Melanoma

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Abbreviations

α-MSH	α-Melanocyte-stimulating hormone
AHM	Amelanotic/hypomelanotic melanoma
AJCC	American Joint Committee on Cancer
ALM	Acral lentiginous melanoma
BAP1	Associated protein 1
BI	Breslow index
BRCA1	Breast cancer 1
CDK4	Cyclin-dependent kinase 4
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CGH	Comparative genomic hybridization
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DD	Digital dermoscopy
FISH	Fluorescence in situ hybridization
IFN-α	Interferon-alfa
ILI	Isolated limb infusion
ILP	Isolated limb perfusion
LDH	Lactate dehydrogenase
LMM	Lentigo maligna melanoma
MAP	Mitogen-activated protein
MITF	Microphthalmia-associated transcription factor
MRI	Magnetic resonance imaging
NAM	Nail apparatus melanoma
NMs	Nodular melanomas
PET	Positron emission tomography
POT1	Protection of telomeres 1
RCM	Reflectance confocal microscopy
SLNB	Sentinel lymph node biopsy
SSM	Superficial spreading melanoma
TBP	Total-body photography
TERT	Telomerase reverse transcriptase
UV	Ultraviolet
WHO	World Health Organization

Key Points

- Melanoma is responsible for 75% of deaths from skin cancer and its incidence has rapidly been increasing.
- Although the increasing incidence of thinner melanomas represents improved surveillance and earlier diagnosis, the overall mortality rate has not declined in many countries.
- Dermoscopy and reflectance confocal microscopy are noninvasive techniques that increase accuracy in melanoma diagnosis and reduce unnecessary biopsies.

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R. Rangel Bonamigo (ed.), *Dermatology in Public Health Environments*,
https://doi.org/10.1007/978-3-031-13505-7_17

- The definitive treatment of primary melanoma is wide local excision associated with sentinel lymph node biopsy when indicated.
- Adjuvant treatment is a standard of care in an expanding subset of high risk resected patients, with clinical benefits detected with immunotherapy and targeted therapies.
- The identification of genetic mutations has led to the development of target drugs to better guide therapy for patients with advanced melanoma.
- Advances in the understanding of immunologic mechanisms in melanoma have promoted the development of interventions with impact on clinical endpoints.
- The paradigm shift promoted by advances in the systemic treatment had a profound impact on response rates and on the survival expectations in metastatic patients.

Epidemiology

Melanoma incidence has rapidly been increasing over the past 50 years, especially in fair-skinned and elderly populations [1, 2]. It is the second most diagnosed cancer among patients under 30 years of age, and one of the cancers with more years of productive life lost, representing a significant public health problem [3]. Even though it represents less than 5% of all cutaneous malignancies, because of its aggressiveness, melanoma is responsible for 75% of deaths from skin cancer [3, 4]. When invasive, melanoma is the cutaneous tumor with the highest metastatic capacity, since it increases by 10% per millimeter of thickness [3].

Despite changes in attitudes toward increased recreational exposure to ultraviolet (UV) radiation, the current trend of increased melanoma is predominantly explained by an increasing incidence of thinner melanomas as a result of improved surveillance and earlier diagnosis [1]. Annually, this incidence increase varies between populations, ranging from 3% to 7%, with the highest rates in Australia and New Zealand, with up to 33.6 cases per 100,000 inhabitants per year [2, 4–6]. In the United States, in the past 10 years, the incidence of melanoma has been increasing an average of 2.6% each year, with 12.6 cases per 100,000 population [2, 7]. In Europe, incidence rates vary between 9 and 18.8 cases per 100,000 population [2].

Population-based studies have shown significant increases in tumors of all histologic subtypes and thicknesses, including thick melanomas (more than 4 mm), especially in older men [8–10]. The increase in incidence has been higher in men aged 65 years and older (fivefold in men versus threefold in women), and mortality rates increased by 157% (from 7.5 to 19.3 per 100,000) among this age group [11, 12]. Besides, there has been an increase of the incidence of melanoma in young adults, specially woman between 25 and 39 years of age, often with high associated mortality [2]. However, melanoma mortality rates are variable worldwide and influenced by geography, age, ethnicity, and sex. Data from the Surveillance, Epidemiology, and End Results (SEER) registry indicate that the melanoma mortality rate decreased by 17.9% in the period 2013–2016 in the United States [2]. Instead, in high-risk regions such as Australia and New Zealand and also in Scandinavia and United Kingdom, mortality rate has steadily increased over the last decade, around 1.5% per year [13].

Fortunately, over the past 20 years, overall 5-year survival has increased in the United States by nearly 91%, likely a result of earlier diagnosis [11]. The association between increased incidence of and survival for melanoma and stabilization of the mortality rate suggests overdiagnosis from increased early detection, either from screening or incidental detection [14].

Etiopathogenesis

Melanoma is a malignant neoplasm of melanocytic lineage that most frequently arises from melanocytes in the skin, but can also arise from autochthonous melanocytes from internal organs, including the central nervous system [15].

Although melanoma can arise from nevi, most primary melanomas do not show an associated precursor nevus [15].

Melanoma as a heterogeneous disease can present with different clinical, histopathologic, and biological aspects [16]. Most melanomas show an intraepithelial component, and the malignant cells are thought to initially proliferate along the basal layer (melanoma *in situ*) [15]. After a period of months to years, the malignant melanocytes not only proliferate radially but also acquire the capacity to invade vertically into the dermis (invasive melanoma) [17]. However, lesions of intraepithelial origin are distinct from melanocytic neoplasms, which consistently lack epithelial involvement; these include uveal melanoma and intradermal melanocytic proliferations [15]. Nodular melanomas (NMs) lack substantial epidermal involvement and radial components, proceeding directly to vertical and rapid growth. Furthermore, NMs frequently present amelanotic coloration [17, 18] (Fig. 17.1).

Genetic profiles and molecular data have been identified for each of the different types of melanomas and have been correlated with distinct clinical and histopathologic aspects and biological behaviors of tumors [16]. Cutaneous primary melanomas usually present typical UV radiation–induced mutations in the mitogen-activated protein kinase (MAPK) pathway, with mutually exclusive driver mutations in BRAF, NRAS, c-KIT, GNAQ, or GNA11 [19]. Melanomas associated with intense, intermittent sun exposure (usually at the trunk and extremities) have high rates of *BRAF* (50%) or *NRAS* (20%) mutations. On the other hand, mucosal and acrolentiginous melanomas have lower rates of *BRAF* mutations (5–20%) and higher rates of *c-KIT* mutations (5–10%). Uveal melanomas usually show mutations in *GNAQ* or *GNA11* [19–21].

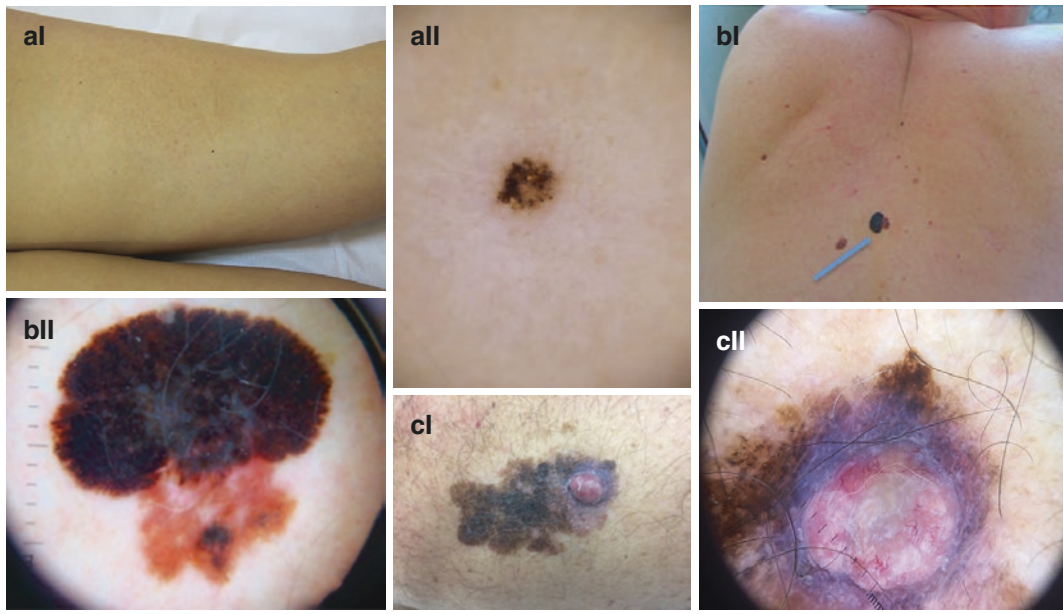

Fig. 17.1 Clinical and dermoscopic presentation of superficial spreading melanoma in three different evolutionary growth stages: incipient, radial growth, and vertical growth. (**aI**) Clinical image of a 2 mm macular brown pigmented lesion on the posterior thigh. (**aII**) Dermoscopic image of an incipient (clinically featureless) in situ superficial spreading melanoma presenting asymmetric clods on the periphery and irregular black, bluish, and brown pigmentation. (**bI**) Clinical picture of a dark pigmented macular lesion on the back (blue arrow). (**bII**) Dermoscopic image of a superficial spreading melanoma in radial growth phase presenting an atypical network, radial lines and pseudopods, a blue-whitish veil, and structureless areas. (**cI**) Clinical picture of a macular-nodular pigmented lesion on the upper arm. (**cII**) Dermoscopic image of a superficial spreading melanoma in vertical growth phase presenting a peripheral atypical network and nodular excentric area with blue-white pigmentation and polymorphic vessels

Risk Factors

Melanoma etiology is complex and involves environmental, phenotypic, and genetic risk factors [3]. The main risk factors for developing cutaneous melanoma are described here.

Environmental Risk Factors
- Intense UV radiation exposure (e.g., sunburn history)
- Chronic, cumulative sun exposure
- Indoor tanning, especially in youth (before age 35 years)
- Immunosuppression (e.g., organ transplantation)

Phenotypic and Genetic Factors
- Phototype I (fair skin, inability to tan)
- Light hair (red or blond)
- Light eyes (blue, green, or gray)
- Increased common nevus count (>100 nevi)
- Atypical melanocytic nevus (>5 nevi)
- High density of freckles
- Premalignant and skin cancer lesions
- Actinic damage indicators (e.g., solar lentigines)
- Personal history of melanoma
- Family history of melanoma (≥1 affected first-degree relative)

Environmental Risk Factors

Exposure to UV radiation is the best-known exogenous risk factor for developing melanoma [11]. UV radiation causes DNA damage and induces melanoma carcinogenesis through the formation of pyrimidine dimers, photoproducts, gene mutations, oxidative stress, inflammation, and immunosuppression [3]. Both intermittent, intense UV exposure (e.g., sunburn history), and chronic, cumulative sun exposure play a role in the pathogenesis of melanoma [22].

Melanomas developing in continuously sun-exposed areas such as the head and neck are more likely to be of the lentigo maligna melanoma subtype and to occur in older patients with a history of solar damage and nonmelanoma skin cancer. On the other hand, individuals with a high number of nevi tend to develop melanomas on intermittently sun-exposed body sites such as the trunk and extremities, mostly belonging to the superficial spreading melanoma or nodular melanoma histologic subtypes [22].

Indoor tanning is considered directly linked to the development of melanoma by the International Agency for Research on Cancer, which classified the whole UV spectrum and indoor tanning devices as carcinogenic to humans (group 1) [23–25]. A meta-analysis showed a 75% increase in the risk for melanoma (from 40% to 228%) when indoor tanning started during adolescence and young adulthood [26]. More recently, a systematic review and meta-analysis found an association between use of sunbeds and a summary relative risk (RR) of 1.25 (1.09–1.43) for melanoma. This risk almost doubled (RR = 1.87) in youth (before 35 years of age), with a 1.8% (0–3.8%) increase in melanoma risk for each additional session of sunbed use per year [26]. A 10-year follow-up study demonstrated that the daily use of sunscreen reduces the melanoma detection rate, suggesting that regular sunscreen use may prevent melanoma development and should be encouraged [27].

Besides UV exposure, other potential environmental risk factors are under study. Occupational exposure to pesticides was associated to a four-fold greater risk of melanoma compared with no occupational exposure (odds ratio [OR] 4.23, 95% confidence interval [CI] 1.94–6.31) [28]. Furthermore, indoor use of pesticides (four or more times per year) was associated with a 44% higher risk of melanoma (OR 1.44, 95% CI 1.11–3.49) [28].

Phenotypic and Host Factors

Melanoma occurs more frequently in Caucasians than other races. Phenotypic features associated with increased risk of melanoma are phototype (I vs. IV: RR = 2.09, 95% CI 1.67–2.58), skin color (fair vs. dark: RR = 2.06, 95% CI 1.68–2.52),

hair color (red vs. dark: RR = 3.64, 95% CI 2.56–5.37), eye color (blue vs. dark: RR = 1.47, 95% CI 1.28–1.69), high density of freckles (RR = 2.10, 95% CI 1.80–2.45), presence of premalignant and skin cancer lesions (RR = 4.28, 95% CI 2.80–6.55), and actinic damage indicators (RR = 2.02, 95% CI 1.24–3.29) [22]. Ephelides and solar lentigines were shown to be independent risk factors for cutaneous melanoma related to sun exposure [22].

The number of melanocytic nevi represents a good predictor for cutaneous malignant melanoma, as the risk increases almost linearly with the number of common melanocytic nevi [29]. The presence of a high nevus count (more than 100 nevi) is associated with an almost sevenfold significant increased risk of melanoma compared with <15 nevi (RR = 6.89; 95% CI 4.63–10.25) [22, 30]. A high number of nevi on the arms may represent an increased total nevus count. People with 11–15 common nevi on the arms present an almost fivefold greater risk of melanoma than those with no nevi (RR = 4.82; 95% CI 3.05–7.62) [30].

Atypical nevi may play an independent role in melanoma risk, as the presence of five atypical nevi increases the risk tenfold compared with the absence of atypical nevi (RR = 10.12; 95% CI 5.04–20.32) [22, 30]. Atypical nevi are usually larger than common nevi with a border not well defined, size 5 mm or more, color variegated, contour uneven, and presence of erythema [22].

Sporadic atypical melanocytic nevi outside the context of dysplastic nevus syndrome and/or familial melanoma are considered independent risk markers for sporadic melanoma [29].

Giant congenital nevi are also associated with increased risk, with a cumulative 5-year risk of cutaneous melanoma estimated at 5.7% [11, 31].

Persons with the atypical or dysplastic nevus syndrome (Clark nevus syndrome) present multiple atypical moles that continue to appear in adulthood and are at much higher risk of melanoma [22]. Individuals with atypical nevus syndrome and at least two family members with melanoma have a 500-fold increase in melanoma risk [30].

Personal or Family History of Melanoma and Genetic Factors

The presence of a history of melanoma or nonmelanoma skin cancer is associated with a threefold relative risk of melanoma [11]. Personal history of melanoma increases 5–8% the risk of developing a second primary melanoma [3, 32, 33].

Approximately 5–10% of melanoma cases occur in a familial setting [3]. A family history of melanoma is considered positive if the patient has reported one or more affected first-degree relative [24]. Patients with a positive family history of melanoma have an RR of 1.74 compared with those with a negative family history [34].

In high-risk families, melanoma susceptibility is inherited following an autosomal dominant inheritance pattern with incomplete penetrance [35]. Multiple primary melanoma patients may also have inherited melanoma susceptibility and often present atypical mole phenotype [3, 26, 36, 37].

Two main genes are described as melanoma high-susceptibility genes: cyclin-dependent kinase inhibitor 2A (*CDKN2A*) and cyclin-dependent kinase 4 (*CDK4*). Germline CDKN2A mutations have been described in 20–50% of melanoma-prone families and in up to 15% of multiple primary melanoma patients irrespective of family history [38, 39]. However, the probability to have *CDKN2A* mutations in sporadic melanoma patients without personal or family history of melanoma is about 1% [3]. The penetrance for melanoma in *CDKN2A* carriers at the age of 80 years was reported to be 58% in Europe, 76% in the United States, and 91% in Australia [40]. Carriers of *CDKN2A* mutations also have an increased risk for developing pancreatic, breast, lung, and other tobacco-related cancers [41–43].

Another gene, the α-melanocyte-stimulating hormone (α-MSH) receptor 1 (*MC1R*), is considered a low to moderate gene risk and its variants are associated with skin and hair pigmentation. *MC1R* is one of the key regulatory genes in human pigmentation and is highly polymorphic in the Caucasian population [42]. The R variants are highly associated with red hair color phenotype (p.D84E, p.R142H, p.R151C, p.I155T, p.

R160W, p.D294H) and are those most implicated with melanoma susceptibility. Carriers of two R alleles are at four- to sixfold higher risk of developing melanoma compared with individuals without these variants [42]. Recently, it was shown that carriers of *MC1R* variants had increased melanoma risk independent of sun exposure [44].

Germline mutations in other genes such as breast cancer 1 (*BRCA1*) associated protein 1 (*BAP1*), telomerase reverse transcriptase (*TERT*), protection of telomeres 1 (*POT1*), and microphthalmia-associated transcription factor (*MITF*) were described in *CDKN2A* wild-type melanoma-prone families and may be responsible for a lower number of familial melanoma cases.

Genetic counseling and specific dermatologic follow-up should be offered to individuals belonging to melanoma-prone families or families with melanoma-related cancers (sarcoma, early-onset breast cancer, brain tumors, or pancreatic cancer) and/or with multiple primary melanomas [45, 46]. Genetic testing should only be performed in individuals with at least a 10% chance of carrying a mutation before the test is done [47, 48].

Other Factors

There is an increase in incidence and poorer prognosis of melanoma in patients after organ transplantation associated with medical immunosuppression [11]. On the other hand, a melanoma diagnosed during pregnancy do not carry a different prognosis or outcome for the woman. Melanocytic lesions during pregnancy should be managed in the same way as in the nonpregnant patient. Exogenous hormones may be used in women with personal history of melanoma [49].

Clinical Presentation

The World Health Organization (WHO) classification distinguishes four major clinical-histopathologic subtypes of melanoma: superficial spreading melanoma (SSM), nodular melanoma (NM), acral lentiginous melanoma (ALM), and lentigo maligna melanoma (LMM) [50–52]. Although these proposed categories represent distinct clinical and histopathologic presentations that are valuable for recognition and diagnosis, the impact of this classification on predicting prognosis and defining clinical management has been limited [29, 50].

SSM is the most frequent histopathologic subtype of melanoma in fair-skinned individuals [29]. It accounts for approximately 65% of all melanomas, and the median age of diagnosis is between 40 and 60 years [29, 52]. SSM is most frequently seen on intermittently sun-exposed skin of the trunk of men and the legs of women, but may arise at any site. It usually begins as an asymptomatic brown to black macule with color variegation and irregular borders, sometimes also exhibiting pink discoloration. After a slow macular radial growth phase, a papular or nodular vertical growth phase develops (Fig. 17.1). Gray pigmentation and hypopigmentation are signs of regression associated with a host immune system response. Early-stage melanomas of ≤5 mm diameter may present asymmetry of pigmentation and borders [29].

NM represents around 20% of all primary melanomas diagnosed and often fails the ABCD categorization of suspicious lesions. The more aggressive biology of NM accounts for a shorter duration and advanced thickness of NM at presentation, and supports the importance of the "E" for evolution to the ABCD criteria [52]. Nodular melanoma usually presents as a black or blue nodule, sometimes pink to red (amelanotic), which may be ulcerated or bleeding (Fig. 17.2) [29].

Usually, NM is firm and elevated with a history of fast growth. The acronym "EFG" (E = elevated, F = firm, and G = growing progressively for more than a month) indicates clinical clues for diagnosis [53, 54].

LMM represents approximately 10% of melanomas and usually develops in the seventh decade and later (Fig. 17.3) [29].

LMM occurs in chronically sun-exposed areas such as face and neck, and less frequently in the upper trunk and extremities [55]. Recognition of

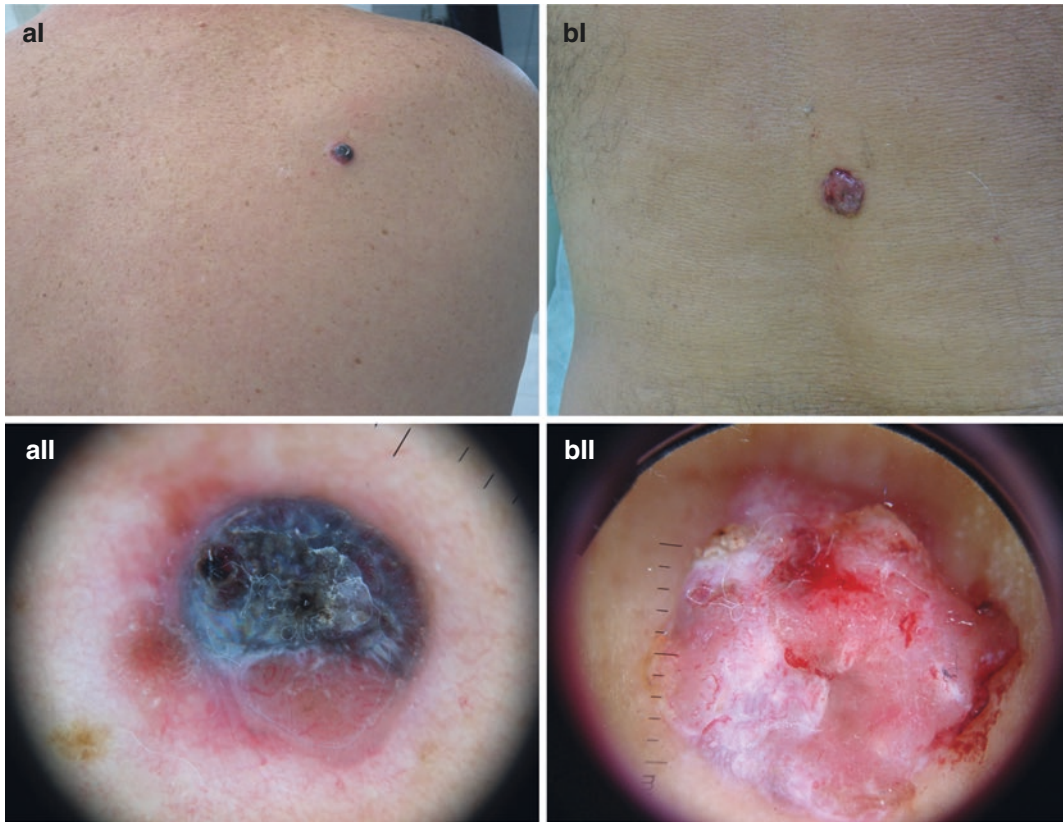

Fig. 17.2 Clinical and dermoscopic presentation of pigmented and amelanotic nodular melanoma. (**aI**) Clinical picture of a pigmented nodular lesion on the back. (**aII**) Dermoscopic image of a nodular melanoma presenting blue color, polymorphic vessels, shiny white streaks, and a small ulceration. (**bI**) Clinical picture of a nodular red tumor on the lumbar region. (**bII**) Dermoscopic image of an amelanotic nodular melanoma presenting white and red colors, atypical linear and dotted vessels, and large ulcerated areas

LMM in early stages is often difficult because its presentation can be quite subtle, and delayed diagnosis is common [55]. According to the English language literature, the entity is called "lentigo maligna" when it is confined to the epidermis (in situ) and as "lentigo maligna melanoma" when it invades the dermis. Currently, it is generally believed that lentigo maligna and LMM belong to the same evolutionary spectrum, i.e., the same entity at different stages of development [55, 56]. In daily clinical practice, the diagnosis of facial lentigo melanoma may be a diagnostic challenge because of its similar clinical features to other lesions such as solar lentigines and pigmented actinic keratosis [57].

ALM is an infrequent subtype of melanoma arising on the palms, soles, and nail apparatus. It represents approximately 5% of all melanomas and up to 70% of melanomas diagnosed in black individuals. At acral sites, melanoma typically presents as an asymmetric brown to black macule with color variation and irregular borders (Fig. 17.3). ALM may be amelanotic and are easily misdiagnosed as verrucae or other benign conditions [29].

Nail apparatus melanoma (NAM) is rare and accounts for 0.18–2.8% of all melanomas. The relative incidence of NAM among Africans and Asians is much higher than that found among Caucasians [58]. Melanoma mainly arises from the nail matrix but it is also found in the nail bed and lateral folds [58]. NAM of the nail matrix can present as longitudinal pigmentation (also known as melanonychia striata longitudinalis),

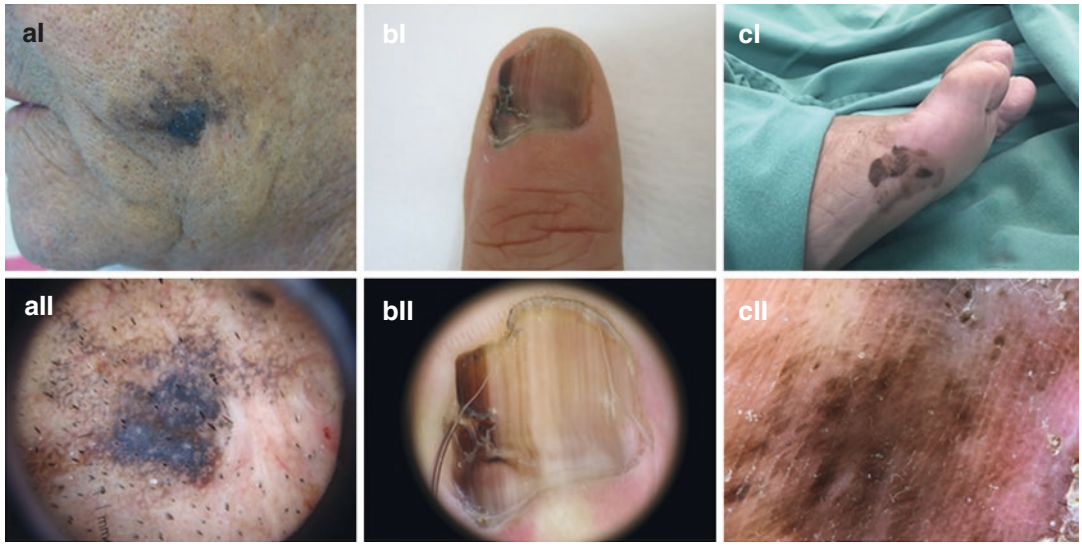

Fig. 17.3 Clinical and dermoscopic picture of melanoma at special sites: facial, nail, and acral. (**aI**) Clinical picture of a brown-black macule on the face. (**aII**) Lentigo maligna melanoma showing annular-granular pattern with gray dots, asymmetric pigmented follicular openings, rhomboidal structures, and obliterated hair follicles. (**bI**) Clinical picture of a melanonychia striata longitudinalis on the index finger. (**bII**) Dermoscopy shows a nail apparatus melanoma with brown background of pigmentation and irregular pattern of the longitudinal microlines that are irregular in color, thickness, and spacing; there is also erosion of the nail plate with dystrophy. (**cI**) Clinical picture of a black- to brown-colored pigmented patch on the lateral plantar region. (**cII**) Dermoscopy of an acral lentiginous melanoma with parallel ridge pattern and irregular diffuse pigmentation

as shown in Fig. 17.3. Early pigmented nail-unit melanoma is characterized by brown background associated with longitudinal lines that are irregular in color, width, spacing, and parallelism. Nail melanoma may also present as a black background with areas of different hue of pigmentation, with barely visible lines. About 20–30% of cases of NAM are amelanotic [58]. When arising in the nail bed, NAM presents as a nodule that can be ulcerated and bleeding with partial destruction of the nail plate. The use of the "ABCDEF" rule was suggested to evaluate suspicious melanonychia: A stands for "age, Asian and African American"; B for "brown, black, breadth, and borders"; C for "change or absence of change, despite adequate treatment"; D for "digits (thumb, hallux, index finger)"; E for "extension of pigment (Hutchinson sign)"; and F for "familial history of melanoma" [59]. The Hutchinson sign describes the presence of pigment on the proximal, lateral, or distal fold, which represents the radial growth phase of subungual melanoma.

Mucosal melanomas account for approximately 1.3–1.4% of all melanomas. In early stages, mucosal melanoma presents clinically as brown-black macules with shades of gray, sometimes with multifocal distribution. Advanced mucosal melanomas usually develop black to dark brown nodules combined with the macular part at the base of a tumor [60].

Less prevalent melanoma variants with distinct clinical-epidemiologic presentations are spitzoid, nevoid, desmoplastic, malignant blue nevus, and ocular melanoma. Amelanotic/hypomelanotic melanoma (AHM) is a rare subtype with no melanin pigmentation under dermoscopy or partially pigmented lesions in which less then 25% of the total area shows melanin pigmentation, respectively (Fig. 17.4) [61].

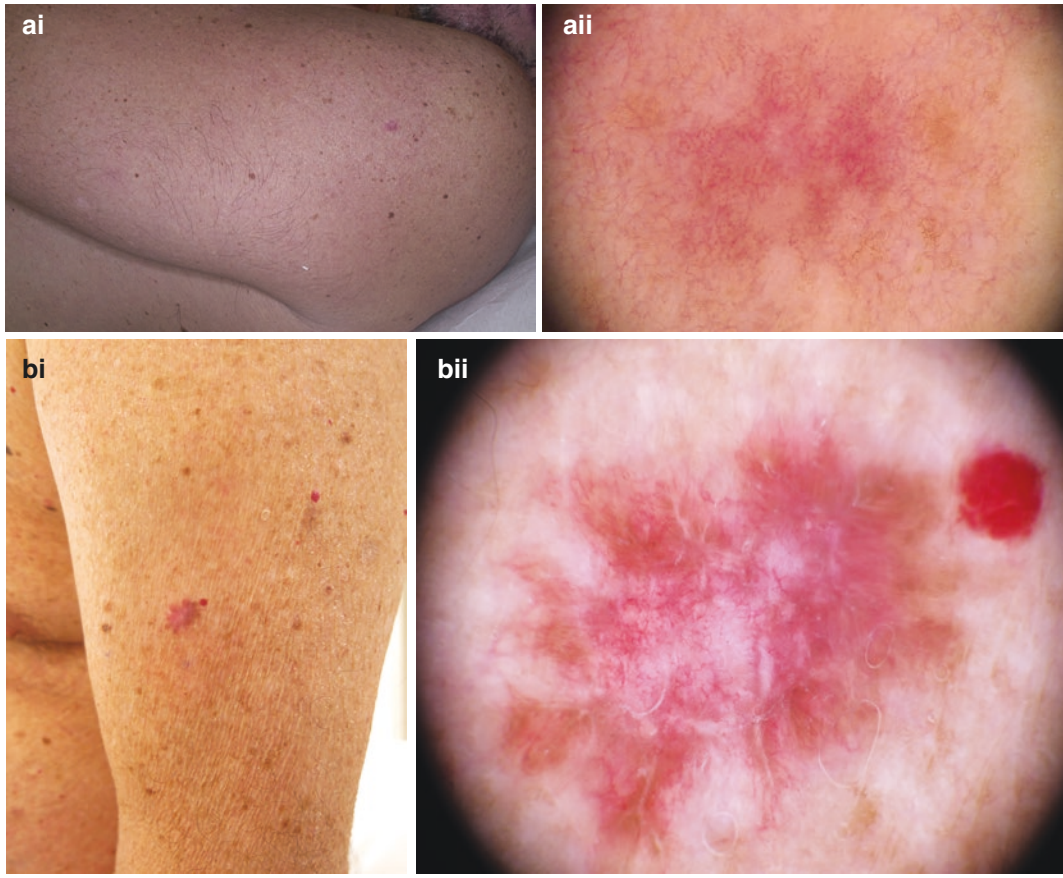

Fig. 17.4 Clinical and dermoscopic presentation of amelanotic and hypomelanotic melanoma. (**aI**) Clinical picture of a uniformly red macular lesion on the upper arm. (**aII**) Dermoscopic image of a amelanotic superficial spreading melanoma showing dotted vessels over a pink background. (**bI**) Clinical picture of a erythematous macule on the upper arm. (**bII**) Dermoscopic image of a hypomelanotic superficial spreading melanoma with linear irregular vessels, white shiny structures and peripheral faint light brown structureless areas

Diagnosis

Melanoma diagnosis is a constant challenge in clinical practice, since it represents a potentially fatal skin cancer and the prognosis is strictly related to early detection.

Clinical recognition is classically associated with the ABCD(E) mnemonic of melanoma, which was designed to provide simple criteria for early diagnosis by physicians and general population. Friedman et al. [62] published the ABCD acronym (asymmetry, border irregularity, color variegation, and diameter >6 mm). The letter E (for evolution) was subsequently added in order to include some tumors that could be missed by other criteria, especially small and nodular melanomas. Clinicians and patients should be attentive to changes (evolving) of size, shape, color, and symptoms such as itching or bleeding [62–65]. The EFG rule stands for an Elevated, Firm, or Growing lesion and helps to identify amelanotic and nodular melanomas, which are often clinically symmetric and uniform in color.

Another important clinical clue for suspicious lesions is the "ugly duckling sign." In a person with multiple nevi, lesions tend to resemble one another. A mole that deviates from that nevus pattern should be carefully analyzed [66, 67]. The main concepts regarding melanoma diagnosis are described in Box 17.1.

Box 17.1 Diagnosis of Cutaneous Melanoma

Clinical presentation: ABCDE rule (asymmetry, border irregularity, color variegation, diameter >6 mm, and evolution/evolving); nodular melanoma: EFG rule (elevated, firm, and growing)
Dermoscopy: noninvasive technique that increases accuracy in melanoma diagnosis
Total-body photography and digital dermoscopy: used for surveillance of high-risk patients, allowing diagnosis of "featureless" melanomas, while minimizing unnecessary biopsies
Reflectance confocal microscopy: noninvasive technique that allows the skin evaluation at cellular level and quasi-histologic resolution, improving diagnostic accuracy for melanoma and reducing unnecessary excisions
Histopathology: excisional biopsy and histopathologic evaluation is the gold standard for melanoma diagnosis

Dermoscopy

Incipient melanomas often do not fulfill some of the clinical ABCD criteria [68]. Dermoscopy increases sensitivity in the clinical diagnosis of melanoma from 60% to up to 90% [69]. It has been proved by three meta-analyses to be more accurate than naked eye examination for the diagnosis of cutaneous melanoma [70–72], and is now widely accepted by dermatologists in routine tumor screening. This noninvasive and low-cost technique allows the recognition of morphologic structures not visible to the naked eye, allowing the detection of clinically unsuspected lesions. Besides the proven value in differentiating benign and malignant melanocytic lesions, it is also very useful in the differential diagnosis with nonmelanocytic melanoma simulators such as pigmented basal cell carcinoma, which have specific dermoscopic features that can lead to a straightforward diagnosis [73].

Multiple algorithms were created and validated to guide the differentiation between benign and malignant melanocytic lesions and help in the decision to perform a biopsy, including the ABCD rule, Menzies method, the seven-point checklist, pattern analysis, and more recently Kittler's algorithm based on pattern analysis. Pattern analysis is the preferred method by experienced dermatologists and has the same sensitivity with higher specificity [69]. This method describes global and local features to be analyzed. Global patterns related to melanoma are multicomponent (association of three or more dermoscopic structures), atypical starburst or starburst pattern in adults, atypical reticular, atypical globular, and nonspecific pattern. Local features that should raise concern for melanoma are atypical pigmented network, irregular dots, globules, streaks or blotches, atypical vessels, and blue-white structures (including blue-white veil and regressive structures). More recently, new structures associated to melanoma were described and are important to raise our suspicion. White lines (negative/inverse pigmented network and shiny white streaks/chrysalis structures) [74–77], prominent skin markings, and multiple hyperpigmented areas, the last two associated to in situ melanomas [78]. Angulated lines (polygons) are important structures of melanomas on chronically sun-damaged skin (Fig. 17.5) [78, 79]. Acral and facial lesions have specific patterns and structures that help to differentiate benign and malignant lesions [55, 80, 81].

Total-Body Photography and Digital Dermoscopy

Despite the great benefit provided by dermoscopy, there remains a small proportion of difficult-to-diagnose melanomas that could require a different approach for recognition. Incipient melanomas may lack dermoscopic features specific to this disease [82], and patients can present multiple clinically and dermoscopically atypical nevi, sometimes impossible to distinguish from early melanomas [83, 84]. Total-body photography (TBP) and digital dermoscopy (DD) are the most reliable approaches to detect initial melanoma in high-risk patients [85–87]. TBP consists of baseline body photographs for follow-up comparison that facilitate the detection of new and changing lesions. This

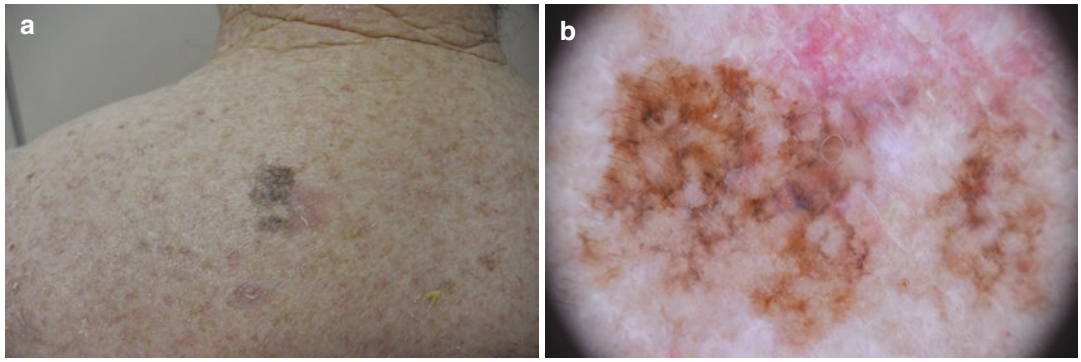

Fig. 17.5 Clinical and dermoscopic picture of an extrafacial lentigo maligna on chronically sun-damaged skin. (**a**) Clinical picture of an ill-defined brownish macula on the back. (**b**) Dermoscopic picture presenting angulated lines (polygons), grey dots, erythematous background, and white shiny lines

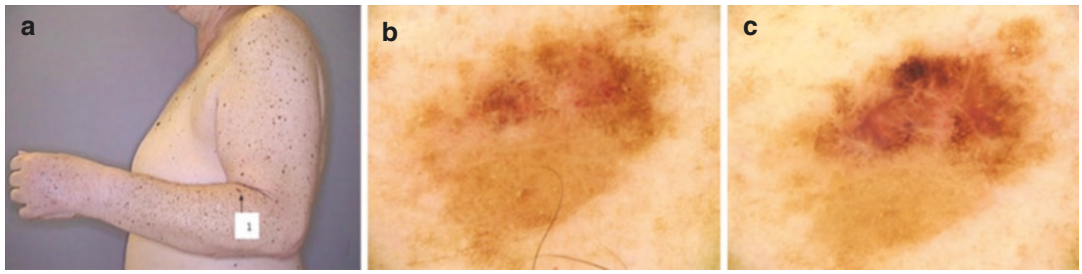

Fig. 17.6 Clinical and dermoscopic picture of an incipient melanoma detected by digital dermoscopy follow-up. (**a**) Clinical picture of a high-risk patient with increased nevus number and atypical melanocytic nevi (dysplastic nevus syndrome). Atypical melanocytic lesion on the left forearm (arrow) is followed by digital dermoscopy. (**b**) Dermoscopic image shows a predominant reticular pattern at baseline with discrete white network and irregular clods. (**c**) The same lesion at 8-month follow-up developed focal hyperpigmentation, dotted vessels, and accentuated white network; the diagnosis of an early invasive melanoma (Breslow 0.4 mm) was confirmed on histopathology

information is very important, as it is well known that melanoma often develops de novo in clinically normal-appearing skin rather than in preexisting melanocytic nevus [88]. DD allows the capture and storage of the dermoscopic images and its monitoring over time, enabling the detection of subtle changes associated with melanoma (Fig. 17.6).

A meta-analysis of digital follow-up demonstrated that this technique allows the diagnosis of "featureless" melanomas, recognized only because of changes [86], while minimizing unnecessary biopsies, since stable atypical lesions are considered benign and can be followed without excision. In high-risk patients, melanomas can be diagnosed at any time, and not just at the beginning of follow-up, suggesting that TBP and DD should be maintained over time [85].

Reflectance Confocal Microscopy

More recently, reflectance confocal microscopy (RCM) has been introduced in dermatologic research to provide important additional information in equivocal melanocytic lesions [89, 90]. This noninvasive technique allows skin evaluation at the cellular level and quasi-histologic resolution with histopathologic correlation. Many studies have demonstrated that RCM is particularly useful as a second-level examination of

doubtful lesions selected by dermoscopy or DD [91, 92], increasing sensitivity and avoiding unnecessary biopsies.

Histopathology

Melanoma diagnosis is established by histopathologic examination. Atypical melanocytes are seen singly and in small nests in the epidermis and papillary dermis in radial growth phase, and characteristically atypical cells show upward (pagetoid) migration in multiple layers within the epidermis. In situ lesions are confined to the epidermis. In the vertical growth phase, nests/nodules of malignant melanocytes expand further into the reticular dermis and beyond. Numerous mitotic figures often are noted, and there is absence of maturation at deeper levels of the dermis.

Breslow tumor thickness (depth of invasion in millimeters), ulceration, and mitotic rate are the three most important characteristics of the primary tumor for predicting outcome [93]. It is also recommended for the pathology report to include deep and peripheral margin status, microsatellites, pure desmoplasia if present, lymphovascular/angiolymphatic invasion, neurotropism/perineural invasion, regression. Microsatellitosis is defined as the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, subcutaneously, or vessels beneath the principal invasive tumor but separated from it by at least 0.3 mm of normal tissue [94].

Some melanocytic lesions can be very challenging and simulate melanoma histopathologically, requiring evaluation by an experienced pathologist, as in the case of atypical nevi and spitz nevi, recurrent, traumatized and UV-exposed lesions, and specific locations such as genital and acral nevi.

It can be considered the use of molecular testing for histologically equivocal lesions (comparative genomic hybridization—CGH and fluorescence in situ hybridization—FISH). This information should be used combined to clinical and expert dermatopathologic examination [94].

Immunohistopathology

Immunohistochemical stains usually are not necessary for diagnosis of cutaneous melanoma, but can be useful in difficult cases to help the differentiation from benign lesions and especially from non-melanocytic tumors. S-100 is the most sensitive marker for melanocytic lesions, although not specific, and HMB45 is highly specific but has limited sensitivity. Ki67 is a proliferation marker and can help to distinguish nevi from melanoma [95].

Complementary Examinations

Although there is scarce epidemiologic data regarding the use of laboratory and imaging tests in the initial evaluation of melanoma patients, they may be necessary to accurately stage patients prior to definitive treatment [96]. The general approach according to clinical/pathologic stage is summarized in Table 17.1.

Table 17.1 Suggested imaging and laboratory evaluation for workup of cutaneous melanoma according to stage according to NCCN Version 1.2021 [94]

Stage	Evaluations
0 (in situ)	Routine imaging or laboratorial tests are not recommended
I and II	Imaging tests only to evaluate specific signs and symptoms
III	Baseline imaging for staging and to evaluate specific signs and symptoms
	CT of the chest, abdomen, and pelvis with or without brain imaging
	or PET/CT in high-risk patients
IV	Baseline imaging for staging and to evaluate specific signs and symptoms
	LDH serum levels
	MRI of the brain and CT of the chest, abdomen, and pelvis and/or PET/CT

CT computed tomography, *PET* positron emission tomography, *LDH* lactate dehydrogenase, *MRI* magnetic resonance imaging

Differential Diagnosis

Differentials to consider in the diagnosis of malignant melanoma include many melanocytic and nonmelanocytic conditions, as follows:
Melanocytic:

- (Atypical) Melanocytic nevi
- Spitz nevi
- Blue nevi
- Combined nevi
- Recurrent nevi
- Congenital nevi
- Halo nevi
- Ink-spot lentigo
- Melanosis of mucosal regions

Nonmelanocytic:

- Basal cell carcinoma
- Bowen's disease
- Seborrheic keratosis
- Pigmented actinic keratosis
- Thrombosed hemangioma, angiokeratoma
- Paget's disease
- Metastatic tumors to the skin
- Adnexal tumors
- Pyogenic granuloma
- Dermatofibroma
- Dermatofibrosarcoma protuberans
- Kaposi's sarcoma
- Subungual hematoma
- Black heel (hemorrhage in stratum corneum caused by trauma)
- Tinea nigra

Staging

The staging system is essential for the best therapeutic choice, owing to the strong correlation between the clinical and pathologic characteristics with the prognosis. In 2017, the American Joint Committee on Cancer (AJCC) eighth Edition updated the TNM staging system [97] (Tables 17.2 and 17.3).

Table 17.2 TNM staging system for cutaneous melanoma according to AJCC 2017

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Melanoma in situ
T1	≤1 mm
T1a	Without ulceration and <0.8 mm in thickness
T1b	<0.8 mm in thickness with ulceration or 0.8–1.0 mm in thickness regardless of ulceration
T2	1.0–2.0 mm
T2a	Without ulceration
T2b	With ulceration
T3	2.0–4.0 mm
T3a	Without ulceration
T3b	With ulceration
T4	>4.0 mm
T4a	Without ulceration
T4b	With ulceration
Regional lymph nodes (N)	
NX	Regional nodes cannot be assessed
N0	Absence of lymph node involvement
N1	One tumor involved lymph node or in-transit, satellite, and/or microsatellite metastasis with no tumor-involved nodes
N1a	One clinically occult (detected by SLNB)
N1b	One clinically detected
N1c	In-transit, satellite, and/or microsatellite metastasis with no tumor-involved node
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastasis with one tumor-involved node
N2a	Two or three clinically occult (detected by SLNB)
N2b	Two or three, at least one of which was clinically detected
N2c	One clinically occult or detected with in-transit, satellite, and/or microsatellite metastasis
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastasis with two or more tumor-involved nodes or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastasis
N3a	Four or more clinically occult (detected by SLNB)
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes

(continued)

Table 17.2 (continued)

N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes with in-transit, satellite, and/or microsatellite metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Evidence of distant metastasis
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node
M1a(0)	LDH level not elevated
M1a(1)	LDH level elevated
M1b	Distant metastasis to lung, with or without M1a sites of disease
M1b(0)	LDH level not elevated
M1b(1)	LDH level elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a, M1b, or M1c sites of disease
M1c(0)	LDH level not elevated
M1c(1)	LDH level elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease
M1d(0)	LDH level not elevated
M1d(1)	LDH level elevated

Table 17.3 Stage groupings for cutaneous melanoma

	Clinical staging[a]				Pathologic staging[b]		
Stage	T	N	M	Stage	T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0		T1b	N0	M0
	T2a	N0	M0	IB	T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0

Table 17.3 (continued)

	Clinical staging[a]				Pathologic staging[b]		
Stage	T	N	M	Stage	T	N	M
III	Any T	N1, N2, N3	M0	IIIA	T1a, T1b or T2a	N1a or N2a	M0
				IIIB	T0	N1b or N1c	M0
					T1a, T1b or T2a	N1b/c or N2b	M0
					T2b or T3a	N1a–N2b	M0
				IIIC	T0	N2b, N2c, N3b or N3c	M0
					T1a–T3a	N2c or N3(a,b,c)	M0
					T3b, T4a	Any N > N1	M0
					T4b	N1a–N2c	M0
				IIID	T4b	N3 (a, b, c)	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

[a]Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases

[b]Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy

Therapeutic Approach

Surgical Treatment of Cutaneous Melanoma

Despite the clinical advances in the differentiation of a suspicious lesion on skin, biopsy is required for the evaluation of histology and determining the diagnosis [98, 99]. The treatment of cutaneous primary melanoma is fundamentally surgical. After initial biopsy, the definitive treatment of primary melanoma is wide local excision associated with sentinel lymph node biopsy (SLNB) when indicated. It is important to note that the surgery in two stages is a key concept in the treatment of cutaneous melanoma.

Excisional Biopsy

Excisional biopsy is considered the gold standard in the diagnosis of cutaneous melanoma [100]. It consists of complete resection of suspicious skin lesion, usually through a fusiform incision with scant side edges (2 mm), including the subcutaneous tissue. The analysis of the completeness of the primary tumor is the most accurate way for the recognition and evaluation of the microstaging criteria, especially the depth of invasion (Breslow), which is the most important factor in defining the prognosis (chance of lymph node and systemic involvement) and final resection margins [101, 102].

The incision in the trunk, head, and neck, generally elliptical, must be directed toward the skin tension lines (Langer's lines) to facilitate subsequent surgical treatment (margins of expansion), reaching improved functional and cosmetic results [100, 103]. In the limbs, the guidance should be longitudinal, following and preserving the lymphatic path, preventing loss in detection of SLNB and allowing a less complex subsequent definitive intervention [100].

Incisional Biopsy

In extensive lesions in specific locations (face/distal end) and in those with low index of suspicion for melanoma, where complete removal can cause serious sequelae, incisional biopsy may be indicated [100, 103, 104]. The removal of a fragment of skin lesion containing part of the tumor with positive lateral margins should reach the subcutaneous tissue and include the thicker or darker area, sometimes selected by dermoscopy. Technically, it may be realized with a scalpel through an elliptical incision or "punch." However, it has been shown that the Breslow index (BI) is underestimated in a significant number of cases of incisional biopsy [35].

Shave Biopsy

There are two distinct types of shave biopsy: in the first, the withdrawal of a portion of the skin lesion into the dermis with a straight sharp blade positioned at 45° to the epidermis (incisional) is indicated in the diagnosis of benign skin tumors or when the suspicion of melanoma is low [75, 105]. The second, called saucerization, consists in complete removal of the lesion with a straight blade and convex borders with lateral margins of at most 2 mm, reaching adipose tissue (excision) [98]. The latter technique is accepted as part of the procedure to diagnose cutaneous melanoma [94].

Fine-Needle Aspiration

Fine-needle aspiration is an accurate method for the diagnosis of possible metastatic lesions of cutaneous melanoma, but except in rare situations should not be used to confirm the primary tumor [100, 102]. Although this procedure is able to precisely identify the presence of melanoma, it does not allow the evaluation of relevant information such as the thickness (Breslow), ulceration, and so forth. This technique is valuable for the identification of subcutaneous metastases, soft tissue, and clinically positive nodes, with a high accuracy of 92.1% sensitivity and 99.2% specificity [106, 107].

Biopsy of Special Sites

Melanocytic lesions suspicious located on the mucosal surfaces of the oral or genital cavity should be biopsied by the same techniques as those for the skin. Because of the vascularity of these regions, careful local hemostasis should be performed after the procedure.

In suspected cases of ungual melanoma, one fusiform excision biopsy is recommended, being

narrow, longitudinal, and extending deep into the periosteum. Thus, information is obtained from all elements of the nail unit: proximal nail fold, matrix, bed, and plate [108]. Pigmentation on the matrix provides valuable guidance during surgery, although it is not always present. To minimize the subsequent nail dystrophy biopsy, repositioning of the lateral margins should always be carried out. The use of a "punch" can be advantageous when there is a chance of nail matrix melanoma. This procedure is performed with or without avulsion of the ungual plate [109].

Treatment of the Primary Lesion

In the definitive surgical procedure with wide local excision, all layers of the skin to the muscle fascia should be removed (deep margin). With respect to radial margins, in melanomas in situ the recommended removal is 0.5 cm in complex areas (e.g., on the face) at 1 cm from the lesion or site of biopsy [94, 101]. In tumors of thickness up to 1 mm, the lateral margin recommended is 1 cm [102]. In tumors of thickness 1–2 mm, a resection margin of 1 cm (e.g., on the face) to 2 cm is recommended [94, 110, 111]. Above 2 mm of tumor thickness, it is established that 2 cm is adequate. In thick tumors ≥4 mm, a 2-cm excision margin is appropriate [25] (Table 17.4).

Local recurrences are considered recurrences within 2 cm of the scar from the primary melanoma excision. Local recurrence is reported to be strongly associated with the development of in-transit, regional, and distant metastasis [112].

Table 17.4 Surgical margins for wide excision of primary melanoma

Tumor thickness	Recommended margins (cm)
In situ	0.5–1
≤1.0 mm	1
>1–2 mm	1–2
>2–4 mm	2
>4 mm	2

Adapted from NCCN [94]

Sentinel Lymph Node Biopsy

SLNB is considered the standard of care in evaluating the staging and prognosis of patients with cutaneous melanoma in whom there is a substantial risk of regional node metastasis. This technique is used in an attempt to show early lymph node metastases (micrometastases) and who might benefit from adjuvant systemic treatment [113–116].

The procedure has three distinct phases: lymphoscintigraphy, radio-guided detection of the ganglion, and pathologic evaluation of the specimen. In the first step, conducted in the nuclear medicine sector, identification of the path of lymphatic drainage is made by intradermal injection around the scar of previous biopsy of a radioactive contrast agent (technetium-99m and phytate, or dextran or sulfur colloid) for identification of the nodal basis [117]. In a second step, an intradermal injection of a bluish dye (isosulfan blue or patent blue) is realized intraoperatively for 10–20 min before the incision in the area previously identified by lymphoscintigraphy. After this time, with the aid of a probe that detects radiation (gamma-probe), it proceeds to location of the labeled node. The injection of the radiopharmaceutical added to the blue substance allows the location of the lesion in 99.1% of cases [118]. The third phase comprises the histologic and immunohistochemical evaluation of the surgical specimen. Afterwards, there is the information for the prognosis definition and the after treatment.

The indications of this methodology have many small differences in several guidelines around the world. It's widely known that the BI is the main factor associated with SLNB positivity. The NCCN advocates that the detection of the SLNB must be always performed in the primary melanomas with thickness bigger than 1 mm, and it deserves to be considered in lesions smaller than 0.8 mm with ulceration or in those between 0.8 and 1 mm, with or without the ulceration, and in the ones smaller than 0.8 mm with adverse factors such as: mitotic rate ≥2/mm^2, particularly in the setting of young age (under 55 years old),

lymphovascular invasion or the combination of more than one of these factors [94, 119–121]. At the moment, there are many nomograms that are excellent tools to determine the positivity of SLNB risk and are able to help in the therapeutic planning. In a recent Australian study, for instance, the calculator considers the patient's age and primary lesion factors (Breslow thickness, histological subtype, mitotic index, ulcerations, and lymphovascular invasion) [122]. The information within the lymph node is very important for the management to patients with melanoma [123].

The risk of a positive result on SLNB in melanomas 1.01–2.0, 2.01–4.0, and ≥4.01 mm in size is approximately 12%, 28%, and 44%, respectively [112]. In patients with melanoma 0.75–1.0 mm thick, the positivity of SLNB is around 6.2% [94]. The prognostic significance of SLNB and its impact in survival was accessed by the Multicenter Selective Lymphadenectomy Trial I (MSLT-I) [115]. SLNB was confirmed as a prognostic tool for patients with intermediate (1.2–3.5 mm) and thick (>3.5 mm) melanomas. The melanoma-specific survival rate at 10 years was significantly worse in patients with a positive lymph node biopsy than in those with a negative lymph node biopsy [115]. Although for the overall study population, no treatment-related difference in the 10-year melanoma-specific survival was shown, the 10-year melanoma-specific survival rate was significantly improved in patients with intermediate-thickness melanomas (1.20–3.50 mm) found to have nodal metastases who underwent SLNB and immediate lymphadenectomy compared with those initially managed with observation followed by treatment when they developed clinical disease.

After the release of the DeCOG-SLT [124] in 2016, a doubt of the effectiveness of lymphadenectomy was up in the air. But in June 2017, the international trial MSLT-II confirmed that in patients with melanoma and sentinel-node metastasis, the immediate completion lymph node dissection increased the rate of regional disease control at 3 years, but did not increase melanoma-specific survival, which contrasts with MSLT-I results [124, 125]. It is possible that a survival benefit with early surgery occurred among patients with disease that was limited to the sentinel node and in MSLT-II, it was not seen due to a dilution of therapeutic effect, since the majority of the study population did not have melanoma in non-sentinel lymph nodes [125].

However, it's important to point out, that not long ago, the sentinel lymph node condition was used to identify who could benefit from a radical lymphadenectomy, a procedure that is no longer routinely recommended [126]. Nowadays, the lymph node status is important to identify patients who might have advantage in the adjuvant systemic treatment with target therapy or immunotherapy [121].

Clinically Detectable Regional Lymph Nodes

Complete regional lymphadenectomy is the first-line therapy for patients presenting positive nodes proved by clinical examination, cytology (fine-needle aspirate), or histology (lymph node biopsy) without radiologic evidence of distant metastases [127]. Surgical management in this setting is associated with improved long-term disease-free survival and decreased morbidity caused by mass effect from involved nodes [94]. The prognosis of patients with lymph node metastasis varies with the number of positive lymph nodes, their presentation (micro- or macrometastasis), and characteristics of the primary lesion (thickness, ulceration, and mitosis). Therefore, the surgical approach provides an accurate staging in addition to local control of the disease [128]. We can't forget that in patients with detectable regional diseases, the treatment standard today, is surgery followed by adjuvant systemic therapy.

Locoregional Advanced or Metastatic Disease

Melanoma usually metastasizes first to lymph nodes and then to secondary sites such as skin, subcutaneous soft tissue, brain, and lung.

Metastatic spread is mainly regional in about 70% of patients, presenting as rapidly growing lymph nodes or as in-transit metastasis [29]. Cutaneous metastasis appears as a dermal nodule or plaque, more often in the proximity of the primary tumor. In-transit metastasis is defined as intra-lymphatic tumor in the skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the nearest regional lymph node basin [94].

Surgical indication may have curative intent (completely resectable) or be palliative (quality of survival). For individuals with disease only in lower and upper limbs, an isolated limb perfusion (ILP) or isolated limb infusion (ILI) were alternative treatments with the intention of avoiding amputation. These techniques consist in treatment of the affected limb with regional chemotherapy (with melphalan) associated with hyperthermia, keeping it isolated from the rest of the body by a tourniquet [129, 130]. Another method that used to be common, it was the electrochemotherapy, a nonsurgical procedure used for palliation in patients unable to undergo ILP or ILI with unresectable lesions or metastases in transit (cutaneous and/or subcutaneous) [131, 132]. By this method, the output of electrical pulses through electrodes placed on or near lesions increases cell membrane permeability; it is associated with intravenous chemotherapy, usually bleomycin and cisplatin [133].

Before the arrival of new drugs, in selected patients with Stage IV melanoma, with favorable molecular biology, an adequate "performance status," and lesions completely resectable, surgery could be suggested. Today, with the new era of systemic treatments and their satisfying outcomes, the surgery is no longer the first approach.

Adjuvant Treatment

Adjuvant therapy aims to improve the cure rate for melanoma patients who have already undergone a surgical procedure with curative intent. Various strategies have been tested over the years, including chemotherapeutic (such as cyclophosphamide and dacarbazine) and immunotherapeutic agents [134, 135]. However, consistent benefit in overall survival in unselected melanoma patients has never been detected. As expected in the development of adjuvant strategies, risk stratification was a key factor to establish the current therapeutic standard in melanoma.

There is no benefit of adjuvant treatment in melanoma patients with BI ≤0.75 mm, without ulceration, and mitotic activity <1 mm^2. Cases with BI between >0.76 mm and ≤4 mm, or BI <0.75 mm with ulceration or mitotic activity ≥1/mm^2 were studied in low-dose interferon-α (IFN-α) trials with different treatment durations. Although increased disease-free survival was observed, adjuvant treatment indication remains controversial in this scenario and observation or inclusion in clinical trials remain a viable, and usually preferred, option [136–138].

Predictive factors such as BI >4 mm, presence of ulceration, and regional node involvement are strongly associated with a higher risk of local and systemic recurrence. This population was previously enrolled in high dose interferon-alfa (IFN-α) trials. The ECOG 1684 and the Intergroup E1690 trials showed an increase in melanoma recurrence-free survival in comparison with an observation group, but no overall survival benefit was detected [139–141]. There is meta-analytic proven benefit with adjuvant high doses of IFN-α in the macroscopic or multiple lymphonodal involvement (N2 and N3) population. A meta-analysis that included 14 studies (total of 8122 patients) compared the use of IFN-α with observation, placebo, or GM2-KLH vaccine. Increased disease-free survival was detected (HR for recurrence 0.82, 95% CI 0.77–0.87) and overall survival (OS, HR for death 0.89, 95% CI 0.83–0.96) with IFN-α treatment [142]. IFN-α exposure is associated with significant rates of toxicity and the consequent need of dose reductions and treatment discontinuation [143]. This, combined with current developments in immunotherapy and targeted therapy, lead to IFN-α alfa, no longer having a well-defined role in the adjuvant setting for cutaneous melanoma.

Ipilimumab, an anti-CTLA4 monoclonal antibody, was the first checkpoint inhibitor immunotherapy approved by the US Food and Drug

Administration for adjuvant therapy. The pivotal EORTC 18071 trial included stage III patients and compared placebo with ipilimumab. With a median follow-up of 6.9 years, an increase in relapse-free survival (RFS, HR 0.75, 95% CI 0.63–0.88) and OS (HR 0.73, 0.60–0.89; $p = 0.002$) was observed. The benefit in the ipilimumab group was durable, with an 8.7% absolute difference at 7 years for OS, and consistent across subgroups [144]. It is important to emphasize the significant treatment-related toxicity: 90% of the patients had some immune-related effect and five cases of death were related to the treatment with ipilimumab [145]. This higher dose is no longer in use after subsequent data from the E1609 trial showed benefit and superior safety with a lower 3 mg/kg ipilimumab dosing [146].

In the Checkmate 238 trial, Nivolumab was evaluated in 906 patients with complete resection of (AJCC seventh edition) stage IIIB, IIIC, or resected stage IV disease. Patients with acral and mucosal melanoma were allowed enrollment. They were randomized to nivolumab (3 mg/kg) or ipilimumab (10 mg/kg). With a mean 4-year follow-up, nivolumab demonstrated sustained recurrence-free survival benefit versus ipilimumab (HR 0.71 [95% CI 0.60–0.86]; $p = 0.0003$). With fewer deaths than anticipated, overall survival (HR 0.87 [95% CI 0.66–1.14]; $p = 0.31$) was similar in both groups [147].

The efficacy of adjuvant pembrolizumab was demonstrated in the phase III KEYNOTE-054 EORTC 1325 trial [148]. A total of 1019 patients were randomly assigned to either pembrolizumab or placebo. All patients had completely resected stage III melanoma. At a median follow-up of 15 months, pembrolizumab was associated with significantly longer 1-year recurrence-free survival than placebo in the overall intention-to-treat population (75.4% [95% CI 71.3–78.9] vs. 61.0% [95% CI 56.5–65.1]; HR for recurrence or death, 0.57; 98.4% CI, 0.43–0.74; $p < 0.001$). Adverse events (grade 3 or higher) were more common with pembrolizumab than with placebo (14% vs. 3%), and there was one treatment-related death due to pembrolizumab (myositis).

For patients with melanoma and BRAF V600 driver mutation, treatment targeting the mitogen-activated protein (MAP) kinase pathway with a combination of a BRAF inhibitor and a MEK inhibitor is a viable treatment option. In the COMBI-AD trial, 870 patients with completely resected BRAF V600 mutation-positive stage III were randomly assigned to dabrafenib plus trametinib combination or matching placebos. The combination improved overall survival (OS) at 3 years (HR 0.57, 95% CI 0.42–0.79), with the benefit being observed irrespective of baseline factors [149].

In a phase III trial, melanoma patients' stage IIC or III were randomly assigned to vemurafenib or placebo. The primary endpoint, disease-free survival in the 184 patients with stage IIIC disease, was not superior in the treatment arm [150].

Adjuvant radiotherapy after lymph node dissection can also be considered when factors that impact negatively on local control (such as extranodal tumoral extension) are present. Data showing a decreased rate of local occurrence are available, but no difference in improved overall survival was detected [151, 152]. Thus, there is no routine indication for the use of adjuvant radiotherapy in unselected cases and treatment should be individualized, considering margins and lymph node dissection findings.

Palliative Treatment

For many years, cytotoxic chemotherapy had been widely used as the main therapeutic strategy in patients with advanced melanoma. Although response rates were associated with chemotherapy exposure, no schedule has demonstrated an increased overall survival. Nowadays, with advances in immunotherapy and molecularly targeted therapy, the roles of chemotherapy are restricted to later treatment lines.

There is no consistent clinical benefit advantage with combination versus single agent chemotherapy. The agent most commonly used in patients with metastatic melanoma is dacarbazine [153]. There are experimental data describing limiting activity of temozolomide, fotemustine, platinum compounds, vinca alkaloids, and taxanes [154, 155]. Combinations including cyto-

toxic agents and interleukin-2 and/or IFN-α (biochemotherapy) were previously evaluated with promising results, but with limited incorporation into routine clinical practice because of frequent and severe toxicity and the need for complex and intensive clinical management [156].

The study of genetic mutations on the tumorigenesis of melanoma and the understanding of the role of MAPK pathway activation have led to the identification of several useful strategies and a paradigm shift in advanced melanoma treatment over the last decade. Molecular targets such as BRAF, MEK, RNA, and KIT were evaluated, and many predictors are being routinely used in the initial workup of patients with advanced melanoma as a tool to improve therapy guidance.

BRAF mutations are found in approximately 50% of patients with cutaneous melanoma and are more frequent in young patients and in cases not associated without chronic sun damage [19, 157, 158]. The presence of a V600 BRAF mutation predicts a higher response to BRAF and/or MEK therapeutic inhibition. Clinical activity of vemurafenib, dabrafenib, trametinib, cobimetinib, encorafenib, and binimetinib was detected by clinical trials in this scenario.

Vemurafenib is a potent BRAF inhibitor. It was compared to dacarbazine in a phase III trial and showed increased overall survival (13.6 vs. 9.7 months, HR 0.70, 95% CI 0.57–0.87) [159, 160]. QT interval prolongation was observed in the targeted therapy group, requiring electrocardiogram monitoring. Sun-exposure avoidance and careful skin examination is mandatory since photosensitivity reactions and a high risk of cutaneous squamous cell carcinoma were strongly associated with vemurafenib use.

Dabrafenib is another BRAF inhibitor that showed activity in patients with advanced BRAF V600E mutation melanoma. Dabrafenib was compared to dacarbazine and lead to an increased progression free survival (6.7 vs. 2.9 months, HR 0.35, 95% CI 0.20–0.61) [161, 162]. Long-term outcome analysis showed that overall survival results were similar (3-year OS 31% vs. 28%; 5-year OS 24% vs. 22%) [163].

Trametinib is a MEK inhibitor initially evaluated in combination with dabrafenib in an attempt to retard the development of resistance to BRAF inhibition. The COMBI-d trial showed that the combination led to an increased progression-free survival and OS. With additional follow-up, the OS rate at 3 years was prolonged in those treated with the combination (44% vs. 32%, HR 0.75, 95% CI 0.58–0.96). Furthermore, there was a reduction in the cutaneous toxicity incidence rate with the combination approach [164]. Other studies have shown similar results [165]. In the COMBI-v trial, dabrafenib plus trametinib was compared to vemurafenib: OS was significantly increased with combination (1-year survival rate 72% vs. 65%, HR for death 0.69, 95% CI 0.53–0.89) and 3-year PFS was higher (25% vs. 11%) [166]. In a combined analysis of COMBI-d and COMBI-v, the combination of dabrafenib and trametinib demonstrated a median PFS and OS of approximately 11 and 26 months, respectively. Estimated PFS and OS at 5 years were approximately 19% and 34%, respectively. Among those patients with a complete response (19%), estimated 5-year OS was 71% [167].

The combination of vemurafenib with cobimetinib (a MEK inhibitor) was also evaluated, showing a similar increase in disease-free survival and response rate. The median survival was significantly longer with vemurafenib-cobimetinib compared with vemurafenib-placebo (22.3 vs. 17.4 months, HR 0.70, 95% CI 0.55–0.90) [168–170].

Based on the results of the phase III COLUMBUS trial, the combination of encorafenib plus binimetinib was approved by the FDA for the treatment of patients with metastatic melanoma containing a BRAF V600E or BRAF V600K mutation. The combination improved PFS and OS compared with vemurafenib (HR 0.51, 95% CI 0.39–0.67) and had a

nonsignificant trend towards higher PFS, and OS compared with encorafenib alone [171, 172].

Advances in the understanding of immunologic mechanisms in melanoma tumorigenesis and progression also promoted the development of interventions capable of inducing significant impact on clinically useful endpoints. Ipilimumab is a monoclonal antibody directed against cytotoxic T-lymphocyte antigen 4 (CTLA-4). Although prolonged overall survival was demonstrated in randomized phase III trials, its role has decreased with the development of agents that target PD-1. Anti-PD-1 antibodies (pembrolizumab, nivolumab) are one of the most significant therapeutic innovations in advanced melanoma care and have become the preferred approach to immunotherapy, since these agents are more active and have less toxicity [173–177]. As observed with many similar immunologic interventions, these agents can promote a slower pattern of response rates and a protracted clinical course with longer periods of stable tumoral volumes. In this setting, locoregional palliative therapies may be considered using an individualized approach.

Pembrolizumab showed increased progression-free survival and a better objective response rate in patients previously refractory to ipilimumab [178]. Similarly, when compared directly with ipilimumab, greater progression-free survival and overall survival were observed with pembrolizumab. Nivolumab demonstrated increased overall survival in treatment-naive patients when compared with chemotherapy and an increased response rate in patients previously treated with ipilimumab [179, 180]. Although the original recommended dose of nivolumab was 3 mg/kg based on the phase III trials, the FDA subsequently approved 240 mg every 2 weeks and 480 mg every 4 weeks as those schedules were clinically proven to be equally effective [181, 182].

In addition, the combined administration of nivolumab and ipilimumab in treatment-naïve patients showed improved progression-free survival and treatment-free survival compared with either single-agent ipilimumab or nivolumab [183]. Overall survival was also improved with the combination relative to single agent ipilimumab [183]. However, the combination of is associated with an increased incidence of serious adverse events and the need for treatment discontinuation when compared to single-agent immunotherapy. The combination of checkpoint inhibitor immunotherapy with molecularly targeted therapy is hypothesized to achieve a durable and rapid response but this approach is not yet established.

Pharmacoeconomics concerns, long-term toxicities, optimal management of acute adverse effects, and the development of an optimal treatment sequence based on clinical and molecular stratification remain challenging issues in this rapidly changing scenario.

Follow-Up

Although the prognostic impact of a systematic follow-up approach, in particular with the introduction of new adjuvant interventions, is debatable, the early detection of a resectable locoregional recurrence or a second primary melanoma may lead to a more favorable outcome. The possibility of introducing any of the highly active new interventions before organ dysfunction secondary to metastatic disease may also represent a theoretical goal. Consensus recommendations tend to rely on clinical history and physical examination, saving laboratory tests (particularly serum lactate dehydrogenase), and imaging studies for patients at high risk of recurrence (Table 17.5) [94, 184].

Regional lymph node ultrasonography may be considered in Stage IB or higher and/or in patients with an equivocal lymph node physical examination or in whom SLNB was not possible (or not successful), according to the availability and accessibility of the method (grade of recommendation C) [94, 184].

Dosage of S100 protein serum levels may be valid in Stage IB or higher as a progression marker if available (level of evidence C) [184].

Table 17.5 Follow-up for cutaneous melanoma stages I to IV according to NCCN Version 1.2021 [94]

Stage	Evaluations
0 (in situ)	Clinical history and physical examination every 6–12 months during the first 5 years and every year after 5 years
	Routine imaging or laboratorial tests are not recommended
IA–IIA	Clinical history and physical examination every 4–6 months during the first 2 years, then every 6 months for 5 years and every year after 5 years
	Routine radiologic imaging for asymptomatic cases is not recommended Imaging indicated in the presence of specific signs or symptoms
IIB–IV	Clinical history and physical examination every 3 months during the first 2 years, then every 6 months for 5 years and every year after 5 years
	Routine LDH, chest X-ray, CT, brain MRI, and/or PET/CT scans every 3–12 months for up to 5 years

Consider routine radiologic imaging in Stage ≥IIB according to [94]
CT computed tomography, *PET* positron emission tomography, *LDH* lactate dehydrogenase, *MRI* magnetic resonance imaging

Prognosis

According to AJCC Melanoma Staging Database, among patients with T1 melanomas, the 10-year survival rate was 92%, while it was 80% in T2 patients, 63% in T3 patients, and 50% in T4 patients. Five-year survival rates for Stage III were 78%, 59%, and 40% for patients with Stage IIIA, IIIB, and IIIC melanoma, respectively. In the absence of nodal metastases, patients with intralymphatic metastases have 5-year survival rates of 69%. One-year survival rates among Stage IV patients were 62% for M1a, 53% for M1b, and 33% for M1c melanomas [185].

Prevention and Screening

There is no consensus as to whether screening in the general population for melanoma is likely to be effective in reducing mortality, owing to the absence of randomized trials. However, there is current evidence that melanomas detected by the physician are thinner than those detected by patients or family members and that access to and the use of a dermatologist are correlated with a better prognosis [34, 186–188].

Based upon the available evidence, it is reasonable to recommend to high-risk individuals with a family history or presence of multiple and/or atypical moles to undergo at least annual full-body skin examination for routine screening of melanoma by a trained physician.

For the general population, educational measures such as self-examination and careful observation of the skin may be encouraged. Clinicians should remain vigilant for skin lesions during routine or opportunist visits.

The "ABCD Rule" has been shown to be a valuable tool for teaching patients to identify changes that suggest melanoma. Trained people were more often able to diagnose melanoma than those who did not receive any information about the ABCD Rule [106].

Prevention measures for cutaneous melanoma are as follows:

- Avoiding artificial tanning (tanning beds)
- Avoiding excessive sun exposure
- Wearing sunscreen and protective clothing
- Participating in skin cancer education programs
- Being familiar with the A, B, C, D, and E signs of melanoma
- Close monitoring of any changes in skin examination and seeking medical care
- Patient-based skin self-examination and periodic physician-based total-body skin examination are recommended in patients with multiple and/or atypical nevi
- Individuals at high risk (e.g., with many atypical nevi) may use TBP and DD for surveillance
- The strategy of prophylactic excision of all atypical melanocytic nevi in patients with multiple lesions is not proven to decrease risk

Glossary

Confocal microscopy Noninvasive technique using a confocal laser microscope that allows in vivo evaluation at cellular level and quasi-histologic resolution, improving diagnostic accuracy of melanocytic and nonmelanocytic skin lesions and reducing unnecessary excisions.

Dermoscopy Noninvasive technique that increases diagnostic accuracy of melanocytic and nonmelanocytic skin lesions using a magnifier polarized or nonpolarized light source.

Dysplastic nevus Atypical nevus or Clark's nevus. Melanocytic lesions that are larger than 5 mm, have irregular shape, indistinct borders, and variable pigmentation. Histologic features include disordered growth pattern, random cytologic atypia of melanocytes, and lymphocytic host response.

Sentinel lymph node The first lymph node or group of nodes draining the tumor site.

Target molecular therapy Drugs that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth and spread of cancer.

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