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Review Article

Malignant Melanoma: A Comprehensive Review of Current Concepts in Pathogenesis, Diagnosis, and Therapeutic Innovation

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Abstract

Malignant melanoma represents the most aggressive form of skin cancer, accounting for the majority of skin cancer-related deaths despite comprising less than 2% of cutaneous malignancies. This review synthesizes current understanding of melanoma epidemiology, pathogenesis, diagnostic modalities, and therapeutic approaches. Recent years have witnessed paradigm shifts in both early detection and management of advanced disease. Emerging technologies such as reflectance confocal microscopy and artificial intelligence offer potential to reduce unnecessary interventions while improving diagnostic precision.

Concurrently, the therapeutic landscape has been transformed by immune checkpoint inhibitors and targeted therapies, with novel approaches including mRNA vaccines and treatment deintensification strategies now entering clinical evaluation. This review examines these developments within the context of ongoing challenges, including overdiagnosis, therapeutic resistance, and the need for personalized treatment algorithms.

Introduction

Melanoma is a malignant neoplasm arising from melanocytes, pigment-producing cells of neural crest origin. While cutaneous melanoma constitutes the vast majority of cases, primary melanomas may also arise from mucosal surfaces, the uveal tract, and rarely the leptomeninges. In the United States, anestimated 104,960 new cases of melanoma will be diagnosed in 2025, with 8,430 deaths attributable to the disease. Although melanoma represents approximately 1% of skin cancers, it disproportionately accounts for the highest mortality among cutaneous malignancies.

Incidence and Mortality Trends

Melanoma incidence has increased steadily over recent decades, with rates varying considerably by geographic region and population demographics. In the United States, melanoma is the fifth most common malignancy in men and seventh most common in women overall . Notably, it representsthe most common cancer in Caucasian women aged 25-29 years and the second most common in women aged 30-34 years. Incidence is highest in populations with fair skin residing in sun-rich environments, reflecting the predominant role of ultraviolet (UV) exposure in melanoma pathogenesisRecent epidemiological data reveal important trends. Since the early 2000s, melanoma incidence in individuals younger than 50 years has declined by approximately 1% annually in men and stabilized in women. However, among those aged 50 years and older, incidence has stabilized in men while

continuing to increase by approximately 3% yearly in women . This pattern suggests evolving sun-exposure behaviors and possibly the impact of screening efforts across different demographic groups

Risk Factors

Melanoma risk reflects complex interactions between intrinsic genetic factors and extrinsic environmental exposures. UV radiation exposure constitutes the primary modifiable risk factor. Both UVB (290-310 nanometers), which causes direct DNA damage through pyrimidine dimer formation, and UVA (320-400 nanometers), which induces

oxidative DNA damage, contribute to melanomagenesis . Intermittent intense exposure, particularly blistering sunburns, confers greater risk than chronic cumulative exposure. Artificial UV sources, notably tanning beds, significantly increase melanoma risk and represent a preventable exposure, particularly among young adults.

Genetic predisposition accounts for approximately5-10% of melanomas. Germline mutations in CDKN2A,

encoding p16 and p14ARF, represent the most common high-penetrance susceptibility locus . Family history of melanoma in one or more first-degree relatives increases risk 6- to 8-fold, while families meeting criteria for familial atypical multiple mole melanoma syndrome approach near- complete penetrance. Additional genetic syndromes, including xeroderma pigmentosum, which impairs nucleotide excision repair, confer dramatically elevated risk of all skin cancers, including melanoma.

Pathogenesis and Molecular Classification Genetic Alterations in Melanoma

Melanoma arises through accumulation of genetic alterations that dysregulate key cellular pathways controlling proliferation, survival, and senescence. The advent of comprehensive genomic characterization has revealed four major molecular subtypes of cutaneous melanoma: BRAF-mutant, RAS-mutant, NF1-mutant, and triple wild-type.

Activating mutations in BRAF, most commonly BRAF V600E (valine to glutamic acid substitution at codon 600), occur in approximately 40-50% of cutaneous melanomas. BRAF is a serine/threonine kinase in the MAP kinase pathway, and constitutive activation results in uncontrolled proliferation through downstream MEK and ERK signaling. Importantly, BRAF mutation alone is insufficient for melanomagenesis; additional alterations, such as p53 inactivation or PTEN loss, are required for malignant transformation.

RAS family mutations, particularly NRAS, occur in approximately 15-20% of melanomas. These mutations also activate the MAP kinase pathway while simultaneously engaging PI3K-AKT signaling. NF1 mutations, present in approximately

10-15% of melanomas, result in loss of neurofibromin, a negative regulator of RAS, thereby indirectly activating both MAP kinase and PI3K pathways.

Histological Classification and Prognostic Factors

Traditional histological classification divides melanoma into four major subtypes based on growth pattern and anatomic location. Superficial spreading melanoma, the most common variant comprising approximately 70% of cases, typically exhibits an initial radial growth phase followed by vertical progression . Nodular melanoma (15-30%) demonstrates rapid vertical growth from onset, often presenting as blue-black or occasionally amelanotic nodules with correspondingly poorer prognosis . Lentigo maligna melanoma (4-10%) arises on chronically sun-damaged skin of older individuals, typically displaying prolonged radial growth over years before dermal invasion . Acral lentiginous melanoma (2-8% in whites, 35-60% in darker-skinned individuals) occurs on palms, soles, and subungual sites, often diagnosed at advanced stage due to anatomic location and delayed recognition.

Diagnosis and Emerging Technologies

Early detection remains paramount for melanoma prognosis. The ABCDE mnemonic Asymmetry, Border irregularity, Color variation, Diameter >6 mm, and Evolution provides a framework for recognizing suspicious lesions. Additional warning signs include the "ugly duckling" sign (a lesionappearing different from surrounding nevi), new onset of pruritus, bleeding, or ulceration. Importantly, nodular and amelanotic melanomas may not conform to classic ABCDE criteria, requiring heightened clinical suspicion for rapidly growing or pink/red lesions

Biopsy technique significantly impacts diagnostic accuracy. Suspicious lesions should undergo full-thickness excisional biopsy with narrow margins, allowing complete histologic assessment including accurate micro staging. Shave biopsies or cauterization compromise pathologic evaluation and should be avoided. For large lesions or anatomically sensitive locations, incisional biopsy sampling the most concerning area may be acceptable, though thorough sampling is essential.

Histopathological Evaluation and Ancillary Testing

Pathologic diagnosis requires integration of architectural features, cytologic atypia, and host response. Melanocytic markers, including S100 (sensitive but not specific), MART-1/Melan-A (most sensitive melanocytic marker), HMB-45 (recognizing gp100), and MITF-1 (nuclear stain), facilitate diagnosis, particularly for amelanotic or desmoplastic variants. Desmoplastic melanoma, a rare variant with

predilection for head and neck, demonstrates unique immunohistochemical profile with S100 positivity but frequent MART-1 negativity

Emerging Diagnostic Technologies

Technological innovations promise to enhance diagnostic precision and reduce unnecessary interventions. Reflectance confocal microscopy enables noninvasive, in vivo visualization of cutaneous structures at cellular resolution. Evidence from randomized trials demonstrates that adjunctive reflectance confocal microscopy reduces unnecessary excisions by 43.4% compared withstandard care alone, reducing the number needed to excise from 5.3 to 3.0 while ensuring all delayed-diagnosed melanomas were thinner than 0.5 mm. For lentigo maligna, reflectance confocal microscopy-guided surgery has demonstrated local recurrence rates below 1% when combined with Mohs micrographic surgery, compared with 13% for wide local excision

Treatment Deintensification

As therapeutic efficacy has improved, attention has turned to optimizing treatment intensity to reduce toxicity while maintaining outcomes. Emerging deintensification strategies include shortened duration of anti-PD-1 therapy, dose attenuation, and response-adapted approaches . Neoadjuvant therapy, administered before definitive surgery, offers particular promise by enabling in vivo assessment of treatment response and potentially reducing extent of subsequent surgery. Importantly, incorporation of patient-reported outcomes in deintensification trials remains limited, representing an important area for future investigation

Conclusion

Malignant melanoma represents a paradigm for precision oncology, wherein molecular understanding has translated directly into improved patient outcomes. From recognition of UV-induced mutagenesis to identification of targetable driver mutations and harnessing of antitumor immunity, progress in melanoma has been remarkable. Yet challenges remain: overdiagnosis of indolent lesions, therapeutic resistance in advanced disease, and persistent disparities in outcomes for mucosal

and acral subtypes. Continued integration of emerging technologies—from reflectance confocal microscopy to personalized mRNA vaccines—promises further refinement of diagnostic accuracy and therapeutic efficacy. For clinicians, maintaining vigilant clinical suspicion while embracing evidence-based innovations remains essential for optimizing patient outcomes across the spectrum of melanoma presentation.

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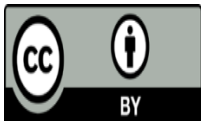

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