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RESEARCH ARTICLE

BEYOND THE SCALPEL: THE EVOLUTION OF MELANOMA CARE IN THE ERA OF PERSONALIZED MEDICINE

TABOURI Sarah[1], ZEROUAL Sarra[2], ADJMI Samir[3] and LARBAOUI Blaha[2]

[1]Department of Medical Oncology, Mixed Hospital for Cancer Control of Sidi Bel Abbes, "Taleb Morad" Faculty of Medicine – Djillali Liabes University – Algeria; [2]Department of Adult Medical Oncology, Emir Abdelkader Hospital - Faculty of Medicine Ahmed Ben Bella – University Oran 1 - Oran – Algeria; [3]Department of Medical Oncology, Regional University Military Hospital of Oran. Oran. Algeria

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Corresponding author:
TABOURI Sarah

ABSTRACT

Background: Malignant melanoma, a tumor arising from melanocytes, remains a significant global health challenge due to its high metastatic potential and increasing incidence, particularly in Western populations. While it represents a small fraction of skin cancers, it accounts for the majority of skin cancer-related deaths. **Objective:** This article provides a comprehensive overview of the current landscape of melanoma, covering its epidemiology, clinical and histological diagnosis, staging, and evolving therapeutic strategies. **Methods:** A review of clinical characteristics (ABCDE criteria), histopathological markers (Breslow thickness, Clark level), and molecular profiles (BRAF, NRAS, KIT mutations) was conducted based on the latest international guidelines, including AJCC 8th edition and ESMO 2025. **Results:** Early diagnosis is critical, as 5-year survival rates exceed 95% for localized lesions (Breslow < 0.75 mm) but drop significantly for regional and distant metastatic disease. The diagnostic process has been enhanced by dermoscopy and specific immunohistochemical markers such as PRAME and HMB-45. Furthermore, the management of advanced stages has been revolutionized by the introduction of neoadjuvant and adjuvant immunotherapies (anti-PD-1) and targeted therapies (BRAF/MEK inhibitors), which have significantly improved progression-free and overall survival. **Conclusion:** The prognosis of melanoma is increasingly dependent on molecular characterization and the timely integration of systemic therapies. While surgical excision remains the gold standard for early-stage disease, the shift toward multidisciplinary neoadjuvant approaches marks a new era in the treatment of high-risk patients.

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INTRODUCTION

Melanoma: a term derived from the Greek "melas" (black) and "oma" (tumor) (1). Melanoma is a malignant tumor arising from pigment cells: melanocytes. Melanomas occur primarily on the skin, but also on the mucous membranes (between 0.8% and 3.7%), including the mucosa of the oral and nasal cavities (15% and 23% of mucosal melanomas, respectively), genital mucosa (22.5%), and rectal mucosa (26.5%); they can also occur in other sites such as the conjunctiva (approximately 3% of malignant melanomas) (2-4). Melanomas can also develop in the choroid of the eye, the leptomeninges (pia mater or arachnoid), and the nail bed, and more rarely in internal organs (2,3). Melanoma is not always dark: 5% of nodular melanomas are "amelanotic" (normal skin color) (2). These tumors develop *de novo*, or from a pre-existing benign lesion: a nevus or mole (20%), with a high metastatic potential, even from just a few 3mm of tumor (1,2).

Epidemiology: Malignant melanoma is one of the most common skin cancers and its incidence has increased considerably in recent decades, by more than 2% per year, particularly in Western countries, although it tends to stabilize in some countries (3). More than 300,000 new cases are diagnosed each year worldwide, with the highest incidence rates in Australia and New Zealand. The incidence is very low in individuals with black skin (3,5). In Europe and North America, melanoma represents approximately 1% to 2% of all skin cancers, but its mortality is higher due to its ability to spread rapidly (2,3). The age of onset varies between 40 and 45 years with a sex ratio of 3 Men/2 Women (2).

Several risk factors are implicated in the pathogenesis of malignant melanoma (6):

Constitutive and genetic factors

- Phototypes I and II; Black and Asian populations.
- Dysplastic Nevus Syndrome.
- Family history of melanoma (RR x3) and familial forms of melanoma (< 10%).
- Personal history of melanoma.
- Giant congenital nevi (> 20 cm).

- Xeroderma pigmentosum.
- Genetic factors: CDKN2A, CDK4, MITF mutations.

Behavioral factors

- Unprotected solar exposure and UV in childhood OR intermittent exposure.
- Cosmetic UV (tanning beds).

Acquired factors

- Immunosuppression: transplant recipients, HIV-positive patients.

Prevention and Screening: Prevention related to the risk induced by photo-exposure is one of the main axes of communication regarding melanoma, through protective clothing and by avoiding exposure during periods of maximum sunlight (11 AM - 4 PM in summer time). Sunscreens, regardless of their index, do not protect against a carcinogenic risk (7). Regular examination of the families of patients with melanoma also constitutes a targeted prevention for an at-risk population. Similarly, patients with numerous dysplastic nevi undergo specialized surveillance (7,8). This screening must be early to be effective, since the later a melanoma is detected, the higher the risk of it being invasive (vertical phase) and giving rise to metastases.

Diagnosis: The diagnosis of malignant melanoma is based on a thorough clinical evaluation and a comprehensive set of diagnostic tests. The clinical examination is the first step in melanoma diagnosis; suspicious lesions must be evaluated according to the ABCDE criteria (Figure 1) (8). The lesion is typically asymmetrical, presenting irregular borders and inhomogeneous color ranging from pale pink to black; its diameter exceeds 6 mm, and it is characterized by rapid evolution or a change in appearance over time (9).

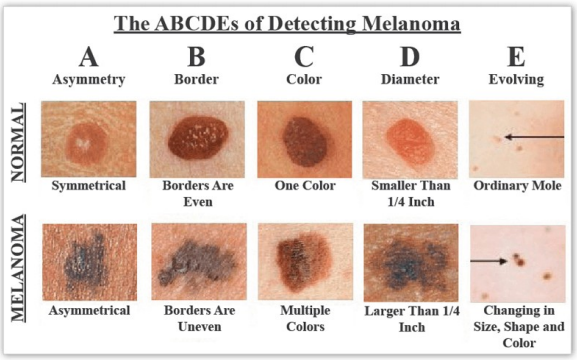

Figure 1. ABCDE Criteria for Skin Melanoma Diagnosis

In cases of late diagnosis, melanoma may be accompanied by pruritus and can become nodular and ulcerated-hemorrhagic. A melanoma can also be completely regressive and revealed solely by its cutaneous or visceral metastases. While occurring at any site, melanoma is more frequent on the lower limbs in women and on the trunk in men (8,10).

Polarized light and immersion contact dermoscopy or video-dermoscopy with digital image recording allow for the differentiation between melanoma and other benign lesions, as well as the evolutionary monitoring of pigmented lesions (10,11); these are specialized examinations that improve diagnostic sensitivity and specificity (11). The definitive diagnosis is made through the histopathological analysis of the biopsy. The biopsy should be an excisional biopsy in most cases, with the exception of those located in anatomically delicate areas or where the aesthetic result would be unacceptable; in these instances, a wide shave biopsy may be performed (6,10,12). For more extensive lesions such as Lentigo Maligna (Dubreuilh's melanosis), superficial shave biopsies of several regions increase the diagnostic yield (12). The serial section technique allows the pathologist to determine the thickness of the melanoma. The histological examination result must precede any radical surgical procedure (12). The histological diagnosis of malignant melanoma relies on the evaluation of several criteria, including lesion dimensions (> 6 mm), asymmetry (assessed at low magnification), and epidermal anomalies. At the epidermal level, one often observes poorly defined borders, the presence of pagetoid melanocytes (isolated dispersed melanocytes, particularly in the upper layers of the epidermis), epidermal consumption/ulceration, irregular distribution of junctional melanocytes, confluent growth, skip areas, nests of varying sizes and shapes, irregular nest distribution, confluent nests, and a discohesive arrangement of melanocytes. These signs indicate an atypical and disorganized proliferation of melanocytes within the epidermis (13,14). The dermal component of cutaneous malignant melanoma is crucial for both diagnosis and classification (13).

Histological Classification, Variants, and Molecular Biology (6,13,14): Malignant melanoma is classified into several subtypes, each presenting distinct histological characteristics (13). Superficial Spreading Melanoma (SSM) is the most common subtype, characterized by an asymmetrical proliferation of atypical melanocytes, a predominance of isolated junctional melanocytic units rather than nests, prominent pagetoid spread, and the BRAF V600E mutation (present in 40% to 50% of cases). Lentigo Maligna Melanoma (LMM) occurs in elderly patients on chronically sun-damaged skin and is characterized by the confluent growth of solitary melanocytic units along the dermo-epidermal junction, extension into hair follicles, prominent solar elastosis, dermal invasion by atypical melanocytes, and non-V600E BRAF, NRAS, or KIT mutations. Acral Lentiginous Melanoma (ALM), more frequent in Afro-Caribbean and Asian populations, is localized on the palms, soles, and subungual regions, featuring asymmetrical lentiginous proliferation > 7 mm and KIT mutations. Nodular Melanoma (NM) does not present a radial growth phase and is characterized by a nodular dermal proliferation of atypical melanocytes.

Rarer variants (6,12,14) include Desmoplastic Melanoma (DM), occurring in elderly patients on chronically sun-damaged skin, which can resemble a sarcoma and involves NF1 and TP53 mutations. Nevoid Melanoma is characterized by a verrucous or dome-shaped silhouette, subtle asymmetry, the absence of a radial growth phase, long thin rete ridges due to packed papillae ("puffy shirt sign"), pseudomaturation, and a high mitotic rate. Melanoma arising in a blue nevus presents a pre-existing blue nevus at the periphery, high cellular density without interposed stroma, areas of necrosis, and BAP1, GNAQ, GNA11, CYSLTR2, EIF1AX, and SF3B1 mutations. Differential diagnosis includes squamous cell or basal cell carcinomas, seborrheic keratosis, atypical nevi, blue nevi, dermatofibromas, hematomas (particularly on the hands and feet), venous lakes, pyogenic granulomas, and warts with focal thrombosis (14,15).

Complementary immunohistochemical (IHC) analysis is necessary to establish a definitive diagnosis. Indicated antibodies include HMB-45 (anti-gp100), which is the most sensitive antibody; however, it may be negative in spindle-cell desmoplastic melanomas with fibrous stroma. Other antibodies include Melan A, anti-tyrosinase T311, C-kit (CD117), and Vimentin (15). New antibodies have been identified and validated, namely: PRAME (16), KBA62, and PNL2 (17). The pathology report must include essential elements, including the extent of invasion, which specifies the progression of the melanoma. This progression is biphasic and includes an intra-epidermal horizontal growth phase, of variable duration depending on the clinico-anatomical type, and a vertical growth phase, which is an invasive stage with a high metastatic risk based on the level of dermal invasion and is a major prognostic factor (18). The exceptional metastatic capabilities of melanoma are due to the reactivation during oncogenesis of a gene called *slug*, which allows for the migration of neural crest-derived cells—including melanocytes—within the embryo (14,18,19). Other essential elements in the pathology report are the Clark level (which quantifies depth of invasion) and the Breslow thickness, which is a micrometric index measuring the

thickness of the melanoma (20) and allows for the evaluation of the 5-year overall survival prognosis (Figure 2) (21). The 5-year survival for melanomas diagnosed early with a Breslow index of less than 0.75 mm is approximately 95%. If this index is greater than 4 mm, the 5-year survival is approximately 60% (19-21). Finally, other indispensable criteria that must appear in the pathology report to classify the melanoma and define the prognosis are the melanocytic nature of the cells, the presence or absence of ulceration, the status of the excision margins (if surgical), the presence of signs of regression, and finally the mitotic index: number of mitoses/mm² (18,19). Optional criteria that may appear on the pathology report include histological subtypes, a pre-existing nevus, the presence of vascular emboli, the notion of permeation, and the presence of a stromal reaction (18-21).

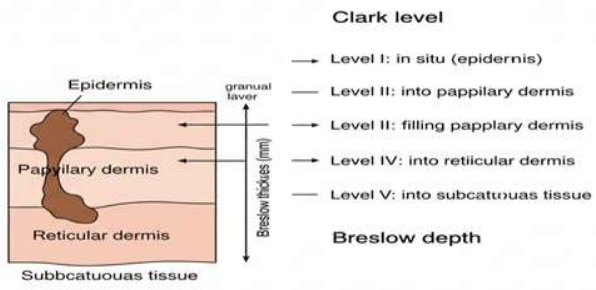

Figure 2. Clark level and Breslow depth

Extension Workup (Staging): It is clinical, radiological, and biological, and depends on the stage of the disease (Table 1) (22,23). The initial extension workup is primarily clinical. After a medical history directed at identifying functional symptoms, it relies on an examination of the entire integument to search for other suspicious pigmented lesions, cutaneous in-transit metastases, or vitiligo that could be paraneoplastic, along with a thorough general examination (lymph node, abdominal, pulmonary, and neurological) (23). The performance of an initial workup must not delay surgical management (24).

TNM Classification: In 2017, the AJCC published the 8th TNM classification for melanoma staging (25). This system constitutes a prognostic factor for survival and the cornerstone of melanoma classification, and it is summarized in Tables 2 to 5. In category N, satellite nodules are tumor foci or nodules (macro- or microscopic) located within 2 cm of the primary tumor. In-transit metastases correspond to cutaneous and/or subcutaneous metastases occurring more than 2 cm from the primary tumor and located anatomically between the primary tumor and the nodal drainage area. It should be noted that mucosal melanomas have a separate classification (26). The clinical staging of melanoma is based on pathological and clinical criteria and corresponds precisely to the classic tumor-node-metastasis (TNM) classification. Melanoma staging is based on pathological and clinical criteria. A distinction is made between local disease (Stages I and II, representing a localized primary melanoma), regional disease (Stage III, corresponding to the presence of regional or distant lymph node metastases), and disseminated disease (Stage IV, with the presence of distant metastatic disease) (27). The stage is strongly correlated with survival. Sentinel lymph node biopsy, a minimally invasive micro-staging technique, is a major advancement allowing for more precise cancer classification (26,27).

Prognostic Factors (25,27): Identifying prognostic factors is essential for evaluating the prognosis and guiding patient treatment. These prognostic factors are directly correlated with survival, namely: tumor thickness (Breslow index), the presence of tumor ulceration, histological type, excision margins, the presence and number of lymph node and visceral metastases, TNM staging, and genetic mutations (BRAF mutations are associated with a better response to BRAF and MEK inhibitors, while NRAS mutations carry an unfavorable prognosis). Furthermore, other factors such as young age and female sex are correlated with a better prognosis as they respond better to treatments.

Treatments

The management of malignant melanoma has undergone major advances with the introduction of immunotherapy and targeted therapies.

For localized stages, wide local excision with safety margins is the cornerstone of treatment; the size of the margins depends on the tumor thickness (28):

- Melanoma < 1 mm: 1 cm margins.
- Melanoma 1-2 mm: 1 to 2 cm margins.
- Melanoma > 2 mm: 2 cm margins.

In the case of invasive melanoma, although lymph node dissection is not indicated if lymphadenopathy is not clinically palpable, the sentinel lymph node (SLN) technique allows for better detection of nodal infiltration and is indicated in such cases (29). The SLN technique is recommended for all patients with tumors from stage T2a onwards and clinically non-palpable nodes (> 1.0 mm Breslow thickness) (29). Lymph node dissection remains the standard if lymphadenopathy is clinically palpable (28-30). For locally advanced malignant melanomas or those with nodal involvement, adjuvant medical treatments, particularly immunotherapy, have revolutionized the prognosis and survival rates of patients. The ESMO 2025 guidelines are summarized in Figure 3.

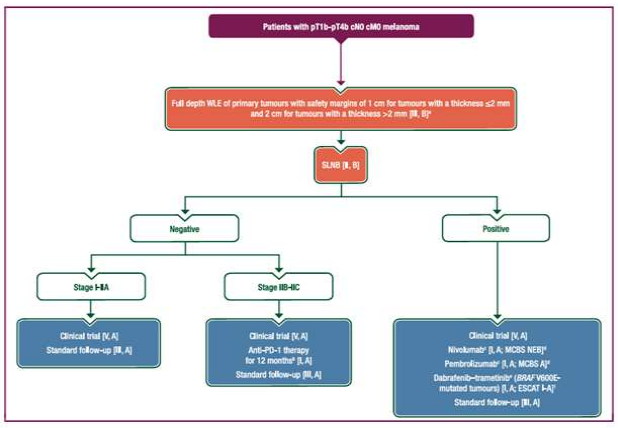

Figure 3. Proposed algorithm for the management of patients with pT1b-pT4b cN0 cM0 melanoma [29]

Purple: algorithm title; blue: systemic anticancer therapy; orange: surgery; white: non-treatment aspects. c, clinical; DMFS, distant metastasis-free survival; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO, Eu ropean Society for Medical Oncology; FDA, Food and Drug Administration; LM, lentigo maligna; M, metastasis; MCBS, ESMO-Magnitude of Clinical Benefit Scale; N, node; NEB, no evaluable benefit; OS, overall survival; p, pathological; PD-1, programmed cell death protein 1; R1, microscopic tumour at the margin; RFS, recurrence free survival; RT, radiotherapy; SLNB, sentinel lymph node biopsy; T, tumour; WG, working group; WLE, wide local excision. a RT can be considered for local tumour control in cases of inadequate resection margins of LM (III, B) and could be discussed for patients with an R1 resection (III, C). Adjuvant RT to the primary excision site should be considered for patients with desmoplastic or neurotropic melanoma for whom adequate (8 mm) pathological resection margins cannot be achieved (IV, C). b Treatment discussions with the patient should include consideration of the RFS benefit but lack of mature OS data (I, A). c Treatment discussions with the patient should consider the DMFS and RFS benefits but lack of mature OS data compared with placebo (I, A). dESMO-MCBS v1.1 was used to calculate scores for therapies/indications approved by the EMA or FDA.The scores have been calculated and validated by the ESMO MCBS WG and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms). e Treatment discussions with the patient should consider the DMFS and RFS benefits and potential OS

Table 1. Staging Workup for Malignant Melanoma

Stage	Type of Examination
IMAGING	
Stage IA	No imaging examination if the patient is asymptomatic.
For other stages	The workup is requested by the dermatologist based on the melanoma stage, clinical focus points, patient history, tumor thickness, and the possibility of adjuvant treatment.
From Stage IB	Lymph node ultrasound of the drainage area and the scar region.
Option for poor-prognosis Stage IIC; Stages III and IV	Thoraco-abdomino-pelvic CT or 18-FDG PET-CT and brain MRI (or CT in case of contraindication).
BIOLOGY (Workup tailored to the patient and the nature of the planned treatment)	
Presence of Metastases	LDH assay (prognostic factor).
	No tumor marker available for routine use.

Table 2. Classification of the Primary Tumor (T)

T	Tumor Thickness	Prognostic Parameters
Tis	Melanoma *in situ*; no invasive component.	
Tx	No information: Tumor thickness cannot be assessed.	
T1	le 1.0mm	**a:**< 0.8mm, without ulceration. **b:**< 0.8mm with ulceration, OR between 0.8 and 1.0 mm with or without ulceration.
T2	> 1.0 - 2.0mm	**a:** Without ulceration. **b:** With ulceration.
T3	> 2.0 - 4.0mm	**a:** Without ulceration. **b:** With ulceration.
T4	> 4.0 mm	**a:** Without ulceration. **b:** With ulceration.

Table 3. Classification of Regional Lymph Nodes (N)

N	Number of Involved Lymph Nodes (N+)
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	1 involved lymph node, or any in-transit, satellite, and/or microsatellite metastasis
N1a	1N+ Clinically occult (microscopic) involvement
N1b	1N+ Clinically detected (macroscopic) involvement
N1c	Satellite nodule or in-transit metastasis without lymph node involvement
N2	Metastasis in 2 or 3 nodes, or lymphatic emboli with nodal metastases
N2a	2-3N+ Clinically occult (microscopic) involvement
N2b	2-3N+ Clinically detected (macroscopic) involvement
N2c	1N+ with presence of satellite nodule or in-transit metastasis
N3	4 or more lymph node metastases, or matted nodal conglomerate, or satellite nodules/in-transit metastases with 2 or more lymph node metastases
N3a	≥4N+ Clinically occult (microscopic) involvement
N3b	≥4N+ Clinically detected (macroscopic) involvement
N3c	≥2N+ with satellite nodules or in-transit metastases with 2 or more lymph node metastases

Table 4. Classification of Distant Metastases (M)

M	Anatomical Site of Metastasis	LDH Level
M0	No distant metastasis	Not applicable
M1a	Metastases to skin, subcutaneous tissue, or lymph nodes beyond the drainage area	Not specified
M1a(0)	Same as above	Normal
M1a(1)	Same as above	Elevated
M1b	Lung metastases	Not specified
M1b(0)	Same as above	Normal
M1b(1)	Same as above	Elevated
M1c	Any other visceral involvement excluding the central nervous system	Not specified
M1c(0)	Same as above	Normal
M1c(1)	Same as above	Elevated
M1d	Metastases to the central nervous system	Not specified
M1d(0)	Same as above	Normal
M1d(1)	Same as above	Elevated

benefit for patients with BRAF V600E-mutated melanoma (I, A). f ESCAT scores apply to genomic alterations only.These scores have been defined by the guideline authors and assisted as needed by the ESMO Translational Research and Precision Medicine Working Group.

Adjuvant treatment with pembrolizumab or nivolumab for 12 months should be considered for patients with stage IIB-IIC disease; these treatments have demonstrated benefit in terms of relapse-free survival, although overall survival (OS) data remain immature (31).

Table 5. Staging of Malignant Melanoma

Stages	pT	N
Stage 0	pTis	N0
Stage I	pT1	N0
Stage IA	pT1a	N0
	pT1b	N0
Stage IB	pT2a	N0
Stage IIA	pT2b	N0
	pT3a	N0
Stage IIB	pT3b	N0
	pT4a	N0
Stage IIC	pT4b	N0
Stage III	Any pT	N1, N2, N3
Stage IIIA	pT1a, T1b, T2a	N1a, N2a
Stage IIIB	pT1a, T1b, T2a	N1b, N1c, N2b
	pT2b-T3a	N1, N2a, N2b
Stage IIIC	pT1a, T1b, T2a, T2b, T3a	N2c, N3
	pT3b, T4a	N1, N2, N3
	pT4b	N1, N2
Stage IIID	pT4b	N3
Stage IV	Any pT	Any N

For resected stage IIIB-IV, adjuvant systemic therapy options include anti-PD-1 (nivolumab for stage IIIB-IV with no evidence of disease or pembrolizumab for stage III), as well as the dabrafenib-trametinib combination for patients with stage III BRAF V600E-mutated melanoma (32). These treatments must be initiated within 12 weeks following complete resection (32,33). Patients with resectable stage IV melanoma may be offered systemic therapy, participation in a clinical trial, metastasectomy, or local ablative therapy followed by adjuvant anti-PD-1 therapy with pembrolizumab (34). The use of the nivolumab-ipilimumab combination, according to the dosing schedule used in the IMMUNED phase II trial, may be an option for certain patients with resected stage IV melanoma (35). For patients with resectable stage III melanoma and histologically proven, clinically or radiologically detectable lymph node metastasis, neoadjuvant treatment with nivolumab-ipilimumab followed by surgery should be offered (36-38). In patients achieving a major pathological response, adjuvant treatment may be omitted. In patients without a major pathological response, subsequent treatment should be discussed (38). Neoadjuvant treatment followed by adjuvant pembrolizumab is also recommended for these patients (36,37). Furthermore for unresectable locally advanced or metastatic stages, the contribution of immunotherapy and targeted therapies—either as monotherapy or in combination—has transformed the treatment landscape of melanoma, offering improved chances for overall survival and progression-free survival (39,40). In Algeria, the first-line standard remains immunotherapy with nivolumab or pembrolizumab, or BRAF inhibitors such as Vemurafenib if an activating BRAF mutation is present (41).

Prognosis of Melanomas: The 5-year cure rate for very superficial lesions is extremely high. Thus, recovery depends on early diagnosis and treatment. 5-year survival rates range from 99.6% for localized melanomas to 73.9% in cases of regional spread and 35.1% in cases of distant metastases (42). For tumors of cutaneous origin (excluding melanomas of the central nervous system and subungual melanomas) that have not metastasized, the survival rate varies according to the tumor thickness at the time of diagnosis. Mucosal melanomas (particularly anorectal melanomas) carry a poor prognosis, even though they often appear localized at the time of discovery (4).

CONCLUSION

Malignant melanoma remains one of the most aggressive forms of skin cancer, yet the therapeutic landscape has been profoundly transformed in recent years. While early clinical detection through the ABCDE criteria and precise histopathological staging (Breslow thickness and TNM classification) remain the cornerstones of management, the shift toward personalized medicine has significantly improved patient outcomes. The integration of immunotherapy (anti-PD-1) and targeted therapies (BRAF/MEK inhibitors) into neoadjuvant and adjuvant protocols has redefined the prognosis for locally advanced and metastatic stages. However, despite these pharmacological breakthroughs, the primary challenge remains early diagnosis. Public health efforts must continue to emphasize photo-protection and regular screening to identify lesions during the horizontal growth phase, where the potential for a complete cure is highest. As molecular biology continues to unveil new biomarkers and resistance mechanisms, the future of melanoma treatment lies in increasingly refined, multidisciplinary strategies tailored to the genetic profile of the tumor and the clinical needs of the patient.

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