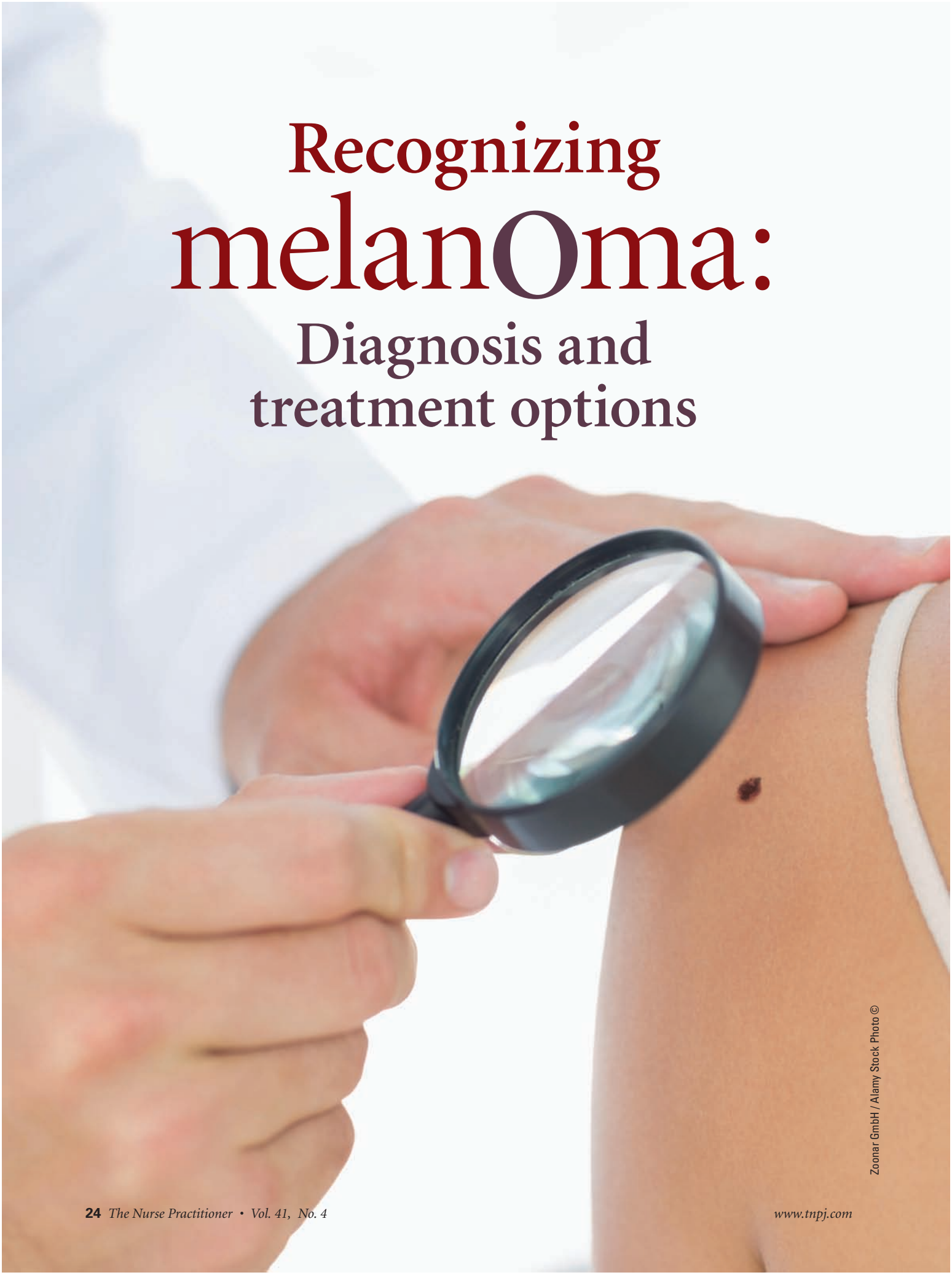
Recognizing melanOma: Diagnosis and treatment options



Zoonar GmbH / Alamy Stock Photo ©

2.0 CONTACT HOURS CE

Abstract: Melanoma is a malignant tumor that is usually cutaneous in origin and is associated with significant morbidity and mortality. As one of the most common cancers seen in young adults, melanoma represents a major public health concern in terms of years of lost productivity.

By Theresa Canavan, MD, and Wendy Cantrell, DNP, CRNP

Over the past several decades there has been a significant rise in cutaneous melanoma incidences in White populations, and it has grown from a very rare malignancy into a disease of considerable clinical importance.[1-5] Between 2007 and 2009, the overall melanoma incidence in the United States was 21.87 cases per 100,000 person-years, which is up significantly from 13.94 cases in 1989 to 1991.[4] The risk of developing melanoma is very low in darkly pigmented populations.[6,7]

Data from the U.S. Surveillance, Epidemiology, and End Results database, which cover approximately 14% of the U.S. population, identified malignant melanoma as the most rapidly increasing cancer in both genders between 1973 and 1997.[8] The male-to-female ratio in melanoma differs depending on the population examined. Men have an increased risk of melanoma in areas with a relatively high incidence of melanoma, such as the United States.

Men in the United States have a 1 in 33 lifetime risk for developing melanoma, compared with 1 in 52 for U.S. women.[9] In contrast to nonmelanoma skin cancers, malignant melanoma affects a younger population with the median age at diagnosis of 55 years.[10] Melanoma is associated with significant morbidity and mortality; however, mortality has leveled over since 1990. Mortality had risen throughout the 1980s around the globe and peaked from 1988 to 1990.[11,12]

The vertical tumor thickness (Breslow depth) is one of the most important prognostic factors in malignant melanoma, with thinner tumors associated with more favorable outcomes.[13] Effective public awareness campaigns over the past few decades have resulted in a trend for diagnosing thinner, less invasive melanomas, and an associated improved mortality (although the portion of thick melanomas has remained relatively constant).[10,14,15]

Risk factors

Malignant melanoma has a multifactorial etiology, with both genetics and environmental exposures contributing to an individual's risk. As with most cancers, melanoma prevention is one of the most important elements in improving patients' lives. It is important to educate patients about melanoma because some of the risks are modifiable. Identifying high-risk populations aids in clinical decision making, including adjusting the threshold for biopsy, tailoring patient education and counseling, and patient surveillance.

The genetics that confer increased risk for melanoma range from rare, high-penetrance germline mutations to common pigmentation genes responsible for increased risk in those with fair skin.[15,16] An estimated 10% of melanoma cases have a first- or second-degree relative with a history of melanoma.[16] Two high-penetrance susceptibility genes have been identified in familial melanoma: cyclin-dependent kinase inhibitor 2A *(CDKN2A)* locus (accounting for susceptibility in between 25% and 40% of melanoma-predisposed families) and the cyclin-dependent kinase-4 *(CDK4)* gene (which has been documented in three melanoma families thus far).[15,17,18] Mutations in *CDKN21*, which encodes p16 and p14 proteins that regulate cell cycle progression via the retinoblastoma (Rb) protein and the p53 pathway, respectively, result in cell progression from G1 arrest to S phase.[19] Less common familial melanoma mutation in-

Keywords: acral lentiginous melanoma, lentigo maligna melanoma, melanoma, melanoma subtypes, nodular melanoma, skin cancer, superficial spreading melanoma

clude protection of telomeres 1 *(POT1)* and telomerase reverse transcriptase *(TERT)*, both of which are involved in protecting telomeres. *POT1* and *TERT* have been found to be mutated in 9% of *non-CDKN21* and *CDK4* associated familial melanoma cases.[20]

Host factors associated with melanoma risk include light brown, blond, or red hair; blue eye color; high freckle density; and skin type.[15,21] Red hair relative to dark hair conferred an increased relative risk of 3.64 (confidence interval 2.56 to 5.37).[15] Multiple low-prevalence genetic variants of the melanocortin-1-receptor gene (which plays a role in melanin production) are associated with red hair, fair skin, and increased melanoma risk.[22-24]

Although melanomas most frequently arise de novo and not from malignant melanocytic or atypical nevi transformations, increased melanocytic and atypical melanocytic nevi are both reflective of UV exposure in genetically susceptible patients, and each are associated with an increased melanoma risk. A patient's risk for malignant melanoma development increases in proportion to the number of common melanocytic nevi present.[15,25,26] Similarly, a direct relationship has been reported between increasing atypical nevi and rising risk for developing melanoma.[25,26]

Although the relationship between sun exposure and melanoma is more complex than that seen in nonmelanoma skin cancers such as squamous cell carcinoma, intermittent sun exposure and history of sunburns are risk factors for developing melanoma.[10] Conflicting reports exist in the literature regarding a possible higher susceptibility for melanoma when children are exposed to excessive UV radiation relative to the risk this exposure confers in adults.[27-29] Nurse practitioners (NPs) should inform patients about the dangers of UV exposure in order to help mitigate melanoma risk.

Tanning beds, which are known to be carcinogenic, represent a significant modifiable risk factor for melanoma development. Tanning beds are currently used by about 30 million North Americans per year, including 2.3 million adolescents.[30] Individuals who have ever used a tanning bed in North America have been reported to have a 23% increased risk for developing melanoma.[31] Although no level of use appears to be safe, the risk of developing melanoma appears strongest when tanning beds are used over 10 times (in one's lifetime) or used by those under age 25.[31]

Pathogenesis

Dysfunction in melanocytic cellular signaling pathways has been identified in several essential pathways in melanomas. The mitogen-activated protein kinase (MAPK) cascade is an important pathway that regulates cellular proliferation and growth.[32] B-Raf proto-oncogene, serine/threonine kinase (BRAF), KIT proto-oncogene receptor tyrosine kinase (KIT), neuroblastoma RAS viral (v-ras) oncogene homolog (NRAS), and retinoblastoma 1 (Rb1) are downstream targets in this cellular pathway. The MAPK pathway's importance on melanoma's pathogenesis can be seen in the high frequency of mutations in its downstream targets. Targeted therapies were developed from identification and the knowledge of specific mutations involved in melanoma's pathogenesis.

Immune surveillance plays an important role in developing melanoma and its progression. Immunosuppressed patients (including solid organ transplant recipients and HIV/AIDS patients—regardless of highly active antiretroviral therapy use) have an increased risk for developing melanoma.[33,34]

Clinical presentation

Melanoma's anatomic site varies by gender. In men, 55% of tumors are found on the trunk, with 39% on the back, while 42% of tumors in women are found on the lower extremities. Melanomas that localize to the head and neck or upper extremities have equal prevalence in both men and women.[10] The anatomic site also varies by age, with a larger proportion of melanomas arising on the head and neck in older adults compared with other age groups.[35]

Four major subtypes of early melanoma have been identified: superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM). (See *Subtypes of melanoma*.) Although the overwhelming majority of melanomas arise as pigmented lesions, each of the four subtypes can arise without pigment, which is then termed amelanotic melanoma.

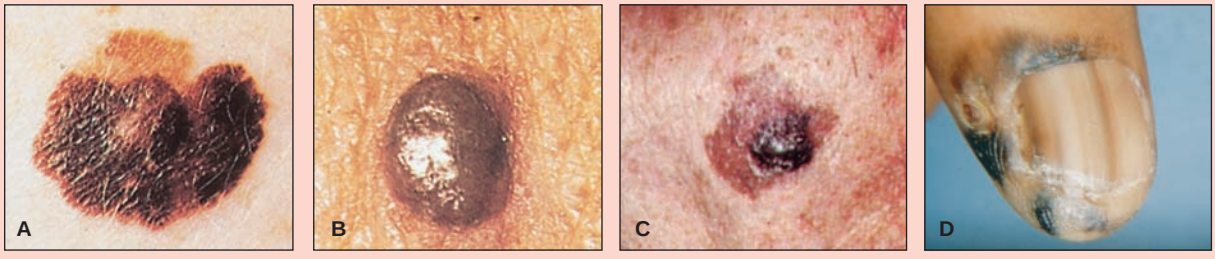
SSM is the most common type of melanoma in White patients and accounts for approximately 60% to 70% of all melanomas. SSM presents in relatively younger patients (median age: 40 to 49) and has a predilection for intermittently sun-exposed areas, such as the trunk in men and legs in women.[36] SSM begins as an asymptomatic brown to black macule with irregular borders and color variation, arising either de novo or from existing nevi. Two growth phases have been described: one that is slow and radial (horizontal and confined to the epidermis) and the other characterized by faster vertical growth (associated with the clinical development of a raised area).

NM is the second most common type of melanoma in White patients, accounting for approximately 15% to 30% of all melanomas.[37] Patients with NM tend to be slightly older (median age: 60 to 69), and these lesions can develop on any area of the body.[36] NM typically develops de novo as rapidly growing blue to black, but sometimes pink or red, nodules that may have associated ulceration or hemorrhage. NM is often diagnosed at a more advanced stage and have a poorer prognosis because these lesions lack the horizontal growth phase seen in SSM.

LMM accounts for around 10% of all melanomas. LMM presents in slightly older patients (median age: 70 to 79) and

Subtypes of melanoma

The following are examples of the four subtypes of melanoma.



A Superficial spreading melanoma with an irregular border
B Nodular melanoma
C Lentigo maligna melanoma
D Acral lentiginous melanoma with pigment spread to the periungual skin

Sources: Nettina SM. *Lippincott Manual of Nursing Practice*. 10th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2014:1166.

Goodheart HP. *Goodheart's Photoguide to Common Skin Disorders Diagnosis and Management*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2009:421.

tend to develop on chronically sun-exposed areas, such as the head and neck.[36] LMM develops as a large, pigmented macule with irregular borders. Around 5% of these superficial lesions eventually progress and become invasive, and this can be associated with thickening, induration, and even ulceration.

ALMs are uncommon and arise in older patients (median age: 60 to 69). By definition, ALM arises on acral sites, including the palms, soles, or around the nail unit.[36] The incidence of ALM is similar across all ethnic groups; therefore, there is a disproportionate percentage of darkly pigmented patients with ALM relative to other types of melanoma. ALM develop as brown to black asymmetric macules with irregular borders (similar to LMM), and although these grow slowly, they are often diagnosed at an advanced stage. Nail matrix melanoma can present with either longitudinal melanonychia or hyperpigmentation extending on to the hyponychium, lateral, or proximal nail fold.

Diagnosis

An early melanoma diagnosis is essential for improving patient prognosis and survival. More superficial, thinner lesions are associated with improved clinical outcomes; therefore, early diagnosis with excisional biopsy is imperative. A full-thickness excisional biopsy is required at the time of initial biopsy in order to determine a potential melanoma's Breslow thickness. Punch and shave biopsies provide insufficient histologic information and are not recommended. The clinical diagnosis of melanoma is based on visual appearance and can be aided significantly by dermoscopy.[38,39]

Dermoscopy is a helpful bedside technique that involves a handheld light magnifier (typically 10-fold magnification) to distinguish between benign and malignant pigmented lesions. Many clinicians may derive significant benefit from learning dermoscopy through taking a course on this topic, as the dermoscopy's clinical utility is operator dependent. Although multiple algorithms exist for diagnosing melanoma using dermoscopy, the pattern approach is one of the most widely used and assesses the following characteristics: general appearance, pigmentation pattern, color, pigmentation network, globules, dots, depigmentation, and the margins.[37]

Tumor staging is based upon a tumor-node-metastases system and includes four distinct stages.[40] At the tumor level, three factors are assessed: Breslow depth, mitotic rate, and presence of ulceration. Nodal evaluation assesses the number of microscopically or clinically affected lymph nodes and the presence of in-transit metastases. The metastatic component evaluates for the presence of distant metastatic lesions and the serum lactate dehydrogenase level.[41]

Unresectable tumors can be evaluated for specific mutations, which, if present, can help determine treatment options. For example, the recently approved cobas 4800 BRAF V600 mutation test can be used to evaluate if a tumor harbors the BRAF (V600E) mutation. Patients with unresectable BRAF V600E positive melanomas have been shown to have significantly enhanced overall and progression free survival when treated with vemurafenib, which is a BRAF kinase inhibitor.[42,43]

Treatment

Treatment modalities are based upon the stage at diagnosis. Surgical excision with adequately conservative margins is the cornerstone of treatment for localized disease without lymph node involvement (stages I and II). Lymph node involvement that is identified clinically or through imaging

is treated with lymph node dissection. Adjuvant therapy is an option for high-risk stage II or III patients, the goal of which is to eliminate subclinical micrometastases.

In the last several years, as the understanding of the molecular genetics of melanoma has expanded, there has been great interest in developing targeted treatments, and there are now numerous adjuvant treatment options. Some of the recently approved treatments have targeted BRAF V600E mutations (cobimetinib, trametinib, dabrafenib, and vemurafenib), some target the programmed cell death 1 receptor (pembrolizumab and nivolumab), while others act through immunomodulation (ipilimumab).[44-48] Talimogene laherparepvec, which is also a novel adjuvant treatment modality, is an oncolytic virus and is the first in its class in treating inoperable tumors.[49]

Stage IV disease, which is associated with a poor prognosis and a median survival of 9 months, is treated with surgery, radiation therapy, systemic chemotherapy, or novel therapies currently under investigation; however, a focus on palliation and improved quality of life is also appropriate. Immunomodulating therapy for melanoma is an area of active research with treatment options that include cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) blockade and cancer vaccines. CTLA-4 is a monoclonal antibody that works by inhibiting the stop-point in T-cell activation and has shown promising results with improved survival rates—especially when combined with systemic chemotherapy.[50,51]

Tumor vaccines attempt to enhance the immune response to recognize and combat the melanoma. Unfortunately, most tumor vaccines have shown mostly negative results in clinical trials; however, newer peptide vaccines are promising options and are currently under investigation. The understanding of the pathogenesis of melanoma and the availability of tumor genotyping has helped make targeted therapies possible, including a novel, small molecule that selectively inhibits the mutant BRAF kinase in patients with specific BRAF mutations.[50,51] BRAF kinase inhibitors can confer rapid tumor responses; however, responses are often unsustainable due to high tumor mutation rates, which lead to drug resistance.

Tumor surveillance

After treatment of melanoma, patients must undergo regular surveillance for locoregional recurrence or secondary skin cancers. There is no consensus regarding optimal follow-up strategies; however, patients should be seen at least annually for a full skin exam and clinical assessment of lymph nodes. Patients who are deemed to be at higher risk may need more frequent evaluation. The NP plays an important role in following these patients for recurrence; therefore, a thorough understanding of melanoma is imperative for caring for these complicated patients.

Modifying risk factors

Malignant melanoma is tumor associated with significant morbidity, mortality, and increasing incidence. Preventing melanoma through identifying and helping patients modify potential risk factors is one of the most imperative aspects of patient care. Because prognosis is closely tied to thinner tumors at diagnosis, it is of great importance to risk stratify patients and identify those at increased risk for developing melanoma. A variety of treatment options are available (depending upon the stage at diagnosis), and ongoing research seeks to identify improved treatment options for patients with advanced disease. NP

REFERENCES

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *Cancer J. Clin*. 2013;63(1):11-30.
2. Hanly P, Soerjomataram I, Sharp L. Measuring the societal burden of cancer: the cost of lost productivity due to premature cancer-related mortality in Europe. *Int. J. Cancer*. 2015;136(4):E136-45.
3. Linos E, Swetter SM, Cockburn MG, Colditz GA, Clarke CA. Increasing burden of melanoma in the United States. *J. Invest. Dermatol*. 2009;129(7):1666–1674.
4. Shaikh WR, Dusza SW, Weinstock MA, Oliveria SA, Geller AC, Halpern AC. Melanoma thickness and survival trends in the United States, 1989 to 2009. *J. Natl. Cancer Inst*. 2015;108(1).
5. Peterson M, Albertini MR, Remington P. Incidence, survival, and mortality of malignant cutaneous melanoma in Wisconsin, 1995-2011. *WMJ*. 2015;114(5):196-201.
6. MacKie RM, Hauschild A, Eggermont AM. Epidemiology of invasive cutaneous melanoma. *Ann Oncol*. 2009;20: Suppl 6.
7. Diepgen TL, Mahler V. The epidemiology of skin cancer. *Br. J. Dermatol*. 2002;146:Suppl 61, 1–6.
8. Lens MB, Dawes M. Global perspectives of contemporary epidemiological trends of cutaneous malignant melanoma. *Br. J. Dermatol*. 2004;150(2):179-85.
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J. Clin*. 2016;66(1):7-30.
10. Garbe C, Leiter U. Melanoma epidemiology and trends. *Clin. Dermatol*. 2009; 27(1):3-9.
11. Hall HI, Miller DR, Rogers JD, Bewerse B. Update on the incidence and mortality from melanoma in the United States. *J Am Acad Dermatol*. 1999; 40(1):35-42.
12. Jemal A, Devesa SS, Hartge P, Tucker MA. Recent trends in cutaneous melanoma incidence among whites in the United States. *J Natl Cancer Inst*. 2001;93(9):678-83.
13. Egger ME, et al. Prognostic factors in melanoma patients with tumor-negative sentinel lymph nodes. *Surgery*. 2016.
14. Armstrong A, et al. Are we seeing the effects of public awareness campaigns? A 10-year analysis of Breslow thickness at presentation of malignant melanoma in the South West of England. *J Plast Reconstr Aesthetic Surg*. 2014;67(3):324-30.
15. Chen ST, Geller AC, Tsao H. Update on the epidemiology of melanoma. *Curr Dermatol Rep*. 2013;2(1)24-34.
16. Hayward NK. Genetics of melanoma predisposition. *Oncogene. 2003;*22: 3053–3062.
17. Zuo L. et al. Germline mutations in the p16INK4a binding domain of CDK4 in familial melanoma. *Nat Genet*. 1996;12(1)97-9.
18. Soufir N. et al. Prevalence of p16 and CDK4 germline mutations in 48 melanoma-prone families in France. The French Familial Melanoma Study Group. *Hum Mol Genet*. 1998;7(2):209-16.
19. Udayakumar D, Tsao, H. Melanoma genetics: an update on risk-associated genes. *Hematol Oncol Clin North Am*. 2009;23(3):415-29.
20. Ransohoff KJ, Jaju PD, Tang JY, Carbone M, Leachman S, Sarin KY. Familial skin cancer syndromes: Increased melanoma risk. *J Am Acad Dermatol*. 2016;74(3):423-34.
21. Gandini S. et al. Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. *Eur J Cancer*. 2005;41(14):2040-59.
22. Valverde P, Healy E, Jackson I, Rees JL, Thody AJ. Variants of the melanocyte-stimulating hormone receptor gene are associated with red hair and fair skin in humans. *Nat Genet*. 1995;11(3):328-30.
23. Raimondi S, et al. MC1R variants, melanoma and red hair color phenotype: a meta-analysis. *Int J Cancer*. 2008;122(12):2753-60.

24. Williams PF, Olsen CM, Hayward NK, Whiteman DC. Melanocortin 1 receptor and risk of cutaneous melanoma: a meta-analysis and estimates of population burden. *Int J Cancer*. 2011;(129)7:1730-40.
25. Gandini S. et al. Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer*. 2005;41(1):28-44.
26. Olsen CM, Carroll HJ, Whiteman DC. Estimating the attributable fraction for cancer: A meta-analysis of nevi and melanoma. *Cancer Prev Res (Phila)*. 2010;3(2):233-45.
27. Dennis LK, Vanbeek MJ, Beane Freeman LE, Smith BJ, Dawson DV, Coughlin JA. Sunburns and risk of cutaneous melanoma: does age matter? A comprehensive meta-analysis. *Ann Epidemiol.* 2008;18(8):614-27.
28. Green AC, Wallingford SC, McBride P. Childhood exposure to ultraviolet radiation and harmful skin effects: epidemiological evidence. *Prog Biophys Mol Biol*. 2011;107(3):349-55.
29. Oliveria SA, Saraiya M, Geller AC, Heneghan MK, Jorgensen C. Sun exposure and risk of melanoma. *Arch Dis Child*. 2006;91(2):131-8.
30. Fisher DE, James WD. Indoor tanning—science, behavior, and policy. *N Engl J Med*. 2010;363(10):901-3.
31. Colantonio S, Bracken MB, Beecker J. The association of indoor tanning and melanoma in adults: systematic review and meta-analysis. *J Am Acad Dermatol*. 2014;70(5):847-57.
32. McKay MM, Morrison DK. Integrating signals from RTKs to ERK/MAPK. *Oncogene.* 2007;26(22):3113-21.
33. Dahlke E, Murray CA, Kitchen J, Chan AW. Systematic review of melanoma incidence and prognosis in solid organ transplant recipients. *Transplant Res.* 2014;3:10.
34. Olsen CM, Knight LL, Green AC. Risk of melanoma in people with HIV/AIDS in the pre- and post-HAART eras: a systematic review and meta-analysis of cohort studies. *PloS One*. 2014;9(4):e95096.
35. Anderson WF, Pfeiffer RM, Tucker MA, Rosenberg PS. Divergent cancer pathways for early-onset and late-onset cutaneous malignant melanoma. *Cancer*. 2009;115(18):4176-85.
36. Scolyer RA, Long GV, Thompson JF. Evolving concepts in melanoma classification and their relevance to multidisciplinary melanoma patient care. *Mol Oncol*. 2011;5(2):124-36.
37. Bolognia J, Rapini R, Nestle FO, Halpern A. Melanoma. In: *Dermatology*. Philadelphia, PA: Elsevier; 2008.
38. Kittler H, Pehamberger H, Wolff K, Binder M. Diagnostic accuracy of dermoscopy. *Lancet Oncol.* 2002;3(3):159-65.
39. Salerni G, Terán T, Alonso C, Fernández-Bussy R. The role of dermoscopy and digital dermoscopy follow-up in the clinical diagnosis of melanoma: clinical and dermoscopic features of 99 consecutive primary melanomas. *Dermatol Pract Concept*. 2014;4(4):39-46.
40. Balch CM, et al. Final Version of 2009 AJCC Melanoma Staging and Classification. *J Clin Oncol.* 2009;27(36):6199-206.
41. Boland GM, Gershenwald JE. Principles of Melanoma Staging. *Cancer Treat Res.* 2016;167:131-48.
42. Kim G. et al. FDA approval summary: vemurafenib for treatment of unresectable or metastatic melanoma with the BRAFV600E mutation. *Clin Cancer Res*. 2014;20(19):4994-5000.
43. Chapman PB, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med.* 2011;364(26):2507-16.
44. Davar D, Tarhini AA, Kirkwood JM. Adjuvant therapy for melanoma. *Cancer J*. 2012;18(2):192-202.
45. Redman JM, Gibney GT, Atkins MB. Advances in immunotherapy for melanoma. *BMC Med*. 2016;14(1):20.
46. Trinh VA, You Y, Hwu WJ. Treatment of BRAF-mutated advanced cutaneous melanoma. *Chin Clin Oncol*. 2014;3(3):28.
47. Hodi FS, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363(8):711-23.
48. Robert C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364(26):2517-26.
49. Kohlhapp FJ, Zloza A, Kaufman HL. Talimogene laherparepvec (T-VEC) as cancer immunotherapy. *Drugs Today (Barc)*. 2015;51(9):549-58.
50. Gray-Schopfer V, Wellbrock C, Marais R. Melanoma biology and new targeted therapy. *Nature*. 2007;445(7130):851-7.
51. Boni A, et al. Selective BRAFV600E inhibition enhances T-cell recognition of melanoma without affecting lymphocyte function. *Cancer Res*. 2010;70(13):5213-9.

Theresa Canavan is a dermatology resident at University of Alabama, Department of Dermatology, Birmingham, Ala.

Wendy Cantrell is an assistant professor and manager of clinical research at University of Alabama, Department of Dermatology, Birmingham, Ala.

The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.

DOI-10.1097/01.NPR.0000481508.24736.81