

Contemporary Diagnosis and Management of Advanced Melanoma

Epidemiology

Skin cancer is the most common type of diagnosed cancer. Although nonmelanoma cancers (eg, basal cell and squamous cell) account for the vast majority of cases, melanoma is the most lethal.^{1,2} In 2017, an estimated 87,110 cases of melanoma will be diagnosed and an estimated 9730 deaths will occur due to the disease.² The 5-year survival rate for patients whose melanoma is diagnosed and treated early, while it is still localized, is 98%. However, melanoma is more likely to spread than other skin cancers and later-stage diagnosis and treatment lead to less favorable outcomes. For patients whose melanoma has spread regionally before treatment, 5-year survival is approximately 68%, and for patients with metastatic disease, 18%.^{1,2}

Risk Factors

Predisposition for melanoma is multifactorial and depends on several risk factors. Environmental, lifestyle, and genetic components contribute significantly to the risk of developing the disease.^{3,4}

The greatest environmental risk factor for melanoma is exposure to ultraviolet (UV) radiation. Paradoxically, intermittent sun exposure is a major determining risk factor for melanoma, whereas regular continuous UV exposure is associated with more nonmelanoma cancers.^{3,5} A higher number of lifetime sunburns correlates with increased risk of melanoma; the risk doubles in persons who have ever had a sunburn compared with those who have not.^{4,5} The use of artificial UV light (eg, tanning beds) is also associated with an increased risk for melanoma, regardless of whether or not skin is burned.^{6,7}

Having a personal or family history of melanoma also increases the risk.² This may be due to genetic factors or shared traits and habits (eg, skin type, frequent sun exposure).⁸ Those who have a first-degree relative who has had melanoma have twice the risk of developing it, and that is before accounting for other risk factors.⁵ Overall, families with a hereditary predisposition to melanoma account for up to 10% of melanoma cases.⁴ Xeroderma pigmentosum, an inherited genetic disorder, confers a higher risk for melanoma, as cells are particularly sensitive to UV radiation and their ability to repair DNA is reduced.⁵

Another important factor is the presence of dysplastic nevi, or atypical moles. Results from a meta-analysis found that an increased number of either type of nevi was associated with an increased risk for melanoma. Individuals with 16 to 40 common nevi had a significantly greater risk for

melanoma versus those with 0 to 14 common nevi, and for those with 100 to 120 common nevi, the risk was nearly 7 times higher. Dysplastic nevi are an even greater indicator of melanoma risk, as individuals with any dysplastic nevi had a 10-fold increase in risk for melanoma over those who had none.⁹

Clinical Features

Currently, there is little direct evidence that the risk of death from melanoma can be sufficiently mitigated by offering general screenings for the condition. Therefore, the US Preventive Services Task Force (USPSTF) cannot assess the benefits (eg, reducing morbidity and mortality) and harms (eg, overdiagnosis and unnecessary excision and biopsy of suspected lesions) of visual skin examinations in healthy adults with no obvious risk factors for melanoma. USPSTF does, however, recommend that individuals with fair skin aged 10 to 24 years receive counseling to reduce their risk of skin cancer by minimizing UV exposure.¹⁰

Clinical presentation of melanoma differs significantly by age and sex. Melanoma occurs primarily in adults, with roughly 70% of new cases diagnosed in people 50 years and older. Children and adolescents account for less than 1% of new diagnoses.¹¹ In men, melanoma occurs more frequently on the trunk (between hips and shoulders) and on the head and neck. In women, it is more commonly diagnosed on the extremities.^{12,13} In a hospital-based study of 4785 patients with melanoma, being of a younger age (<65 y) was associated with significantly longer survival. As seen in other studies, women had significantly longer survival than men, independent of other factors, and experienced significantly less recurrence.¹⁴

Diagnosis

Guidelines for diagnosing melanoma are published by the American Academy of Dermatology (AAD) and the European Society for Medical Oncology (ESMO), which both recognize the American Joint Committee on Cancer (AJCC) melanoma staging system.^{15,16,17} Suspicious lesions are identified visually using the ABCDE rule (Asymmetry, Border, Color, Diameter, Evolution).¹⁵⁻¹⁷ Guidelines recommend excisional biopsy with negative margins upon initial presentation of a suspicious lesion and subsequent histologic evaluation to determine tumor stage and other risk criteria.^{15,16}

At minimum, histologic reporting should include Breslow thickness, mitotic rate, and presence of ulceration, as these are independently associated with poorer prognoses.

Anatomical site, degree of sun damage, type of melanoma (superficial spreading melanoma, lentigo maligna melanoma, acral lentiginous melanoma, nodular melanoma, etc), and the presence or absence of microscopic satellites are also important to report.^{15,16} AAD recommends reporting additional histologic markers in the pathology evaluation, including vertical growth phase, tumor-infiltrating lymphocytes, angiolymphatic invasion, and regression. However, the prognostic value of these features has not been fully elucidated.¹⁵ There is consensus in recommending against sentinel lymph node biopsy (SLNB) in stage I disease. However, for tumors greater than 1 mm in thickness, AAD urges consideration of SLNB, with appropriate cautions regarding the prognostic value of results seen in clinical studies.¹⁵ Testing for gene mutations (eg, *BRAF*, *KIT*) in patients with advanced melanoma is also strongly encouraged.¹⁶

The characteristics of primary and metastatic tumors affect the prognosis of melanoma. Increased tumor thickness (Breslow thickness) and invasiveness (Clark level), higher mitotic index, presence of ulceration, increased lymph node involvement, presence of microscopic satellite metastases around the primary tumor, and elevated serum lactate dehydrogenase are indicative of poorer prognoses.^{15,18} The most important predictors of prognosis are whether or not the disease has metastasized and to which sites metastasis has occurred. Lung or other visceral organ involvement is associated with a worse prognosis than melanoma that has spread subcutaneously or to distant skin or lymph nodes.^{18,19}

Classification of Disease

Internationally accepted, established melanoma staging criteria by AJCC are based on size and invasiveness of the primary tumor (T), regional or distant lymph node involvement (N), and metastases (M). Tumor thickness is rated on a scale of T0 (no evidence of primary tumor) to T4 (>4 mm in thickness). TX indicates that the primary tumor cannot be assessed (eg, due to lack of information).^{16,20} N0 represents no lymph node metastases, whereas N1 to N3 indicate the number of nearby (regional) lymph nodes that are involved. NX indicates that lymph nodes cannot be assessed.²⁰ Metastases are described according to the type of tissues they affect (eg, subcutaneous, skin, or lymph node metastases; metastases to the lungs, other visceral sites, or distant metastases). M0 indicates no detectable metastases. Unknown indicates there is not enough information to assess the stage.

The TNM staging system correlates with the stage 0 (in situ) to IV (metastatic) staging system, where stages I and II describe localized disease and include any stage T with no metastasis. Stage III melanoma is classified as regional disease and represents any stage T, plus involvement of at least 1 regional lymph node but no metastases. Stage IV

represents advanced, metastatic disease, and includes any T, plus any N and M.²⁰ Planned revisions to these staging criteria affecting characterizations within T, N, and M will be implemented January 1, 2018.²¹

Survival varies greatly according to stage at initial diagnosis and other clinical and histologic features. A majority of patients (84%) receive a localized disease diagnosis (stage I-II) and have a 5-year survival rate of 98%. Approximately 9% have regional disease (stage III); the rate of 5-year survival for these patients is 62%. For the 4% of patients who have distant metastases (stage IV), the 5-year survival rate is 18%.^{2,11,20} The presence of ulceration (lack of intact epidermis) with any size tumor is associated with decreased survival. Ulceration of thin lesions results in roughly 4% of patients having reduced 5-year survival versus those with no ulceration. Ulceration increases with tumor thickness, and in patients with tumors that are more than 4 mm thick, survival is reduced by approximately 22%.¹⁸ The presence of microsattellites is also a prognostic feature: 5-year survival in patients with microsattellites is approximately 36% versus 84% in patients with no microsattellites. Visceral metastases also indicate worse prognosis, with metastases to visceral sites other than the lung having the poorest outcomes.²²

Molecular Characterization

Melanoma is associated with a particularly high mutation burden, and identifying these mutations is important to guide appropriate treatment.^{23,24} Point mutations can be identified through direct sequencing of a given stretch of DNA, larger changes can be identified using fluorescence in situ hybridization, or entire exomes or genomes of tumor samples can be sequenced (massively parallel sequencing) to find mutations, alterations, and copy number changes.²⁴

Recently, a whole-exome sequencing analysis of 318 samples of nonglabrous skin identified approximately 17 mutations per megabase.²³ Cutaneous melanoma is categorized into 4 genetic subgroups by MAPK driver mutations and include *BRAF*, *RAS* (*N-RAS*, *H-RAS*, *K-RAS*), *NFI* and triple wild-type (WT) melanomas.²³ Among these common genomic subtypes of approximately 50% of patients who have *BRAF*-mutated disease, 28% have *NRAS* mutations, 14% have *NFI* mutations. Within the triple WT subtype, recurrent *KIT* mutations occur in approximately 3% of melanomas. *BRAF* and *NRAS* mutations have been shown to be mutually exclusive.^{23,25,26}

In addition to mutation burden, melanoma tumors express PD-1 ligand (PD-L1), suppressing cytotoxic T-cell activity and interfering with the antitumor response. In melanoma, PD-L1 is also expressed by tumor infiltrating cells (TILs). TIL expression of PD-L1 has been significantly associated with tumor expression of PD-L1, contributing to an immunosuppressive environment.^{27,28} »

Assessment of Response to Therapy

In 2009, the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, established as a standardized method of assessing response to therapy in solid tumors, were updated (RECIST 1.1). These guidelines define objective criteria for complete and partial tumor responses, disease progression, and stable disease. In addition, baseline tumor measurements and overall tumor burden are considered and best overall response is recorded.²⁹ In advanced melanoma, additional criteria to assess treatment response have emerged as new therapies have become available. Although RECIST criteria were developed to assess responses to chemotherapy regimens, tumor responses with immunotherapies differ from those of cytotoxic agents. Researchers investigating the use of immune-related response criteria (irRC) identified that some patients receiving immunotherapies may be underserved by RECIST criteria. Incorporating a new standard using irRC is being discussed.³⁰

Imaging studies in the management of advanced melanoma include fluorodeoxyglucose positron-emission tomography (PET)/computed tomography (CT) and magnetic resonance imaging (MRI). PET is highly sensitive in identifying metastatic melanoma. Studies have shown between 80% and 100% sensitivity in late-stage disease, and PET and PET/CT have been shown to alter the course of treatment in patients in locoregional or distant recurrent melanoma. For patients with brain metastases or increased risk for developing brain metastases, MRI is recommended as normal brain activity interferes with PET sensitivity around these tissues.³¹

While local recurrence of melanoma is estimated to occur in 3% to 5% of patients with stage I or II disease, the risk of recurrence in patients with stage III melanoma is much higher. In a retrospective analysis, the overall 5-year risk of relapse at any site was 48% in patients with stage IIIA, 78% for stage IIIB, and 85% for stage IIIC melanoma.^{32,33} In patients who relapsed, 5-year survival from the time of first relapse was 20% for stage IIIA and IIIB and 11% for stage IIIC.³³

Treatment Guidelines

Recommendations from ESMO

Whereas recommendations for first-line agents for stage IV metastatic melanoma are under debate, the consensus is that immunotherapy and kinase inhibitors are the foundation of systemic treatment. For patients with confirmed *BRAF*-mutated melanoma, combination therapy with *BRAF* and MEK inhibitors is recommended. In all patients, anti-PD-1 therapy (nivolumab, pembrolizumab) and CTLA-4 inhibitors (ipilimumab) are recommended as first- and second-line treatment. Chemotherapy is considered a second-line therapy, or bridging treatment option.¹⁶

Recommendations from the Society for Immunotherapy of Cancer

For patients with unresectable stage IV melanoma with *BRAF* mutations or *BRAF*WT tumors with good performance status, the Society for Immunotherapy of Cancer (SITC) recommends interleukin-2 (IL-2) as first-line therapy (provided the patient meets IL-2 eligibility criteria and has no central nervous system [CNS] metastases). In these patients, ipilimumab or targeted therapy (for *BRAF*-mutated melanoma) is recommended as a second- and third-line therapy.³⁴

In patients with stage IV melanoma with *BRAF* mutations who show poor clinical performance, treatment with a *BRAF* inhibitor (vemurafenib, dabrafenib, and/or trametinib) should be considered for first-line therapy. In these patients, ipilimumab or chemotherapy should be considered for second-line therapy.³⁴

In patients with *BRAF*WT tumors who show poor clinical performance or have uncontrolled CNS metastases, first-line treatment with ipilimumab, clinical trial participation, or chemotherapy is recommended.³⁴ For patients who have advanced melanoma with a known *KIT* mutation, SITC recommends participation in a clinical trial evaluating *KIT* inhibitors. Second-line recommendations in these patients include IL-2, ipilimumab, and chemotherapy.³⁴

Conclusions

Early diagnosis and treatment of melanoma are associated with favorable outcomes, while the prognosis for patients with advanced melanoma is considerably worse. Men and women present differently with the disease, and women and younger patients experience better survival than men and older patients. Both environmental and hereditary components are implicated in its etiology, and further disease mutations complicate treatment. Although research is ongoing, several institutions have outlined strategies for the management of advanced melanoma, recommending first-line immunotherapies and targeted treatments to improve survival. ♦

REFERENCES

1. Toy EL, Vekeman F, Lewis MC, Oglesby AK, Duh MS. Costs, resource utilization, and treatment patterns for patients with metastatic melanoma in a commercially insured setting. *Curr Med Res Opin*. 2015;31(8):1561-1572. doi: 10.1185/03007995.2015.1062356.
2. American Cancer Society. Cancer facts and figures 2017. ACS website. cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf. Published 2017. Accessed November 2, 2017.
3. Rastrelli M, Tropea S, Rossi CR, Alaibac M. Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. *In Vivo*. 2014;28(6):1005-1011.
4. Volkovova K, Bilanicova D, Bartonova A, Letašiová S, Dusínska M. Associations between environmental factors and incidence of cutaneous melanoma: review. *Environ Health*. 2012;11(suppl 1):S12. doi: 10.1186/1476-069X-11-S1-S12.

5. Markovic SN, Erickson LA, Rao RD, et al; Melanoma Study Group of the Mayo Clinic Cancer Center. Malignant melanoma in the 21st century, part 1: epidemiology, risk factors, screening, prevention, and diagnosis. *Mayo Clin Proc*. 2007;82(3):364-380. doi: 10.4065/82.3.364.
6. Lazovich D, Vogel RI, Berwick M, Weinstock MA, Anderson KE, Warshaw EM. Indoor tanning and risk of melanoma: a case-control study in a highly exposed population. *Cancer Epidemiol Biomarkers Prev*. 2010;19(6):1557-1568. doi: 10.1158/1055-9965.EPI-09-1249.
7. Vogel RI, Ahmed RL, Nelson HH, Berwick M, Weinstock MA, Lazovich D. Exposure to indoor tanning without burning and melanoma risk by sunburn history. *J Natl Cancer Inst*. 2014;106(7):1-3. doi: 10.1093/jnci/dju219.
8. American Cancer Society. Risk factors for melanoma skin cancer. ACS website. cancer.org/cancer/melanoma-skin-cancer/causes-risks-prevention/risk-factors.html. Updated May 20, 2016. Accessed November 8, 2017.
9. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer*. 2005;41(1):28-44. doi: 10.1016/j.ejca.2004.10.015.
10. Bibbins-Domingo K, Grossman DC, Curry SJ, et al; US Preventive Services Task Force. Screening for skin cancer: US Preventive Services Task Force recommendation statement. *JAMA*. 2016;316(4):429-435. doi: 10.1001/jama.2016.8465.
11. National Cancer Institute. Cancer stat facts: melanoma of the skin. Surveillance, Epidemiology, and End Results Program website. <https://seer.cancer.gov/statfacts/html/melan.html>. Updated April 2017. Accessed November 2, 2017.
12. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. 2001;19(16):3622-3634. doi: 10.1200/JCO.2001.19.16.3622.
13. National Cancer Institute. Melanoma treatment (PDQ)—health professional version. NCI website. cancer.gov/types/skin/hp/melanoma-treatment-pdq. Updated August 25, 2017. Accessed November 10, 2017.
14. Lasithiotakis K, Leiter U, Meier F, et al. Age and gender are significant independent predictors of survival in primary cutaneous melanoma. *Cancer*. 2008;112(8):1795-1804. doi: 10.1002/cncr.23359.
15. Bichakjian CK, Halpern AC, Johnson TM, et al; American Academy of Dermatology. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol*. 2011;65(5):1032-1047. doi: 10.1016/j.jaad.2011.04.031.
16. Dummer R, Hauschild A, Lindenblatt N, Pentheroudakis G; ESMO Guidelines Committee. Cutaneous melanoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2015;26(suppl 5):v126-v132. doi: 10.1093/annonc/mdv297.
17. Abassi NR, Shaw HM, Rigel DS, et al. Early diagnosis of cutaneous melanoma: revisiting the ABCD criteria. *JAMA*. 2004;292(22):2771-2776. doi: 10.1001/jama.292.22.2771.
18. Homsy J, Kashani-Sabet M, Messina JL, Daud A. Cutaneous melanoma: prognostic factors. *Cancer Control*. 2005;12(4):223-229.
19. Zybtek B, Carlson JA, Granese J, Ross J, Mihm MC, Slominski A. Current concepts of metastasis in melanoma. *Expert Rev Dermatol*. 2008;3(5):569-585. doi: 10.1586/17469872.3.5.569.
20. American Joint Committee on Cancer. Melanoma of the skin staging: 7th edition. AJCC website. cancerstaging.org/references-tools/quickreferences/Documents/MelanomaSmall.pdf. Published 2009. Accessed November 9, 2017.
21. American Joint Committee on Cancer. 8th Edition Implementation Project. AJCC website. cancerstaging.org/8thEdImplementation/Pages/default.aspx. Accessed November 12, 2017.
22. Tas F. Metastatic behavior in melanoma: timing, pattern, survival, and influencing factors. *J Oncol*. 2012;(2012):1-9. doi: 10.1155/2012/647684.
23. Rajkumar S, Watson IR. Molecular characterisation of cutaneous melanoma: creating a framework for targeted and immune therapies. *Br J Cancer*. 2016;115(2):145-155. doi: 10.1038/bjc.2016.195.
24. Wilson MA, Nathanson KL. Molecular testing in melanoma. *Cancer J*. 2012;18(2):117-123. doi: 10.1097/PP0.0b013e31824f11bf.
25. Cancer Genome Atlas Network. Genome classification of cutaneous melanoma. *Cell*. 2015;161(7):1681-1696. doi: 10.1016/j.cell.2015.05.044.
26. Lyle M, Long GV. Diagnosis and treatment of KIT-mutant metastatic melanoma. *J Clin Oncol*. 2013;31(26):3176-3181. doi: 10.1200/JCO.2013.50.4662.
27. Philips GK, Atkins M. Therapeutic uses of anti-PD-1 and anti-PD-L1 antibodies. *Int Immunol*. 2014;27(1):39-46. doi: 10.1093/intimm/dxu095.
28. Taube JM, Klein A, Brahmer JR, et al. Association of PD-1, PD-1 ligands, and other features of the tumor microenvironment with response to anti-PD-1 therapy. *Clin Cancer Res*. 2014;20(19):5064-5074. doi: 10.1158/1078-0432.CCR-13-3271.
29. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi: 10.1016/j.ejca.2008.10.026.
30. Hodi FS, Hwu WJ, Kefford R, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *J Clin Oncol*. 2016;34(13):1510-1517. doi: 10.1200/JCO.2015.64.0391.
31. Emmett L, Ho B. Imaging for melanoma and non-melanoma skin cancers. *Cancer Forum*. 2012;36(3):1-4. cancerforum.org.au/wp-content/uploads/2015/06/CFNOV12-Forum-Emmett-Ho.pdf. Published November 2012. Accessed November 12, 2017.
32. Dong XD, Tyler D, Johnson JL, DeMatos P, Siegler HF. Analysis of prognosis and disease progression after local recurrence of melanoma. *Cancer*. 2000;88(5):1063-1071. doi: 10.1002/(SICI)1097-0142(20000301)88:5<1063::AID-CNCR17>3.0.CO;2-E.
33. Romano E, Scordo M, Dusza SW, Coit DG, Chapman PB. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. *J Clin Oncol*. 2010;28(18):3042-3047. doi: 10.1200/JCO.2009.26.2063.
34. Kaufman HL, Kirkwood JM, Hodi FS, et al. The Society for Immunotherapy of Cancer consensus statement on tumour immunotherapy for the treatment of cutaneous melanoma. *Nat Rev Clin Oncol*. 2013;10(10):588-598. doi: 10.1038/nrclinonc.2013.153.