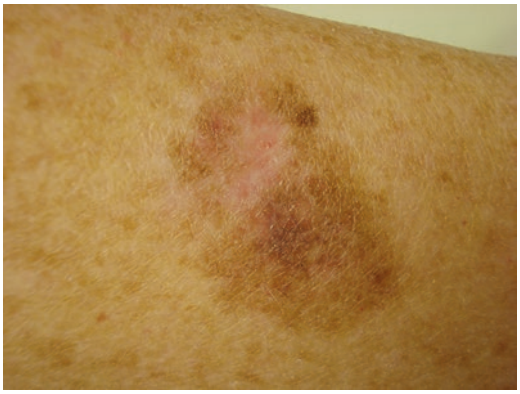

Fig. 6.2 Lentigo maligna melanoma (Photo courtesy of Darrel Ellis, MD)

individual's nevi resemble one another, and the clinically different or "ugly duckling" nevus is worrisome for melanoma [20]. For instance, a small, dark nevus is an outlier among a field of large, light brown nevi, the patient's signature nevi. The "ugly duckling" sign is especially helpful in evaluating patients with multiple nevi including familial melanoma syndrome.

The four most common types of invasive melanoma include superficial spreading (Fig. 6.1), nodular (Fig. 6.2), lentigo maligna (Fig. 6.3), and acral lentiginous melanoma (Fig. 6.4). Most invasive melanomas arise from melanoma in situ, a tumor with malignant melanocytes localized to the epidermis and/or hair follicle epithelium (Chapter 5). After a prolonged horizontal growth phase, melanoma in situ can transform into a vertical growth phase leading to invasive lentigo maligna, superficial spreading, or acral lentiginous subtypes. Clinical indications of invasion include areas of induration or a firm papule within the lesion.

Nodular melanoma grows quickly in a vertical manner and often appears as a dome-shaped, blue, black, or red firm papule most commonly on the trunk, head, or neck. Nodular melanoma accounts for 10–15% of melanomas but is responsible for over 40% of melanoma deaths. Median Breslow depth at the time of diagnosis is

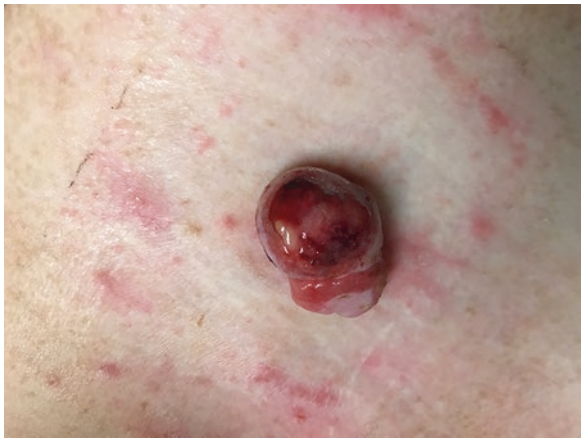

Fig. 6.3 Nodular melanoma (Photo courtesy of Zachary Jones, MD)

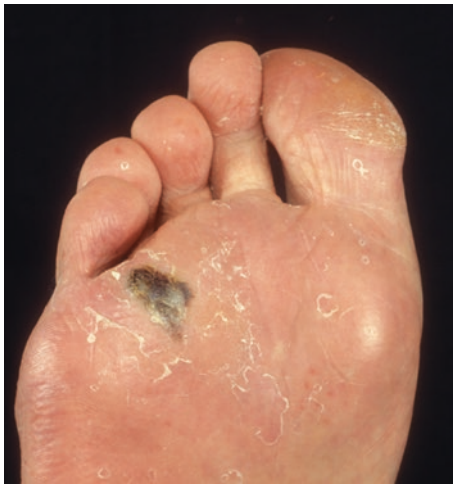

Fig. 6.4 Acral lentiginous melanoma (Source: Bristow IR, Acland K. Acral lentiginous melanoma of the foot and ankle: A case series and review of the literature. Journal of Foot and Ankle Research. 2008;1:11, Fig. 1, Open Access under the Creative Commons Attribution License 2.0)

significantly greater (2.6 mm) than superficial spreading melanoma (0.6 mm) [21]. Breslow depth and ulceration at the time of diagnosis are the most critical factors affecting prognosis of localized melanoma [22]. Nodular melanoma forming within giant congenital nevi usually begins as a deep dermal process resulting in poor survival [23].

Less common melanoma types include amelanotic melanoma (Fig. 6.5), mucosal melanoma, desmoplastic and neurotropic melanoma, and nail matrix melanoma (Fig. 6.6). Amelanotic melanoma lacks pigment and presents as a pink to erythematous macule or patch. Mucosal melanoma can present in the mouth, nasopharynx, and vagina. Desmoplastic and neurotropic melanoma can present as a flesh colored

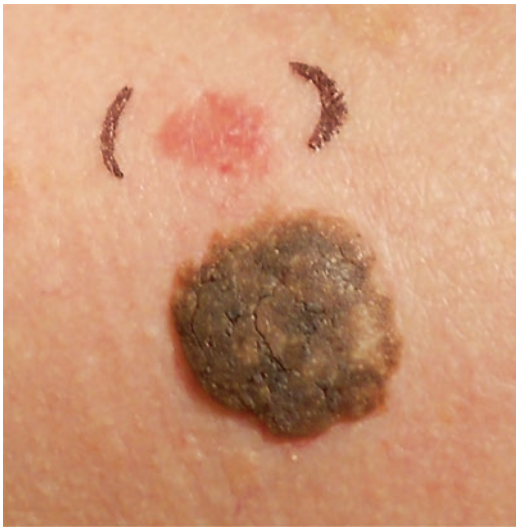

Fig. 6.5 Amelanotic melanoma (Clinical photo of amelanotic melanoma with adjacent seborrheic keratosis)

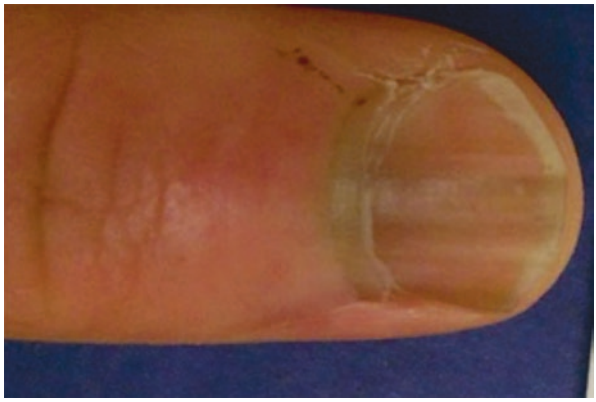

Fig. 6.6 Nail matrix melanoma

or pink to pigmented firm nodule. Desmoplastic and neurotropic melanoma can have an overlying lentigo maligna. Nail matrix melanoma presents as new or evolving melanonychia. Involvement of the nail cuticle is a worrisome feature for melanoma.

Diagnostic Techniques

Dermoscopy is an emerging field and has aided dermatologist in separating benign from malignant lesions. Regular use of dermoscopy helps reveal malignant features that are not visible to the naked eye leading to earlier melanoma diagnosis while simultaneously decreasing excision of benign lesions if reassuring features are seen

[24]. Features suggesting invasion are asymmetry along two axes, two or more colors, and pseudopods [25]. Nodular melanomas are more likely to have symmetric shape and pigment network as seen clinically but may have large vessels, predominant peripheral vessels, homogenous blue pigmentation, blue-white veil, black color, pink color, and milky red-pink areas [26].

When malignancy is suspected, various biopsy techniques are employed. The American Academy of Dermatology guidelines state that the preferred biopsy technique is narrow excisional biopsy that encompasses the entire breadth of the lesion with clinically negative margins to the depth sufficient to ensure the lesion is not transected. This may be accomplished by elliptical or punch excision with sutures or shave removal to depth below the anticipated plane of lesion. While no one option is more correct, the outcome should always be to provide the pathologist with the entirety of the lesion (usually extending 1–3 mm past clinically evident pigment) to obtain the most correct and complete diagnosis to best guide patient care. Guidelines further state that partial sampling (incision biopsy) is acceptable in select clinical circumstances: facial or acral location, low clinical suspicion or uncertainty of diagnosis, or very large lesions [27].

Histology

Histologic examination of suspected melanoma is required to differentiate from clinical mimickers (solar lentigo, seborrheic keratosis, thrombosed hemangioma, dermatofibroma, pigmented actinic keratosis, pigmented squamous cell carcinoma, and pigmented basal cell carcinoma). Melanoma is defined by an increased number of atypical, pleomorphic, single or nested melanocytes. The changes range from extremely subtle to profound. Differentiation from dysplastic nevus, which also has atypical melanocytes, and from benign junctional melanocytic hyperplasia of sun-damaged skin, which has an increased number of single-cell but relatively normal-appearing melanocytes, remains a challenge and results in significant variability in pathologist interpretation [28–30]. When invasive lesions are arising from melanoma in situ, an asymmetric, poorly circumscribed proliferation of melanocytes of varying size and shape, often larger than their benign counterpart with abundant eosinophilic and finely granular cytoplasm, is seen in the overlying epidermis often extending far beyond the dermal component. Less often the cells are small or spindle-shaped. The melanocytes grow in linear arrays of single cells with occasional irregular and confluent nesting and uneven distribution along the dermal-epidermal junction (Fig. 6.7). Upward extension in the epidermis, referred to as pagetoid spread, and downward migration into adnexal structures are other indicators of malignancy (Fig. 6.8).

Compared to the wide lateral extension of epidermal tumor present in invasive melanoma arising from melanoma in situ, nodular melanomas have a well-defined overlying epidermal involvement that does not extend past the dermal component. This correlates with the clinical exam. Ulceration may be encountered. A complete

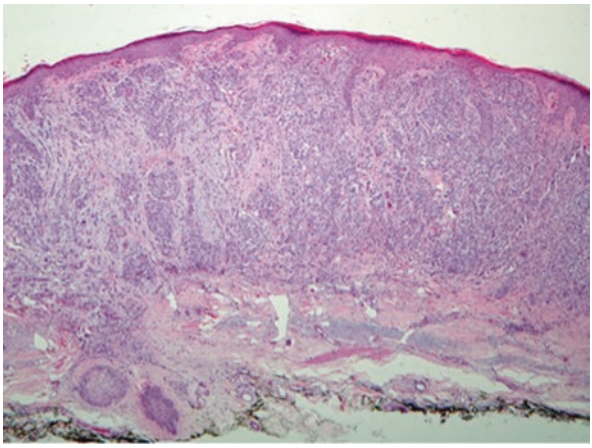

Fig. 6.7 Invasive superficial spreading melanoma (Photo courtesy of Jeffrey Zwerner, MD, PhD)

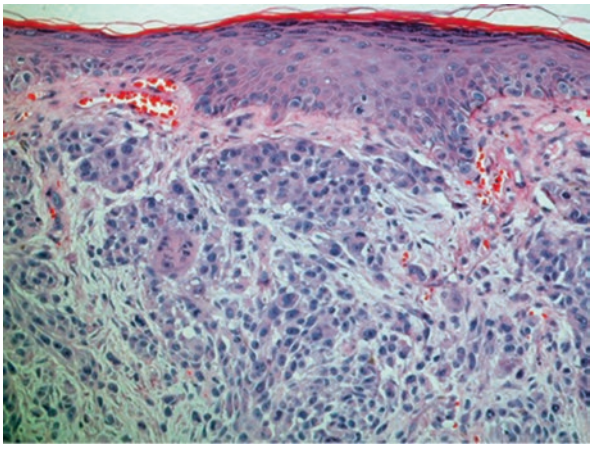

Fig. 6.8 Invasive superficial spreading melanoma (Photo courtesy of Jeffrey Zwerner, MD, PhD)

lack of epidermal involvement raises concerns for a metastatic lesion. Otherwise, the invasive components are indistinguishable. Nests of melanocytes that do not mature with increasing depth characterize dermal invasion. In benign compound and intradermal nevi, the size of the nests and size of the nuclei taper with depth down to lymphocyte-sized single cells at the base. In contrast, melanocytes at the base of an invasive melanoma remain in large nests and sheets with the same large nuclei and abundant cytoplasm seen in the more superficial portion. The Breslow depth is measured in millimeters from the granular layer of the epidermis (or the surface of ulceration) to the deepest area of tumor invasion [31]. Mitotic activity varies widely and necrotic melanocytes can be present. An asymmetrical lymphocytic inflammatory infiltrate supports the diagnosis of melanoma. It can be brisk, mild, or even absent. Areas of regression might be identified. Pleomorphic spindle-shaped cells, epithelioid cells, and balloon cells can all be seen in a single lesion [32]. Structured pathology reporting protocols aim to improve clinical management,

Table 6.1 College of American Pathologists melanoma reporting protocol

Procedure
Specimen laterality
Tumor site
Tumor size
Macroscopic satellite nodules
[a]Macroscopic pigmentation
Histologic type
Maximum tumor thickness
[a]Anatomic level
Ulceration
Margins
Mitotic rate
Microsatellitosis
Lymph-vascular invasion
[a]Perineural invasion
[a]Tumor-infiltrating lymphocytes
[a]Tumor regression
[a]Growth phase
Lymph nodes (only if present in specimen)
TNM staging

[a]Data elements are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management

data collection, and research worldwide. In the United States, the College of American Pathologists encourages all pathologists to include details shown in Table 6.1 in every melanoma report.

A wide spectrum of histologic morphology of melanoma promotes the use and development of immunohistochemistry to distinguish it from the many mimickers and aid in differentiating benign from malignant melanocytic proliferations. Histologic differential diagnosis of melanoma includes numerous malignant entities including carcinomas like neuroendocrine tumors, sarcomas, lymphomas, and germ cell tumors, as well as a variety of benign tumors. S100 is a widely used marker with excellent sensitivity for melanoma but poor specificity, staining nerve sheath, myoepithelial, adipocyte, and Langerhans cell tumors. It is the most sensitive marker for desmoplastic melanoma [33]. HMB-45, a monoclonal antibody to melanoma, is less sensitive but more specific than S100 and can be used to distinguish benign from malignant melanocytic lesions [34]. MelanA/MART1 is highly sensitive and specific for melanocytes but stains benign and malignant cells alike. Ki-67, a stain for active cellular proliferation, remains the most useful stain in distinguishing benign from malignant melanocytes [35]. Some studies suggest that the density of

Ki-67 immunoreactivity may serve as a prognostic indicator for metastasis [36]. Other less commonly used markers include tyrosinase, MITF, NKI/C3, and vimentin.

Staging and Prognosis

The American Joint Committee on Cancer (AJCC) published the eighth edition of the melanoma staging system in 2017 [37]. The updated staging system incorporates the seventh edition with new evidence-based recommendations. The staging system includes primary tumor (T) characteristics, regional lymph node (N), and distant metastatic sites (M) to determine the patient's prognosis. Primary tumor thickness and histopathologic evidence of ulceration determine the tumor (T) classification (Table 6.2)**.** Tx and T0 were added to the primary tumor staging in the eighth addition. Tx designates when the primary tumor thickness cannot be assessed and T0 when there is no evidence of a primary tumor. The tumor mitotic rate is an important prognostic factor in all tumor categories but is no longer included in the staging system. T1 tumors were subdivided in the eighth edition to incorporate differences in melanoma-specific survival in patients with thin melanomas [38]. Regional lymph node involvement is classified as not clinically present but found microscopically or clinically detected and confirmed histologically (Table 6.3). The specific size of metastasis is no longer associated with lymph node staging.

Table 6.2 American Joint Committee on Cancer eighth edition melanoma staging guidelines

Primary tumor (T)		
T classification	Thickness (mm)	Ulceration status
TX	Not applicable	Not applicable
T0	Not applicable	Not applicable
Tis	Not applicable	Not applicable
T1 T1a T1b	≤1.0 mm <0.8 mm <0.8 mm 0.8 to 1 mm	Unknown Without ulceration With ulceration With or without ulceration
T2 T2a T2b	>1 to 2 mm >1 to 2 mm >1 to 2 mm	Unknown Without ulceration With ulceration
T3 T3a T3b	>2 to 4 mm >2 to 4 mm >2 to 4 mm	Unknown Without ulceration With ulceration
T4 T4a T4b	>4 mm >4 mm >4 mm	Unknown Without ulceration With ulceration

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Table 6.3 American Joint Committee on Cancer eighth edition melanoma staging guidelines

Regional lymph node (N)		
N category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite and/or microsatellite metastases
NX	Regional nodes not assessed	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult node detected by SLN	No
N1b	One clinically detected	No
N1c	No regional node disease	Yes
N2	Two to three tumor-involved nodes or in-transit, satellite, or microsatellite metastases with one tumor-involved node	
N2a	Two to three clinically occult nodes detected by SLN biopsy	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected node	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, or microsatellite metastases with two or tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult nodes detected by SLN	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number matted nodes	No
N3c	Two or more clinically occult or clinically detected and /or presence of any number of matted nodes	Yes

Microsatellite, satellite, and in-transit and/or subcutaneous metastases are types of melanoma metastases between the primary tumor and the draining lymph node basin. These localized metastases are stratified according to the number of tumor-involved lymph nodes. Distant metastases are categorized by anatomical location. In the eighth edition, the metastases staging includes serum lactate dehydrogenase (LDH), an important independent factor for patients with metastatic melanoma. Melanoma metastasis is divided into M1a, metastases to distant skin, subcutaneous or lymph node; M1b, lung metastases; M1c, metastases to other visceral sites, excluding the central nervous system; and M1d, metastases to the central nervous system, with or without involvement of other sites (Table 6.4). The M1d is a new category and is associated with a poor prognosis. LDH serum levels subcategorize the metastasis groups into either 0 for a non-elevated LDH or 1 for an elevated LDH.

The TNM classification is then translated into clinical staging when clinical and radiologic data is the only evaluation of lymph nodes and pathological staging when

Table 6.4 American Joint Committee on Cancer Eighth Edition Melanoma Staging Guidelines

Distant metastasis (M)		
M category	Anatomic site	Lactate dehydrogenase level
M0	None	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to the skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)	Distant metastasis to the skin, soft tissue including muscle, and/or nonregional lymph node	Not elevated
M1a(1)	Distant metastasis to the skin, soft tissue including muscle, and/or nonregional lymph node	Elevated
M1b	Distant metastasis to the lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)	Distant metastasis to the skin, soft tissue including muscle, and/or nonregional lymph node	Not elevated
M1b(1)	Distant metastasis to the skin, soft tissue including muscle, and/or nonregional lymph node	Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not elevated
M1c(1)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not elevated
M1d(1)	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Elevated

pathologic information about regional lymph nodes is available (Table 6.5). The clinical and pathologic stage can then be used to provide the clinician and patient with a survival prognosis (Table 6.5). Melanoma in situ is stage 0. Stage I patients have ≤1 mm of invasion with or without ulceration or 1–2 mm of invasion without ulceration and are considered low risk. Stage II patients have increased risk of mortality with increasing Breslow depth and presence of ulceration. Stage III patients have regional metastasis and the most variable survival range. Stage IV patients have distant metastatic disease.

Independent and confounding risk factors that impact survival include tumor thickness, ulceration, anatomical location of the primary tumor, age at diagnosis, and gender. For localized disease (stages I and II), Breslow depth is the most powerful prognostic indicator for survival in patients with lesions ≤1 mm, while ulceration, age, and site are the most significant predictive factor for lesions 2–4 mm

Table 6.5 Clinical and pathological staging of melanoma with 5- and 10-year survival [27, 42]

Stage	5-year survival (%)	10-year Survival (%)	Clinical staging			Pathologic staging		
0			Tis	N0	M0	Tis	N0	M0
IA	97	95	T1a	N0	M0	T1a	N0	M0
1B	92	86	T1b T2a	N0	M0	T1b T2a	N0	M0
IIA	81	67	T2b T3a	N0	M0	T2b T3a	N0	M0
IIB	70	57	T3b T4a	N0	M0	T3b T4a	N0	M0
IIC	53	40	T4b	N0	M0	T4b	N0	M0
III			Any T	N1–3	M0			
IIIA	78	68				T1-4a T1-4a	N1a N2a	M0
IIIB	59	43				T1-4b T1-4b T1-4a T1-4a T1-4a	N1a N2a N1b N2b N2c	M0
IIIC	40	24				T1-4b T1-4b T1-4b Any T	N1b N2b N2c N3	M0
IV	15–20	10–15	Any T	Any N	Any M1	Any T	Any N	Any M1

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[27]. Older patients are more likely to present with thicker and ulcerated melanomas and are more likely to carry comorbidities that affect survival. Older patients are also more likely to be male and have a poor prognosis. Women tend to develop melanoma at a younger age, seek care at earlier stages, and have better outcomes. Tumors on the head, neck, and trunk are higher risk and occur more frequently in people older than 65 and in men. Those on the extremities occur more frequently in younger patients and females. Stage I disease has excellent 5-year survival at 92–97%. Stage II 5-year survival drops significantly with increasing thickness and ulceration from 81% for stage IIA down to 53% for stage IIC [39].

For patients with regional metastasis (stage III) which includes regional lymph node, satellite, and/or in-transit metastasis, three factors are most important for survival and listed in descending significance: (1) the number of metastatic nodes, (2) the tumor burden of the affected nodes, and (3) the ulceration of the primary tumor. Survival is best predicted with delineation of 1, 2, 3, and 4+ nodes. Ulceration is the only primary tumor characteristic that is an independent risk factor for survival of stage III patients. This heterozygous group of patients has a wide range of 5-year survival rates from 78% for stage IIIA down to 59% and 40% for stages IIIB and

IIIC, respectively. Stage IIIA patient survival is more closely linked to primary tumor characteristics such as thickness and ulceration, like stage II patients, and more closely matches stage II survival rates than those of stages IIIB and IIIC [31].

Stage IV disease is defined as distant metastasis. It has very poor 5-year survival rates at 15–20%. Metastasis to non-visceral sites (distant skin, subcutaneous tissue, and lymph nodes) has improved survival over metastasis to visceral sites. Metastasis to the lung has a slight 1-year survival advantage with rates more similar to non-visceral sites but drops to match that of other visceral sites by 2 years. Recently, elevated serum LDH is an independent and highly predictive indicator for poor survival [31].

Routine blood tests and imaging screening of asymptomatic patient with melanoma of any thickness are generally not recommended. Serum LDH is insensitive and nonspecific at detecting metastatic disease and only provides additional prognostic value when distant metastasis is already known. Routine chest radiograph is nonspecific, does not correlate with sentinel lymph node results, is cost ineffective, exposes patients to unnecessary radiation, and may result in unnecessary follow-up imaging or procedures. Workup should be driven based upon physical exam finding, review of system complaints, and index of suspicion [40].

Sentinel Lymph Node

Sentinel lymph node (SLN) biopsy for melanoma is controversial. It was developed as a conservative alternative to lymph node dissection, a practice that started in 1892 and carries 37% complication rate including lymphedema and infection. Sentinel lymph node biopsy is currently offered as an elective procedure for patients with primary tumor thickness ≥1 mm, or <1 mm with ulceration, and clinically negative lymph node exam. It provides prognostic information and predicts the status of the other regional lymph nodes. SLN biopsy is not offered when regional lymph node involvement is blatant or when distant spread is already known. SLN biopsy is not therapeutic and does not improve survival outcomes. If SLN biopsy is positive, a complete lymph node dissection is recommended, and the patient can be stratified into the correct stage III substage, allowing for survival information and clinical trial enrollment for emerging adjuvant therapy. SLN is not risk-free, however. It carries a 10% complication rate including delayed wound healing, infection, false negative results if the cancer has already metastasized to other lymph nodes in the basin or distant organs, false positives due to the normal and relatively common presence of benign nevi in the lymph nodes, and anaphylaxis to the blue dye [41–43].

Advocates for SLN biopsy claim benefits including more accurate staging. This provides patients, their family, and providers with information which may impact treatment of the melanoma as well as other comorbidities. SLN status is often used to identify patient who may benefit from additional therapies and allows for clinical trial enrollment. Positive SLN allows the opportunity for early complete lymph

node dissection. Some studies show early complete lymph node dissection improves morbidity and mortality over waiting until clinically evident lymphadenopathy is present in some patient subsets. Although no improved short-term or long-term survival exists with SLN biopsy, some have also found an increased disease-free survival time and an arguably improved quality of life during that period, making SLN biopsy preferred over observation alone [41, 44]. Other studies have not found improved survival with early complete lymph node dissection or improved disease-free survival with SLN biopsy [45, 46]. A recent prospective trial examining observation versus complete lymph node dissection after a positive SLN showed that immediate complete lymph node dissection increased the rate of regional disease control but did not increase melanoma-specific survival in sentinel lymph node positive patients [47].

Those opposed to SLN biopsy argue that Breslow thickness and ulceration provide adequate stratification information. Only 17% of patients who undergo SLN biopsy have positive results, and the vast majority of patients have N1a or N2a disease that matches their clinically stage I and II counterparts well enough. SLN biopsy has several potential complications. It is expensive, especially if general anesthesia is used. A positive SLN may lead to an unnecessary complete lymph node dissection which can cause greater adverse events. The premise behind the SLN biopsy was to have a procedure that would improve survival. But with evidence showing no survival benefit, less invasive and less expensive testing on primary and circulating tumor cells that could provide similar prognostic information would be preferred but is still under development [48, 49].

Treatment

Surgical

Surgical excision is the treatment of choice for primary localized melanoma. Wide local excision (WLE) is recommended as tumor cells often spread several millimeters, and at times even centimeters, past the clinically apparent melanoma. The goal is to achieve complete removal and reduce local recurrence of disease. Current guidelines recommend a 1 cm margin for lesions of ≤1 mm thickness, 1–2 cm margin for lesions 1.01–2.0 mm thickness, and 2 cm margins for tumors of >2 mm thickness. Greater than 2 cm margins is of no advantage. Surgical excision should extend to the depth of the muscular fascia whenever reasonable or at least to the level of the deep adipose tissue if abundant adipose tissue is present. Histologic examination should be thorough, and Mohs micrographic surgery or request for tissue specimen be cut "en face" by surgical pathology can be considered. Both techniques allow for 100% of the deep and lateral margin to be examined, rather than the <1% that is routinely examined with standard bread-loafing technique [27].

Radiation Therapy

Radiation therapy is used with notable success for unresectable local disease and as palliative care for distant metastasis. Whole brain radiotherapy, surgical resection, and more recently stereotactic radiosurgery are mainstay treatments for cerebral metastasis [50, 51]. Other indications include bone metastasis and spinal cord compression. Radiation therapy is not recommended as adjuvant therapy after lymph node dissection [52].

Chemotherapy

For patients with metastatic melanoma (stages III and IV), traditional cytotoxic chemotherapy agents have limited efficacy and use. Dacarbazine is the only FDA-approved chemotherapy agent for melanoma to be tried in advanced disease for palliative measures to slow tumor growth or temporarily decrease tumor burden, but a survival advantage has not been proven. Dacarbazine along with temozolomide, nab-paclitaxel, paclitaxel, cisplatin, carboplatin, and vinblastine may also be used alone or in combination with each other or added to newer therapies known as biochemotherapy or chemoimmunotherapy. Melphalan and actinomycin-D are used for isolated-limb-perfusion chemotherapy which can increase efficacy and reduce systemic toxicities for extremity-localized advanced disease [53, 54].

Immunotherapy

Due to poor response to cytotoxic chemotherapy and the recognized importance of host immunity in melanoma, particular attention has been paid to immunotherapy (modalities that boost patients own tumor-fighting capabilities). In addition to the medications already on the market described below, numerous other therapies are currently in clinical trial.

Cytokines

Cytokines interleukin-2 (IL-2) and interferon-alpha (IFN-alpha) were the first FDA-approved immune-stimulating drugs. Interleukin-2 enhances CD8+ T cells and NK cells and produces a 15–20% objective response rate and ~5% long-term, durable complete response. IL-2 must be given intravenously at high doses with substantial side effects limiting its use including fever, chills, malaise, flushing, hypotension, and capillary leak syndrome [55, 56]. Interferon-alpha has been more extensively

studied but with conflicting results leading to a sudden rise and then fall in popularity. Dosing schedules for high-dose, intermediate-dose, low-dose, and pegylated formulations have been suggested. Some evidence of a dose-response relationship exists with a significant recurrence-free survival with increased doses. It remains unclear if a worthwhile overall survival benefit is present [57]. Mechanism of action includes direct antiproliferative effect on tumor cells, enhanced NK activity, increased T helper lymphocytes and tumor-specific CD8+ T cells, and increased tumor-infiltrating T lymphocytes [58]. Side effects of interferon-alpha include fever, chills, malaise, nausea and vomiting, hepatitis, neutropenia, depression, and suicide. Further research is needed to determine optimal dose, duration, and appropriate patient profile for optimized response to this toxic medication [59].

Checkpoint Inhibitors

Immune checkpoint inhibitors are among the fastest-growing categories of immunotherapy. T-cell activation requires stimulation by antigen-presenting cells. In addition to co-stimulatory molecules, inhibitory molecules are also present on T cells and antigen-presenting cells to control the level of immune response and avoid autoimmunity. Similar inhibitory molecules are present on tumor cells and can prevent killing of tumor cells by T cells. Blocking these inhibitory signals acts to remove the brakes of this antitumor arm of the immune systems. Checkpoint inhibitors come with a slow response time and may take several months to begin shrinking tumors. It is not uncommon for tumors to swell within those first months and thus appear larger on scans, a concept known as pseudo-progression.

Ipilimumab, an anti-CTLA-4 monoclonal antibody, is the first checkpoint inhibitor FDA approved for the treatment of metastatic or unresectable melanoma. Ipilimumab binds to CTLA-4 on the surface of activated T cells to prevent antigen-presenting cell inhibition of T-cell activation through the CTLA-4/CD80/CD86 interaction. Early trials showed improved overall survival from 6.4 months in the control group to 10.1 months in the treatment arm. Long-term data is increasing with patients surviving 2, 5, and even 10 years showing a durable response [60, 61]. Objective response rates range from 7% to 15% as a single agent and increase to 20.8% when combined with dacarbazine and up to 57.6% when combined with nivolumab [60, 62, 63].

Nivolumab and pembrolizumab followed as the next generation of checkpoint inhibitors to be FDA approved in 2014. Programmed cell death protein 1 (PD-1) is a T-cell surface molecule that functions to recognize self and suppress autoimmunity. Programmed death-ligand 1 (PDL-1) present on melanoma cells binds to PD-1 on activated antigen-specific T cells and prevents tumor cell-mediated immune responses. Nivolumab and pembrolizumab are humanized monoclonal antibodies which bind to PD-1 and prevent its binding with PDL-1. In the absence of PDL-1 and PD-1 ligation, T cells remain in an active state and cytotoxic to the tumor. Pembrolizumab has demonstrated an overall objective response rate of 33%

including those who failed ipilimumab and upward of 45% for treatment-naïve patients [64]. In addition to a greater response rate over ipilimumab, pembrolizumab also has significantly longer progression-free survival [65]. Nivolumab has equal response rates of pembrolizumab at 33% irrespective of prior therapy and BRAF status [66]. As mentioned previously, combination therapy of ipilimumab with nivolumab produces an additive effect with nearly 60% response rate and is quickly becoming the gold standard of therapy when available [63].

Blocking T-cell checkpoints comes with the risk of immune-mediated side effects. Autoimmune-mediated dermatitis, mucositis, colitis, hepatitis, pneumonitis, and endocrinopathies have been observed as the overactive immune system attacks other body organs besides the intended cancer cells. Less commonly nephritis, pancreatitis, meningitis, myelitis, cardiomyositis, as well as a variety of bone marrow suppression and ophthalmic inflammation can occur. Immune-mediated adverse events are typically transient but can be severe or fatal. For moderate (grade 2) reactions, checkpoint inhibitors should be withheld until symptoms decrease or resolve. Corticosteroids should be started if the reaction has not improved in 1 week. For patients with severe or life-threatening (grade 3 or 4) reaction, checkpoint inhibitors should be permanently discontinued, and high-dose corticosteroids should be started immediately. If corticosteroids fail to promptly improve symptoms within a few days, infliximab should be considered [64]. In the largest set of reported data, ipilimumab immune-mediated adverse events were reported in 85% of patients, with 35% requiring corticosteroids and 10% requiring infliximab. Pembrolizumab has shown significantly fewer grade 3–5 adverse reactions than ipilimumab (10–13.3% compared to 19.9%) [65]. Nivolumab grade 3 and 4 adverse events occurred in 2.8–11.7% of patients [66, 67].

Oncolytic Virus Therapy and Therapeutic Vaccines

Oncolytic virus therapy is another promising new approach for cancer treatment. The concept emerged in the 1970s when the bacille Calmette-Guérin (BCG) vaccine was injected intralesionally with anecdotal but nonstatistically significant reproducible results. The research persisted, and talimogene laherparepvec, a genetically engineered herpesvirus (HSV-1), became the first and currently only FDA-approved oncolytic virus therapy for metastatic melanoma, approved in 2015 [68]. The virus is modified to remove two genes, one responsible for immune system evasion and another for the ability to replicate within healthy cells. The gene for human granulocyte-macrophage colony-stimulating factor (GM-CSF) is added as well with hopes of boosting immune recognition. The virus is injected directly into the tumor where it preferentially replicates within cancer cells until the cancer cells rupture. The effect is twofold with both direct cancer cell death and increased tumor antigen presentation after tumor cell particles are released. Phase III trial shows an overall response rate of 26.4% and a durable response rate at 16.3%. There was no statistically significant difference in the overall survival between the treatment arm

and control arm. Adverse events include fever, chills, and fatigue but are mostly mild to moderate. Grade 3 and 4 adverse events only occurred in 2% with no deaths [67, 68].

Therapeutic cancer vaccines aim to boost the immune system's capability to recognize and destroy tumor through cytotoxic T cells or antibody-mediated cell death. Therapeutic vaccination is far less effective than preventative cancer vaccines, such as those for HPV and hepatitis B, at stimulating an immune response. For those patients with proven immune response by enzyme-linked immunospot assays, overall survival was increased from 10.8 to 21.3 months [69].

Other Avenues of Immunotherapy: Adoptive Cell Therapy, Monoclonal Antibodies, and Adjuvant Immunotherapy

Advancements in immunotherapy are ongoing. In adoptive cell therapy, T cells are removed from the patients, genetically modified with melanoma receptors or otherwise enhanced in activity or number, and then reintroduced back into the patient. Monoclonal antibodies directed to tumor antigens to promote immune response are under development as well. Other adjuvant immunotherapies in clinical trial include the use of innate immunity Toll-like receptors 3, 8, and 9.

Targeted Molecular Therapy

Understanding of the molecular pathways involved in the pathogenesis of melanoma has led to the development of *MAPK* pathway inhibitors with targets including *BRAF*, *MEK*, *NRAS*, and *KIT*. *BRAF* mutations are present in up to 66% of all melanomas. Vemurafenib and dabrafenib are FDA-approved monoclonal antibodies that target mutated *BRAF* molecules. When compared to treatment with dacarbazine, *BRAF* inhibitors have a remarkable higher response rate and significantly greater median overall survival [70, 71]. Despite their impressive initial responses, when given as monotherapy, inhibition is eventually overcome, and resistance develops. Common adverse events include cutaneous squamous cell carcinoma, keratoacanthoma type, rash, photosensitivity, arthralgia, diarrhea, and fatigue. Severe adverse events are rare.

Trametinib and cobimetinib are inhibitors of *MEK*, an enzyme downstream of *BRAF* in the *MAPK* pathway. Trametinib shows modest activity when used as monotherapy for patients with *BRAF* mutations but is subpar to *BRAF* inhibitors. Cobimetinib has not been studied as monotherapy. *MEK* inhibitors are generally well tolerated, and adverse events include rash, diarrhea, fatigue, edema, cardiac dysfunction, and interstitial lung disease. Similar to *BRAF* inhibitors, resistance develops.

To overcome high rates of resistance, improve response rates, and decrease toxicity, clinical trials with dual therapy with *BRAF* + *MEK* inhibitors were conducted. Combination therapies with dabrafenib plus trametinib and vemurafenib plus cobimetinib have objective response rates of 79% and 68%, respectively. Both combinations have improved progression-free survival and overall survival compared to *BRAF* monotherapy. Resistance remains nearly inevitable and an unresolved hurdle. Side effects are reduced when dabrafenib is combined with trametinib but unchanged when vemurafenib is combined with cobimetinib [72, 73]. Head-to-head comparison of the two combinations has not been performed, but indirect comparison suggests vemurafenib plus cobimetinib is of equal efficacy but associated with increased adverse events [74].

Existing *KIT* inhibitors such as imatinib and nilotinib appear to have a narrow but significant role in melanomas harboring such mutations [75]. *NRAS* inhibitors are currently in trial. In addition, inhibition of *mTOR* and *AKT* also shows promise [76, 77]. Combination therapy with targeted molecular inhibitors and immunotherapy are being studied.

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