10 - 81 Cancer of the Skin

81 Cancer of the Skin

Premedication with histamine H1 and H2 receptor antagonists and glucocorticoids reduces the incidence of hypersensitivity reaction to taxanes, particularly paclitaxel. Despite premedication, hypersensitiv ity reactions may still occur. In these cases, rapid desensitization in the intensive care unit setting or re-treatment may be attempted with care, but the use of alternative agents may be required. Skin testing is used to assess the involvement of IgE in the reaction. Tryptase levels measured at the time of the reaction help to explain the mechanism of the reac tion and its severity. Increased tryptase levels indicate underlying mast cell activation. Candidate patients for desensitization include those who have mild to severe hypersensitivity type I, with mast cell–medi ated and IgE-dependent reactions occurring during a chemotherapy infusion or shortly thereafter.

■ ■FURTHER READING Azizi AH et al: Superior vena cava syndrome. JACC Cardiovasc Interv 13:2896, 2020. Castells M et al: Hypersensitivity to antineoplastic agents: Mechanisms and treatment with rapid desensitization. Cancer Immunol Immunother 61:1575, 2012. Castinetti F et al: Endocrine side-effects of new anticancer therapies: Overall monitoring and conclusions. Ann Endocrinol (Paris) 79:591, 2018. Conte P et al: Drug-induced interstitial lung disease during cancer PART 4 Oncology and Hematology therapies: Expert opinion on diagnosis and treatment. ESMO Open 7:1, 2022. Durani U, Hogan WJ: Emergencies in haematology: Tumour lysis syndrome. Br J Haematol 188:494, 2020. Fajgenbaum DC, June CH: Cytokine storm. N Engl J Med 383:2255, 2020. Gonzalez Castro LN, Milligan TA: Seizures in patients with can cer. Cancer 126:1379, 2020. Lawton AJ et al: Assessment and management of patients with metastatic spinal cord compression: A multidisciplinary review. J Clin Oncol 37:61, 2019. Paik WH, Park DH: Endoscopic management of malignant biliary obstruction. Gastrointest Endosc Clin N Am 34:127, 2024 Schusler R, Meyerson SL: Pericardial disease associated with malignancy. Curr Cardiol Rep 20:92, 2018. Thomas MR, Scully M: How I treat microangiopathic hemolytic anemia in patients with cancer. Blood 137:1310, 2021. Vogelbaum MA et al: Treatment for brain metastases: ASCO-SNOASTRO Guideline. J Clin Oncol 4:492, 2022. Brendan D. Curti, John T. Vetto,

Sancy A. Leachman

Cancer of the Skin MELANOMA Pigmented lesions are among the most common findings on skin exam ination. The challenge for the physician is to distinguish benign lesions from cutaneous melanomas and nonmelanoma skin cancers (NMSCs), both of which are increasing in frequency. Melanoma accounts for over half of the deaths resulting from skin cancer, although recent advances in immunotherapy and targeted therapy used in the neoadjuvant, adju vant, and advanced disease settings have significantly improved sur vival. Genomic analysis of melanoma has improved our understanding of prognosis, and informed treatment and surveillance strategies

beyond traditional surgical staging. Melanoma is an aggressive malig nancy of melanocytes, pigment-producing cells that originate from the neural crest and migrate to the skin, meninges, mucous membranes,

upper esophagus, and eyes. Melanocytes in each of these locations have the potential for malignant transformation, but most melanomas arise in the skin, facilitating detection when complete surgical excision can lead to cure. Cutaneous melanoma occurs in people of all ages and all colors. Noncutaneous melanomas have a different biology and a lower probability of response to the immunotherapy agents that have transformed the care of cutaneous melanoma. Examples of malignant melanoma of the skin, mucosa, eye, and nail are shown in Fig. 81-1. ■ ■RISK FACTORS AND EPIDEMIOLOGY The epidemiologic patterns seen in melanoma reflect the genetic and biologic features of melanocytes and their response to environmental ultraviolet radiation (UVR). Clinical features that confer an increased risk for melanoma include: (1) vulnerability to sun damage (light/red coloration of skin, hair, or eyes; photodamaged skin; history of expo sure to natural or artificial UVR; prior history of skin cancers of any type); (2) abnormal growth of melanocytes (increased absolute number of nevi, increased size of nevi, or atypical features of moles such as mul tiple colors, speckles, or shapes); and (3) immunosuppression (innate, functional, or drug-induced). Table 81-1 summarizes melanoma risk factors and the relative risk associated with these factors. The incidence and mortality rates are strongly influenced by ethnic, geographic, and environmental factors. For instance, the incidence of melanoma is 1/100,000 per year in populations with high skin eumelanin (a brown-black pigment that absorbs ultraviolet [UV] photons efficiently as they enter the epidermis) and up to 27/100,000 per year in populations with low skin eumelanin. Men are affected slightly more than women (1.4:1), and the median age at diagnosis is 66. Melanoma is one several cancer types with increasing incidence in the United States and is now the fifth leading cancer in men (59,170 new cases in 2024; probability 1:28) and the sixth leading cancer in women (41,460 new cases in 2024; probability 1:41). Although these rankings are based on the total number of new invasive melanoma cases in 2024, estimated at 100,640, an addi tional 99,700 cases of melanoma in situ (MIS) occurred in 2024. Mortality rates begin to rise at age 55, with the greatest mortality in men age >65 years. In contrast to the increasing incidence, the mortal ity rates for melanoma are decreasing, though this trend appears less dramatic outside of the United States. The most likely reason for the decreased mortality is the influence of immunotherapy and targeted therapy on melanoma-specific survival. After U.S. Food and Drug Administration (FDA) approval of ipilimumab and vemurafenib in 2011, the 1-year relative survival rate increased from 42% (2008–2010) to 55% (2013–2015). The mortality rate from 2013 to 2017 dropped annually by 7% in those aged 20–64 years old and dropped 5–6% per year for individuals aged ≥65 years. ■ ■GLOBAL CONSIDERATIONS The incidence of both nonmelanoma and melanoma skin cancers around the world has been increasing. Every year, between 2 and

3 million people develop NMSC, and in 2020, there were 324,635 cases of melanoma. A disproportionate number of cases and deaths occur in North America, Europe, Australia, and New Zealand. The highly variable melanoma incidence rates in different populations are due to the interplay between risk factors, including host genetics and environmental factors, which distribute risk unevenly across these populations and account for the absolute risk in different ethnic groups and geographic areas. Dark-skinned populations (such as those of India and Puerto Rico), blacks, and East Asians also develop melanoma but at rates 10–20 times lower than those in whites. Cutaneous melanomas in dark-skinned populations are more often diagnosed at a higher stage,

and patients tend to have worse outcomes. Surveillance, Epidemiology, and End Results (SEER) data (2016–2020) reveal that whites have the highest incidence of melanoma at 37.9 (men) and 25.2 (women) per 100,000 and that the incidence drops substantially in Hispanics (4.5 [men] and 4.3 [women] per 100,000), Native Americans (8.7 [men] and 7.8 [women] per 100,000), Asians/Pacific Islanders (1.3 [men] and 1.1 [women] per 100,000), and blacks (1 [men] and 0.9 [women] per 100,000). In nonwhite (Asian and dark-skinned) populations, the

A B C D E F G H I FIGURE 81-1 Types of melanoma. A. Hypomelanotic melanoma. B. Superficial spreading melanoma. C. Melanoma arising in a nevus. D. Seborrheic keratoses-like melanoma arising on the scalp. E. Nodular melanoma. F. Cutaneous melanoma metastases at a surgical margin (also known as melanoma satellites when <2 cm from the primary tumor and in-transit melanoma when >2 cm). G. Mucosal melanoma arising in the vulva. H. Ciliary body melanoma, note visible tumor in the pupil and areas of involvement in the iris and sclera. I. Acral melanoma with Hutchinson's sign on the proximal nail fold. (Parts A-G and I photos courtesy of Dr. Leonard Swinyer Collection, © Copyright 2020 University of Utah and Oregon Health & Science University. Part H photo courtesy of Dr. Alison Skalet, © Copyright 2022 Oregon Health & Science University [OHSU].) frequency of non–sun-exposed melanomas, such as acral (subungual, plantar, palmar) and mucosal melanomas, is much higher; the inci dence of melanoma in black and Hispanic populations is not associated with UV exposure. In China, ~20,000 new melanomas are reported each year, and in contrast to the United States, mortality is increasing. Non–sun-exposed melanomas have a different biology, have a lower probability of response to immunotherapy, and carry a poorer prog nosis than cutaneous melanomas, thus accounting for the increase in mortality of this melanoma subgroup. Little is known about the effects of mixed ethnicity on melanoma risk. ■ ■GENETIC SUSCEPTIBILITY TO MELANOMA Approximately 20–40% of hereditary melanomas (0.2–2% of all melanomas) are due to germline mutations in the cell cycle regulatory gene cyclin-dependent kinase inhibitor 2A (CDKN2A). In fact, 70% of all cutaneous melanomas have mutations or deletions affecting the CDKN2A locus on chromosome 9p21. This locus encodes two distinct tumor-suppressor proteins from alternate reading frames: p16 and ARF (p14ARF). The p16 protein inhibits CDK4/6-mediated phosphory lation and inactivation of the retinoblastoma (RB) protein, whereas ARF inhibits MDM2 ubiquitin-mediated degradation of p53. The loss of CDKN2A results in inactivation of two critical tumor-suppressor

 pathways, RB and p53, which control entry of cells into the cell cycle. Several studies have shown an increased risk of pancreatic cancer among melanoma-prone families with CDKN2A mutations. A second high-risk locus for melanoma susceptibility, CDK4, is located on chro mosome 12q13 and encodes the cyclin-dependent kinase inhibited by p16. CDK4 mutations, which also inactivate the RB pathway, are much rarer than CDKN2A mutations. Germline mutations in the melanoma lineage-specific oncogene microphthalmia-associated transcription factor (MITF), BRCA1-associated protein 1 (BAP-1), protection of telomeres 1 (POT-1), and telomerase reverse transcriptase (TERT) also predispose to familial melanoma with a not yet quantified high pen etrance, based on families that have been tested. The melanocortin-1 receptor (MC1R) gene is a moderate-risk inherited melanoma susceptibility factor. UVR stimulates the produc tion of melanocortin (α-melanocyte-stimulating hormone [α-MSH]), the ligand for MC1R, which is a G-protein-coupled receptor that signals via cyclic AMP and regulates the amount and type of pigment produced by melanocytes. MC1R is highly polymorphic, and many among its ~80 variants result in partial or full loss of signaling and lead to the production of non-photoprotective

red/yellow pheomelanins, rather than photoprotective brown/black eumelanins. The red hair color (RHC) phenotype produced by MC1R mutations includes lightly

TABLE 81-1 Melanoma Risk Factors and Relative Risk RISK LEVEL RISK FACTOR RELATIVE RISK 1 atypical nevus versus 0 1.5 Total common nevi, 16+ versus <15 1.5 Blue eye color versus dark 1.5 Hazel eye color versus dark 1.5 Green eye color versus dark 1.6 Light brown hair versus dark 1.6 Indoor tanning in any gender versus never 1.7 Elevated Fitzpatrick skin type II versus IV 1.8 Fitzpatrick skin type III versus IV 1.8 History of sunburn versus no sunburn 2.0 Blond hair versus dark 2.0 2 atypical nevi versus 0 2.1 Fitzpatrick skin type I versus IV 2.1 High density of freckles versus none 2.1 Total common nevi 41–60 versus <15 2.2 Family history of melanoma in 1 or more first-degree relatives 1.7–3.0 3 atypical nevi versus 0 3.0 Moderately elevated PART 4 Oncology and Hematology Total common nevi 61–80 versus <15 3.3 Red hair versus dark 3.6 Chronic lymphocytic leukemia 3.9 History of actinic keratoses and/or keratinocyte carcinoma versus not 4.3 Indoor tanning in women aged 30–39 versus never 4.3 4 atypical nevi versus 0 4.4 Transplant recipient versus not 2.2–4.6 Indoor tanning in women aged <30 versus never 6.0 5 atypical nevi versus 0 6.4 High Total common nevi 81–120 versus <15 6.9 Personal history of melanoma 8.2–13.4 CDK2NA mutation carrier 14–28 colored skin, red hair, freckles, increased sun sensitivity, and increased risk of melanoma. In addition to its weak UV-shielding capacity rela tive to eumelanin, increased pheomelanin production in patients with inactivating polymorphisms of MC1R also provides a UV-independent carcinogenic contribution to melanomagenesis via oxidative damage and reduced DNA damage repair. Other more common, low-penetrance polymorphisms in genes related to pigmentation, nevus count, immune responses, DNA repair, metabolism, and the vitamin D receptor have small effects on melanoma susceptibility. In sum, ~50–60% of the genetic risk for hereditary mela noma can be attributed to known melanoma predisposition genes, with ~40% of the known genetic risk attributable to CDKN2A. The other com ponents of inherited risk are most likely due to the presence of additional modifier genes and/or shared environmental exposures of the host. ■ ■PREVENTION AND EARLY DETECTION Primary prevention of melanoma and NMSC is based on protection from the sun. Public health initiatives, such as the SunSmart program that started in Australia and is now operative in Europe and the United States, have demonstrated that behavioral change can decrease the incidence of NMSC and melanoma. Preventive measures should start early in life because damage from UV light begins early even though cancers develop years later. Early episodes of sunburns may be a greater risk than chronic tanning. Some individuals tan compulsively. There is now greater understanding of tanning addiction and the cutaneousneural connections that may give rise to this behavior. Compulsive tanners exhibit differences in dopamine binding and reactivity in

reward pathways in the brain, such as the basal striatum, resulting in cutaneous secretion of β-endorphins after UV exposure. Identifying individuals with tanning addiction may be another prevention method. Regular use of broad-spectrum sunscreens that block UV-A and UV-B with a sun protection factor (SPF) of at least 30 and protective clothing should be encouraged. Physical blockers such as zinc oxide and tita nium dioxide have less likelihood of being absorbed or of generating an allergic reaction than chemical sunscreens. Avoidance of sunburns, tanning beds, and midday sun exposure is recommended. Secondary prevention comprises education and screening with the goal of early detection and can be individualized based on risk factors. A full-body skin exam is warranted in populations at higher risk for melanoma such as patients with clinically atypical moles (dysplastic nevi) and those with a personal history of melanoma.

Surveillance in high-risk patients should be performed by a dermatologist and include total-body photography and dermoscopy where appropriate. Individuals with three or more primary melanomas and families with at least one invasive melanoma and two or more cases of melanoma and/or pancreatic cancer, ocular melanoma, mesothelioma, or renal cell carcinoma among first- or second-degree relatives on the same side of the family may benefit from genetic testing. Atypical nevi and MIS should be completely removed with at least a 5-mm margin. Early detection of small lesions allows the use of simpler treatment modali ties with higher cure rates and lower morbidity. Monthly self-screening augments provider-based screening. Patients should be taught to recognize the clinical features of melanoma and advised to report any change in a pigmented lesion. There is evidence supporting the ability of media campaigns to reduce cancer mortality in lung cancer, and results from Australia's skin cancer campaigns demonstrate improve ment in attitude and behavior and a reduction in melanoma incidence. A benefit/cost analysis in Australia showed a return of $3.85 for every $1 invested. Although the U.S. Preventive Services Task Force states that there is insufficient evidence to recommend skin screening for the general population, additional research is anticipated to find best practices for skin cancer detection and prevention. ■ ■DIAGNOSIS Early detection of melanoma before it becomes invasive and lifethreatening metastases have occurred is essential and may be facili tated by applying the ABCDEs: asymmetry (benign lesions are usually symmetric); border irregularity (most nevi have clear-cut borders); color variegation (benign lesions usually have uniform light or dark pigment); diameter >6 mm (the size of a pencil eraser); and evolving (any change in size, shape, color, or elevation or new symptoms such as bleeding, itching, and crusting). In addition, any nevus that appears atypical and different from the rest of the nevi on that individual (an "ugly duckling") should be considered suspicious. The entire skin surface, including the scalp and mucous membranes, as well as the nails should be examined in each patient. Bright room illumination is important, and a hand lens or dermatoscope is helpful for evaluating variation in pigment pattern. Any suspicious lesions should be biopsied, evaluated by a specialist, or recorded by chart and/ or photography for follow-up. Dermoscopy employs low-level magni fication of the epidermis with polarized light or water interface and permits a more precise visualization of patterns of pigmentation than is possible with the naked eye. Biopsy Any pigmented cutaneous lesion that has changed on exami nation or has the other features previously discussed is a candidate for biopsy. An excisional biopsy with 1- to 3-mm margins (narrow-margin excision) is suggested. This facilitates histologic assessment of the lesion, permits accurate measurement of thickness if the lesion is mela noma, and constitutes definitive treatment if the lesion is benign. For lesions that are large or involving anatomic sites where excisional biopsy may not be feasible (such as the face, hands, and feet) or when suspicion of malignancy is low, an incisional biopsy (e.g. shave, saucerization, or punch) to include the most nodular or darkest area of the lesion is acceptable. Incisional biopsy does not appear to facilitate the spread of melanoma. For suspicious lesions, every attempt should be made to preserve the ability to assess the deep and peripheral margins and to

perform immunohistochemistry. All biopsies should be deep enough to include the deepest component of the entire lesion, and any pigment at the base of the lesion should be removed and included with the biopsy specimen. Punch biopsies are more likely to clear the deep margin but more likely to be positive at the radial margins; the opposite is true for shave biopsies. The choice of biopsy type should be guided by which is most likely to remove the entire lesion for histologic evaluation. The biopsy should be interpreted by a pathologist experienced in pigmented lesions, and the report should include Breslow thickness, mitotic rate, presence or absence of ulceration,

lymphatic/vascular/ neural invasion, regression, microsatellitosis, and the status of the peripheral and deep margins. Breslow thickness is the greatest thickness of a primary cutaneous melanoma measured on the slide from the top of the epidermal granular layer, or from the ulcer base, to the bottom of the tumor. To distinguish melanomas from benign nevi in challenging cases, genetic expression profiles (GEPs), fluorescence in situ hybridiza tion with multiple probes, or comparative genomic hybridization can be helpful. GEPs have also been developed to determine prognosis. ■ ■CLASSIFICATION AND PATHOGENESIS Clinical More recent classifications of melanoma are based on association with cumulative solar damage and nine different pathways related to genomic attributes summarized in Table 81-2. This revised classification incorporates traditional histopathologic designations such as superficial spreading, lentigo maligna, acral lentiginous, and desmoplastic, among others, but more precisely incorporates the pathophysiology and genetic drivers of melanoma subtypes. At present, genomic alteration pathways for melanomas are not incorporated into American Joint Committee on Cancer (AJCC) stag ing or prognostic considerations, yet characterizing the genomic and mutational profiles of melanoma has become increasingly common in clinical practice. It is anticipated that genomic pathway characteriza tion will become increasingly important in determination of mela noma prognosis and may influence surveillance strategies, surgical decisions, and medical therapy. Genomic The advent of next-generation sequencing has led to whole exome sequencing of thousands of cutaneous melanomas derived from nonglabrous (hair-bearing) skin. This has revealed very complex genomic changes resulting from both germline (see “Genetic Suscepti bility to Melanoma” above) and somatic mutations. Cutaneous melano mas have one of the highest somatic mutation rates (>10 mutations/Mb) among all cancers; the majority (76% of primary tumors and 84% of TABLE 81-2 Major Histologic Subtypes of Malignant Melanoma TYPE SITE APPEARANCE ASSOCIATED MUTATIONS Lentigo maligna Sun-exposed surfaces, particularly malar region and temple In flat portions, brown and tan predominate, but whitish gray sometimes present; in nodules, reddish brown, bluish gray, bluish black. Superficial spreading Any (more common on upper back and, in women, lower legs) Brown mixed with bluish red, bluish black, reddish brown, and often whitish pink. The lesion border is often visibly and/or palpably raised. Nodular Any Reddish blue, purple, or bluish black; can be uniform or mixed with brown and black. Acral lentiginous Palm, sole, nail bed, mucous membrane In flat portions, dark brown; in raised lesions (plaques), brown-black or blue-black. Desmoplastic Any (more common on head and neck) Highly variable; pigmentation is frequently absent. Can mimic nodular basal cell carcinoma. Uveal Choroid, ciliary body, iris Dome or mushroom shaped. Display low internal reflectivity on ocular ultrasound. Mucosal Oral cavity, conjunctiva, sinuses, alimentary tract including rectum and anus, vulva Can display radial growth pattern with ABCDE features associated with cutaneous melanomas. Often present with advanced tumors infiltrating local tissues Abbreviation: ABCDE, asymmetry (benign lesions are usually symmetric); border irregularity (most nevi have clear-cut borders); color variegation (benign lesions usually have uniform light or dark pigment); diameter >6 mm (the size of a pencil eraser); and evolving (any change in size, shape, color, or elevation or new symptoms such as bleeding, itching, and crusting).

metastatic melanomas) exhibit mutations indicative of UVR expo sure. The mutation rate varies based on body site; melanomas arising in chronic sun-damaged skin harbor substantially more mutations than melanomas from non–sun-damaged skin.

Melanomas can harbor thousands of mutations, but only a few are “driver” mutations that promote cell proliferation or inhibit normal pathways of apoptosis or DNA repair and confer a growth

advantage to the neoplastic cell. Some of the driver mutations for cutaneous melanoma are depicted in Fig. 81-2 along with the clinical evolution of melanoma lesions. Driver mutations are often found in combination with mutations to germline susceptibility genes such as p16, which affect cell cycle arrest, and ARF, which result in defective apoptotic responses to genotoxic damage. As melanocytes accumulate DNA damage, they can undergo malignant transformation characterized by invasion, metastasis, and angiogenesis. A genomic classification of cutaneous melanoma has been proposed based on the pattern of the most prevalent mutated genes, BRAF, RAS, and NF1, along with a triple wild type (WT), lacking mutations in these three genes. The pattern of DNA mutations can vary with the site of origin and should be determined along with the histologic subtype of the tumor. The proliferative pathways affected by the mutations include the mitogen-activated protein (MAP) kinase and phosphatidylinositol 3′ kinase/AKT pathways. RAS and BRAF, members of the MAP kinase pathway, which mediates the transcription of genes involved in cell proliferation and survival, undergo somatic mutation in melanoma and thereby represent potential therapeutic targets. NRAS is mutated in ~20% of melanomas, and somatic activating BRAF mutations are found in most benign nevi and 40–50% of cutaneous melanomas. Neither mutation by itself appears to be sufficient to cause melanoma; thus, they often are accompanied by other mutations, such as in TERT. The BRAF mutation is most commonly a T→A point mutation that results in a valine-to-glutamate amino acid substitution (V600E). V600E BRAF mutations are more common in younger patients and are present in most melanomas that arise on skin with intermittent sun exposure and are less common in melanomas from chronically sun-damaged skin (i.e., those of older patients). CHAPTER 81 Cancer of the Skin Melanomas may harbor mutations in AKT (primarily in AKT3) and PTEN (phosphatase and tensin homolog). AKT can be amplified, and PTEN may be deleted or undergo epigenetic silencing that leads to constitutive activation of the PI3K/AKT pathway and enhanced cell survival by antagonizing the intrinsic pathway of apoptosis. A loss-offunction mutation in NF1, which can affect both the MAP kinase and PI3K/AKT pathways, has been described in 10–15% of melanomas. BRAF 28% NRAS 15% PTEN BRAF 57% NRAS 18% BRAF 47% NRAS 33% NRAS 25% c-KIT 5-10% BRAF 10% MAPK and PI3K 73% High tumor mutational burden, BRAF and NRAS uncommon BAP1, GNAQ, GNA11 KIT, NRAS, KRAS or BRAF NF1

Driver Mutations BRAF: 10% NRAS: 10% C-KIT: 5–10% NF1: 48% of BRAF and NRAS WT melanoma in older patients BRAF: 50% NRAS: 20% C-KIT: 0% Nonchronic Sun Damage Chronic Sun Damage A B C Photodamage De Novo Nevus Dysplastic Nevus F D PART 4 Oncology and Hematology G E FIGURE 81-2 Cutaneous melanoma development and associated driver mutations. Chronic sun damage (with prominent solar elastosis) (A) predisposes to a lentigo maligna (in situ) (B), which can evolve into lentigo maligna melanoma (invasive) (C). Similarly, nonchronic sun damage can initiate melanoma de novo or in nevomelanocytes, where clinical and histologic changes of atypia may be seen prior to complete transformation. Nevi (D, E) can evolve into atypical lesions (F, G), in situ melanoma (H, I), and eventually invasive nodular (J) or superficial spreading melanomas (K). Images E, G, and I are dermascopic photos of images D, F, and H, respectively. (Part A photo courtesy of Dr. Sancy Leachman, Parts B, C, J, and K photos courtesy of Dr. Leonard Swinyer Collection, Parts D–I photos courtesy of Dr. Elizabeth Berry,) In melanoma, these two signaling pathways (MAP kinase and PI3K/ AKT) enhance tumorigenesis, chemoresistance, migration, and cell cycle dysregulation. ■ ■PROGNOSTIC FACTORS The most important clinical prognostic factors for a newly diagnosed patient are incorporated in the AJCC staging classification. The best pre dictor of recurrence is Breslow thickness, followed by ulceration,

which together make up the T stage for melanoma. The anatomic site of the primary tumor also influences prognosis; favorable sites are the forearm and leg, and unfavorable sites include the scalp, hands, feet, and mucous membranes. Women with stage I or II disease have better survival than men, perhaps in part because of earlier diagnosis; women frequently have melanomas on the lower leg, where self-recognition is more likely compared to the back, where melanoma is more likely in men. Older individuals, especially men >60, have a tendency toward delayed diagnosis (and thus thicker tumors), have more head and neck and acral melanomas (which tend to have earlier vertical growth and distant metastases), and are more likely to develop melanomas in chronically UVR-damaged skin (which are more often BRAF wild type, with fewer options for therapy). All these factors help explain the worse prognosis in older males. Other important adverse factors include high mitotic rate and lymphatic/vascular invasion. Clinical features such as microsatellite lesions and/or in-transit metastases, evidence of nodal involvement, elevated serum lactate dehydrogenase (LDH), and certain sites of distant metastases (e.g., brain, liver, and bone) all portend a higher stage and worse prognosis. GEPs and machine-learning algorithms that associate genomic changes with clinical outcomes have been used to estimate the prog nosis of melanoma. A commercially available 31-gene GEP is available that predicts for all-site (particularly distant) relapse and incorporates the increased and decreased expression, as well as the dysregulation, of

Lentigo Maligna Lentigo Maligna Melanoma Nodular Melanoma In Situ J H Superficial Spreading K I genes involved in many of the cellular processes leading to melanoma progression described earlier. Although this 31-gene GEP can estimate the probability of distant relapse, it has not supplanted the prognostic estimates derived from surgical staging. GEPs have been incorporated into management guidelines for breast, thyroid, and other cancers, but their use in cutaneous melanoma care is still under investigation. ■ ■STAGING The purpose of staging is to estimate melanoma prognosis and deter mine treatment selection. The current melanoma staging criteria and estimated 10-year survival by stage are depicted in Table 81-3. The clinical stage is determined after the microscopic evaluation of the melanoma skin lesion and clinical and radiologic assessment. The pathologic stage incorporates the results from microscopic examina tion of clinically negative regional lymph nodes obtained at sentinel lymph node biopsy (SLNB), any enlarged nodes found on exam or imaging, and any suspected metastases amenable to open or imageguided biopsy. All patients should have a complete history, with attention to symp toms that suggest metastatic disease, such as new palpable masses, malaise, weight loss, headaches, vision changes, alterations in bowel habits, hemoptysis, and pain. The provider should look for persistent melanoma at the biopsy site, dermal or subcutaneous nodules that could represent satellite or in-transit metastases, and lymphadenopa thy. A complete blood count, complete metabolic panel, and LDH should be performed. Although these tests rarely lead to detection of occult metastatic disease, a microcytic anemia would raise the possibil ity of bowel metastases, elevated liver function tests can suggest liver metastases, and LDH is part of the AJCC system for stage IV disease. Abnormal test results should prompt a more extensive evaluation, including computed tomography (CT) scan or a positron emission tomography (PET) scan (or CT/PET combined). Magnetic resonance

TABLE 81-3 Staging and Survival 10-YEAR MELANOMASPECIFIC SURVIVAL ESTIMATE STAGE TNM

TisN0M0

> 99% IA T1aN0M0, T1bN0M0 98% IB T2aN0M0 94% IIA T2b-T3aN0M0 88% IIB T3b-T4aN0M0 81–83% IIC T4bN0M0 75% IIIA T1a-T2aN1a-2aM0 71–88% IIIB T2b-T3aN1a-N2bM0 60–77% IIIC T3b-4bN1a-N3cM0 44–60% IIID T4bN3a-N3cM0 24–30% IV M1a Any T, any N, skin, soft tissue, or distant nodal sites 50% at 5 years IV M1b Any T, any N, lung + any M1a sites 35–50% at 5 years IV M1c Any T, any N, skin, non-CNS visceral disease, any M1a or M1b sites ~25% at 5 years IV M1d Any T, any N, CNS metastasis + any M1a,b,c sites <5% at 5 years Abbreviations: CNS, central nervous system; TNM, tumor-node-metastasis. imaging (MRI) of the brain with contrast is recommended for the initial evaluation of patients who present with neurologic symptoms or have advanced disease on imaging or examination. Despite all the above considerations, >80% of patients at presenta tion will have disease confined to the skin and a negative history and physical examination, in which case imaging is not indicated. One study suggests that imaging should be considered for node-negative low-stage melanoma with a high-risk GEP, but this is not yet standard. Imaging is sometimes done for very-high-risk primaries (e.g., >4 mm with ulceration, clinical stages IIB and IIC) in which the chance for occult distant metastases is higher than that for a positive SLNB, and the prognosis is worse compared to stage IIIA disease. Medical oncolo gists now routinely provide consultation for stage IIB and IIC patients to assess the potential value of adjuvant therapy (see “Treatment”). TREATMENT Melanoma MANAGEMENT OF CLINICALLY LOCALIZED MELANOMA (STAGE I, II) For a newly diagnosed cutaneous melanoma, surgical wide exci sion (WE) of the lesion with a margin of normal skin is necessary to remove all malignant cells and minimize the probability of local recurrence. The National Comprehensive Cancer Network (NCCN), based on data from six randomized trials, recommends the following radial margins for a primary MIS, 0.5–1.0 cm; inva sive up to 1 mm thick, 1 cm; >1.01–2 mm, 1–2 cm; and >2 mm, 2 cm. Smaller margins may be used for “anatomically constrained” locations such as the face, hands, feet, and genitalia due to the higher likelihood of surgical morbidity in these regions, and in some instances, Mohs with immunostaining is advantageous. In all instances, inclusion of subcutaneous fat in the surgical speci men facilitates adequate thickness measurement and assessment of surgical margins by the pathologist. When feasible, excision should go down to fascia, with fascial resection for thick (T4) lesions. Topical imiquimod, a toll-like receptor agonist, can stimulate skin macrophages to induce an immune response useful to treat lentigo maligna in cosmetically sensitive locations with narrow resec tion margins by promoting local immune response resulting in decreased local recurrence. SLNB provides prognostic information to identify patients at high risk for relapse who may be candidates for adjuvant therapy.

The first (sentinel) draining node(s) from the primary site is (are) located by injecting a blue dye and a gamma-emitting radioisotope around the primary site. The sentinel node(s) then is (are) identified using a handheld gamma detector brought sterilely into the opera tive field. The surgeon

makes an incision of the area of uptake and looks for the blue-stained, “hot” node(s), which is (are) removed and subjected to histopathologic analysis with serial sectioning using hematoxylin and eosin and immunohistochemical stains (e.g., S100, HMB45, MART-1, and MelanA) to identify melanocytes.

NCCN guidelines recommend SLNB for patients with a 10% or greater chance of having tumor in the node. This includes patients with tumors >1 mm thick (T2) or T1 tumors that have ulceration (T1b). Patients with a 5–10% risk of node positivity (NCCN “Dis cuss and Consider” category), such as those with tumors measuring between 0.75 and 1.0 mm, transected tumors, regressed tumors, or lymphovascular invasion, should also be considered for SLNB. The NCCN does not recommend SLNB for patients with a risk of a positive SLNB ≤5% such as those with melanomas ≤0.75 mm thick and no high-risk features. In these patients, WE alone is the usual definitive therapy. There are computer nomograms that estimate the risk of sentinel lymph node involvement based on melanoma depth, clinical features (age, site), and histology (ulceration, mitotic rate, lymphovascular invasion). GEPs in combination with these other factors are being investigated as a sentinel lymph node risk assessment tool in ongoing prospective trials. CHAPTER 81 Patients with negative SLNB can either be followed or considered for adjuvant therapy if the primary lesion is considered high risk. Patients with thick and/or ulcerated stage IIB or IIC melanomas have a significant risk of recurrence after wide local excision and (negative) SLNB, estimated at 13–18% probability of death at

5 years using the AJCC melanoma database. Adjuvant anti-PD-1 immunotherapy using pembrolizumab or nivolumab for 1 year sig nificantly reduces the risk of melanoma recurrence or death in stage IIB or IIC melanoma and has become a standard of care. Cancer of the Skin Patients with a positive sentinel lymph node should undergo CT or PET/CT imaging to rule out distant metastatic disease, and if none is found (i.e., stage III), adjuvant therapy should be offered (see next section). Complete lymphadenectomy following identifi cation of a positive sentinel lymph node improves relapse-free but not overall survival, and therefore, it is no longer offered routinely, but should be considered in patients who cannot comply with follow-up and/or forgo adjuvant therapy. This avoids the morbidity of regional node dissection in most patients. However, patients not undergoing immediate completion node dissection should have nodal bed surveillance with physical examination and nodal bed imaging (ultrasound or CT) at 4- to 6-month intervals for approxi mately 3 years to rule out isolated nodal bed progression. Mohs micrographic surgery (MMS) is an alternative to WE and is particularly useful in areas where tissue preservation is important (e.g., face, genitalia, hands) and for lesions with extensive MIS. MMS improves the probability of achieving negative margins, decreases local recurrence, and enhances cosmesis compared to WE in selected patients. It does not preclude SLNB, which can be done before the MMS procedure. MANAGEMENT OF REGIONALLY METASTATIC MELANOMA (STAGE III) Stage III melanoma comprises patients with a positive sentinel lymph node, resected regional nodal macrometastases, or resected locoregional disease (e.g., recurrences in the wide excision site, within 2 cm of the site [“satellite metastases”], or >2 cm from the site [“in-transit metastases”]). Even after complete resection of stage III disease, the risk of developing distant metastases (stage IV) may be high, and adjuvant systemic therapy should be offered. Melanomas may recur at the edge of the incision or graft, as satellite metasta ses, in-transit metastases, or most commonly, regional spread to a draining lymph node basin. Each of these presentations is managed surgically followed by postsurgical adjuvant systemic immuno therapy or targeted therapy (for BRAF-mutant

tumors), after which

there is the possibility of long-term disease-free survival. Topical therapy with imiquimod has been useful for patients with lowvolume dermal lesions, but survival benefit has not been confirmed with this approach. Talimogene laherparepvec is an engineered, oncolytic herpes simplex virus type 1 that is FDA approved for injection of primary or recurrent melanomas including cutaneous and subcutaneous lesions or lymph node deposits that cannot be completely removed by surgery.

Radiotherapy can reduce the risk of local recurrence after lymph adenectomy but does not improve overall survival. Patients with large nodes (>3–4 cm), four or more involved lymph nodes, or extranodal spread on microscopic examination should be consid ered for radiation as local recurrence in these high-risk patients has significant morbidity. Systemic adjuvant therapy can also be considered for patients with completely resected stage IV disease. Current options for adjuvant systemic therapy include anti-PD-1 (nivolumab or pembrolizumab) or targeted therapy with BRAF/MEK inhibitors in melanomas that harbor a BRAF V600 mutation. Both anti-PD-1 and targeted therapy have been shown to confer disease-free and overall survival benefits in patients with stage III and stage IV melanoma (see below for further discussion). A subset of patients with stage III melanoma has bulky disease (usually palpable nodal involvement) at presentation (stages IIIC and IIID) that may be difficult to resect with negative margins. Even if surgery is feasible and postsurgical adjuvant immunotherapy or targeted therapy is offered, the prognosis of these patients is poor. A recent randomized phase II study comparing neoadjuvant therapy followed by resection and adjuvant pembrolizumab versus resection followed by adjuvant pembrolizumab showed significant improvements in event-free and overall survival for the neoadjuvant approach. Other randomized phase II clinical trials investigating neoadjuvant plus adjuvant ipilimumab and nivolumab or relatlimab plus nivolumab in patients with palpable nodal disease at diagnosis have demonstrated a >50% probability of achieving a pathologic complete response with neoadjuvant treatment and a low probability of recurrence at 1 and 2 years. Neoadjuvant plus adjuvant targeted therapy in patients with stage IIIC or IIID BRAF-mutated melanoma has demonstrated a similar high probability of achieving pathologic complete response and improved event-free survival in single-arm phase II studies. Long-term follow-up data from randomized con trolled studies of neoadjuvant immunotherapy are not yet mature, and comparisons of immunotherapy to targeted therapy in the neoadjuvant setting have not yet been performed. GEP may help to identify patients with stages II or III melanoma who are at lower risk of recurrence and could avoid the toxicity and expense of adjuvant therapy, although prospective data on this approach are needed. PART 4 Oncology and Hematology TREATMENT Metastatic Disease At diagnosis, 84% of patients with melanoma will have stage I or II disease and 4% will present with metastases. Many others will develop metastases after initial therapy for locoregional disease; 60% of deaths from melanoma occur in patients who were initially diagnosed as stage I or II. The probability of recurrence is related to initial stage, ranging from <5% with stage IA to >90% for subsets of patients with stage IIID disease at presentation. Patients with a history of melanoma who develop signs or symptoms suggesting recurrent disease should undergo restaging imaging as described earlier. Distant metastases (stage IV) commonly involve skin and lymph nodes as well as viscera, bone, or the brain. The prognosis is better for patients with skin and subcutaneous metastases (M1a) than for lung (M1b) and worst for those with metastases to bone or other visceral organs (M1c) or brain (M1d). An elevated serum LDH is a poor prognostic factor and places the patient in stage M1c regardless of the metastatic sites. The 15-year survival of patients with stage IV melanoma was <10% before

2010; however, the development of targeted therapy and immunotherapy has improved

TABLE 81-4 Treatment Options for Metastatic Melanoma Immunotherapy Immune checkpoint blockade Anti-PD-1: pembrolizumab or nivolumab Anti-CTLA-4: ipilimumab Combined ipilimumab and nivolumab Combined relatlimab (anti-LAG-3) and nivolumab T-cell engager Tebentafusp (selected patients with uveal melanoma) Cytokine-based immunotherapy High-dose interleukin 2 Clinical trials investigating adoptive cellular therapy with tumor-infiltrating lymphocytes for advanced disease and personalized vaccine targeting neoantigens in high-risk resected melanoma Oncolytic virus Talimogene laherparepvec Targeted therapies BRAF inhibitors: vemurafenib, dabrafenib, encorafenib MEK inhibitors: trametinib, cobimetinib, binimetinib Local modalities Surgery Stereotactic radiation disease-free and overall survival, especially for patients with M1a and M1b disease, in whom the 15-year survival is nearly 50%. Even patients with M1c disease may have prolonged survival, and those who are progression-free for >2 years after immunotherapy or targeted therapy have a high probability of living >5 years from the onset of metastasis; some of these individuals may be cured. FDA-approved agents since 2011 include three immune T-cell checkpoint inhibitors (ipilimumab, nivolumab, and pembroli zumab), combination immunotherapy (ipilimumab plus nivolumab or relatlimab plus nivolumab), six oral agents that target the MAP kinase pathway (the BRAF inhibitors vemurafenib, dabrafenib, and encorafenib, and the MEK inhibitors trametinib, cobimetinib, and binimetinib), and the oncolytic virus talimogene laherparepvec. Adoptive cellular therapy using tumor-infiltrating lymphocytes (TILs) administered with interleukin 2 is undergoing FDA review and may become a new standard of care for patients with progres sion on checkpoint immunotherapy (Table 81-4). Local modalities, such as surgery and stereotactic radiosurgery, should be considered for patients with a limited number of meta static sites (oligometastatic disease) because they may experience long-term disease-free survival after metastasectomy or ablative high-dose-per-fraction radiation. Patients with solitary metastases are the best candidates, but local modalities can also be offered to patients with metastases at more than one site if a complete resec tion or treatment of all sites can be achieved with reasonable side effects. Patients rendered free of disease can be considered for adjuvant therapy or a clinical trial because their risk of developing additional metastases remains high. Surgery can also be used as an adjunct to systemic therapy if only one or a few oligometastases remain after systemic therapy. Surgery can be used to obtain tumor for mutational profile analysis or to harvest tumor for TIL therapy. IMMUNOTHERAPY Immune Checkpoint Blockade Immunotherapies are based on an understanding of the control mechanisms of the normal immune response. Inhibitory receptors or checkpoints, including CTLA-4, PD-1, and lymphocyte activation gene 3 (LAG-3), are upregulated on T cells after engagement of the T-cell receptor by cognate tumor antigen in the context of the appropriate class I or II human leu kocyte antigen (HLA) molecules during the interaction between a

T cell and antigen-presenting cell. Immune checkpoints are needed to ensure proper regulation of a normal immune response; however, the continued expression of inhibitory receptors during chronic

infection (hepatitis, HIV) and in cancer patients leads to exhausted T cells with limited potential for proliferation, cytokine production, or cytotoxicity. Ipilimumab, a fully human IgG1 antibody that binds CTLA-4 and blocks inhibitory signals, was the first drug shown in a randomized trial to improve survival in patients with metastatic melanoma. Anti-CTLA-4 monotherapy has been supplanted by anti-PD-1 monotherapy or checkpoint combinations due to higher objective response

rates and longer durations of response. The PD-1 blockers, nivolumab and pembrolizumab, have been approved to treat patients with advanced melanoma. Combination T-cell checkpoint therapy, blocking both inhibitory pathways with ipilimumab and nivolumab, leads to superior antitumor activity compared to treatment with either agent alone. Combined therapy with IV ipilimumab and nivolumab is administered in the out patient setting every 3 weeks for four doses (induction), followed by nivolumab given every 2–4 weeks (maintenance) for up to

1 year, and is associated with an objective response rate of 56% and enhanced survival compared to ipilimumab monotherapy. Patients who have >5% expression of PD-1 on T cells in a melanoma biopsy sample derive a similar level of clinical benefit from nivolumab mono therapy, although using PD-1 expression to select therapy remains problematic as some patients whose melanoma has no detectable PD-1 expression can still respond to immunotherapy. Other elements of genomic analysis, including an estimate of tumor mutational bur den (TMB), can be clinically useful as TMB is correlated with a higher probability of objective response and longer progression-free survival in patients treated with checkpoint antibody therapy in melanoma and other solid tumors. TMB appears to be a more robust predictor of response compared to PD-L1 expression in melanoma. LAG-3 is another checkpoint present on CD4+ and CD8+ T cells and is upregulated after chronic antigen exposure. The combination of anti-LAG-3 using relatlimab and anti-PD-1 with nivolumab results in objective responses comparable to ipilimumab plus nivolumab with fewer side effects. Relatlimab plus nivolumab has been approved by the FDA for the first-line treatment of advanced melanoma, has activity after progression on other checkpoint inhibitors, and is being investigated in the neoadjuvant setting as detailed above. T-cell checkpoint antibodies can also interfere with normal immune regulatory mechanisms, producing a novel spectrum of side effects. The most common immune-related adverse events were skin rash (discussed in depth in the Dermatology Drug Eruption section in Chap. 63) and diarrhea (sometimes severe, life-threatening colitis), but toxicity can involve almost any organ resulting in thyroiditis, hypophy sitis, hepatitis, nephritis, pneumonitis, myocarditis, and neuritis. The severity and frequency of toxicity are greatest when anti-CTLA-4 and anti-PD-1 are combined, followed by anti-CTLA-4, anti-LAG-3 plus anti-PD-1, and then anti-PD-1 monotherapies. Vigilance, interruption of therapy, and early intervention with steroids or other immuno suppressive agents, such as anti–tumor necrosis factor antibodies or mycophenolate mofetil, can mitigate toxicity and prevent permanent organ damage. Using immunosuppressive agents to mitigate toxicity does not diminish antitumor activity, and benefit is manifest even in patients who must discontinue immunotherapy due to immune-medi ated toxicity. Checkpoint immunotherapy can be administered safely to selected patients with preexisting autoimmune conditions using a multidisciplinary approach with input from endocrinology, rheuma tology, and other specialty services as clinically necessary. The use of T-cell checkpoint antibodies for metastatic melanoma has become commonplace, but there is controversy about whether all patients need combined anti-CTLA-4 and anti-PD-1 and whether biomarkers can be used to select patients who may benefit from anti-PD-1 alone. There is also a significant economic impact with any anticancer therapy, which must be placed in the context of the survival benefit. TARGETED THERAPY The RAS-RAF-MEK-ERK pathway delivers proliferation and sur vival signals from the cell surface to the cytoplasm and nucleus and is mutated in approximately 50% of melanomas. Inhibitors of BRAF and MEK can induce regression of melanomas that harbor a

BRAF mutation. Three BRAF inhibitors, vemurafenib, dabrafenib, and encorafenib, have been approved for the treatment of patients whose melanomas harbor a mutation at position 600 in

BRAF. Monotherapy with BRAF inhibitors has been supplanted with com bined BRAF and MEK inhibition to address the rapid adaptation of melanomas that use MAP kinase pathway reactivation to facilitate growth when BRAF is inhibited. Combined therapy with BRAF and MEK inhibitors (dabrafenib and trametinib, vemurafenib with cobimetinib, or encorafenib and binimetinib) improved progres sion-free and overall survival compared to monotherapy with a BRAF inhibitor. Long-term results of inhibition of the MAP kinase pathway confirm that some patients achieve long intervals of dis ease control, yet the major limitation of both monotherapy and combined therapy appears to be the acquisition of resistance. The mechanisms of resistance are diverse and reflect the genomic het erogeneity of melanoma; however, most instances involve reactiva tion of the MAPK pathway, often through RAS mutations or mutant BRAF amplification. Patients who develop resistance to BRAF and MEK inhibition are candidates for immunotherapy or clinical trials.

Targeted therapy is accompanied by manageable side effects that differ from those experienced during immunotherapy. Headache, pyrexia, and arthralgias are common. A class-specific side effect of BRAF inhibitor monotherapy is the development of hyperprolifera tive skin lesions, including well-differentiated squamous cell skin cancers (SCCs) in up to 25% of patients. Paradoxical activation of the MAP kinase pathway occurs from BRAF inhibitor–mediated changes in BRAF wild-type cells, and the activation is blocked by MEK inhibitor, which explains why these lesions are infrequent during combined therapy. Metastases from treatment-induced SCCs have not been reported, and BRAF and MEK inhibitors can be continued safely following simple excision of the SCCs. Cardiac and ocular toxicities, although infrequent, can occur with BRAF and MEK inhibitors and require medical evaluation, management, and usually discontinuation of targeted therapy. CHAPTER 81 Cancer of the Skin Activating mutations in the c-kit receptor tyrosine kinase are found in a minority of cutaneous melanomas with chronic sun dam age but are more common in mucosal and acral lentiginous subtypes. When activating mutations of c-kit are present, imatinib therapy can achieve clinically meaningful responses, similar to gastrointestinal stromal tumors. The probability of objective response in patients whose melanomas harbor a c-kit mutation is 29%, although most responses are transient. N-RAS mutations occur in 15–20% of mela nomas. At present, there are no effective targeted agents for these patients, but N-RAS inhibitors are being investigated in clinical trials. Targeting proteins that are differentially expressed on melanoma has been the basis for many clinical trials investigating vaccines and engineered biologics. An engineered bispecific fusion protein targeting gp100 on melanoma and CD3 on T cells, called teben tafusp, has garnered FDA approval for the treatment of metastatic uveal melanoma in patients who have the HLA-A*02.01 tissue type. Uveal melanoma is an aggressive melanoma subtype with a propensity for metastasis to the liver and a much lower probability of response to checkpoint immunotherapy than cutaneous melano mas. Objective response to tebentafusp is <10%, but overall survival and progression-free survival are significantly improved compared to checkpoint immunotherapy. Other systemic therapies used to treat stage IV melanoma patients include high-dose interleukin 2, which is also associated with dura ble remissions in some patients. Chemotherapy using dacarbazine or taxanes is infrequently used and confers no survival benefit. INITIAL APPROACH TO PATIENT WITH METASTATIC DISEASE Upon diagnosis of stage IV disease, a sample of the patient’s tumor should be submitted for molecular testing to determine whether a BRAF or c-kit mutation is present. Analysis of a metastatic lesion biopsy is preferred, but any sample will suffice because there is little discordance between primary and metastatic lesions. Treatment algorithms start with determining the melanoma’s BRAF status.

For BRAF wild-type tumors, immunotherapy is recommended. The best sequence of targeted therapy and immunotherapy in patients with BRAF-mutated melanomas has been controversial. A randomized study that compared anti-CTLA-4 plus anti-PD-1 followed by BRAF/MEK targeted therapy at progression to the opposite sequence in patients with advanced melanoma showed that immunotherapy followed by targeted therapy conferred sta tistically significant better overall survival at 2 years and a trend toward better progression-free survival. Toxicities were similar comparing the treatment sequences. The patient's history, includ ing sites of disease, symptom burden, and history of autoimmune conditions, influences the final recommendation for immuno therapy or targeted therapy, but survival data favor the initial use of combined checkpoint immunotherapy in the advanced disease setting. Despite improvements in therapy, most patients with meta static melanoma will not be cured, so enrollment in a clinical trial is always an important consideration. Many will be poor candidates for therapy because of extensive disease burden, poor performance status, or concomitant illness; thus, the timely integration of pallia tive care and hospice remains an important element of care. FOLLOW-UP AND SURVIVORSHIP Skin examination and surveillance at least once a year are recom mended for all patients with melanoma. Routine blood work and imaging for patients with stages IA–IIA (NCCN low risk) disease is not recommended unless symptoms are present. Surveillance diag nostic imaging can be considered in patients with stages IIB–III (NCCN high risk) disease but is mainly reserved for patients with signs or symptoms of recurrent disease or to follow response to ther apy. The NCCN does not recommend surveillance imaging in asymp tomatic patients who had advanced melanoma and are free of disease 5 or more years out from treatment. For stage-specific recommenda tions, please consult the NCCN guidelines (see "Further Reading").

PART 4 Oncology and Hematology The increasing incidence of melanoma has been met with more interest in advocacy and survivorship. Several national and inter national advocacy groups have called attention to issues such as genetic screening, sun awareness, and the care of chronic treat ment-related side effects. These include, but are not limited to, skin changes (such as vitiligo), lymphedema, neuropathies, and gastrointestinal and endocrine disorders. Lymphedema can now be managed in specialty clinics that offer support, nonsurgical treat ments, and newer surgical therapies such as lymphovenous bypass and vascularized lymph node transplants. NONMELANOMA SKIN CANCERS NMSCs (mostly SCCs and basal cell cancer [BCC]) are the most com mon cancers in the United States. Although tumor registries do not routinely gather data on the incidence of NMSCs, it is estimated that the annual incidence is more than 5.3 million cases in the United States; SCCs and BCCs account for 80 and 18%, respectively. While less com mon, the incidence of Merkel cell carcinoma (MCC) has tripled over the past 20 years. There are now an estimated 2600 cases per year with an annual increase in incidence of 8%. NMSCs can metastasize, but MCCs do this most commonly, with sentinel lymph node positivity rates of 25% (compared to 12–19% for melanoma) and mortality rates approaching 33% at 3 years. SCCs, particularly those with high-risk features, can also metastasize and account for 2400 deaths annually. Recent advances in systemic therapy using checkpoint antibodies have improved survival in patients with advanced NMSCs. ■ ■PATHOPHYSIOLOGY AND ETIOLOGY Like melanoma, the most significant cause of NMSCs is UVR, with a dose-response relationship between tanning bed use and the incidence of NMSC. As few as four tanning bed visits per year confers a 15% increase in BCC and an 11% increase in SCC. The risk of lip or oral SCC is increased with cigarette smoking and, like SCC of the ear, has a worse prognosis than SCC found on other body sites. Human papillomavi ruses and UVR may act as co-carcinogens. Inherited disorders of DNA repair, such as xeroderma pigmentosum, are associated

with a greatly

increased incidence of skin cancer and help to establish the link between UV-induced DNA damage, inadequate DNA repair, and skin cancer. The genes associated with UV damage in SCC include p53 and N-RAS, whereas BCC is primarily associated with damage to hedgehog signaling pathway (Hh) genes, which lead to basal cell proliferation. This is usually the result of loss of function of the tumor-suppressor patched homolog 1 (PTCH1), which normally inhibits the signaling of smoothened homolog (SMO). Immunosuppression has also been associated with the development of NMSCs; chronically immunosuppressed solid organ transplant recipients have a 65-fold increase in SCC and a 10-fold increase in BCC. The frequency of skin cancer is proportional to the level and duration of immunosuppression and the extent of sun exposure before and after transplantation. SCCs in this population are particularly aggressive, demonstrating higher rates of local recurrence, metastasis, and mortal ity. Tumor necrosis factor (TNF) antagonist therapy of inflammatory bowel disease and autoimmune disorders, such as rheumatoid and psoriatic arthritis, may also confer an increased risk of NMSC. Other risk factors for NMSCs include HIV infection, ionizing radiation, thermal burn scars, BRAF inhibitor monotherapy, and chronic ulcerations. Albinism, xeroderma pigmentosum, Muir-Torre syndrome, Rombo’s syndrome, Bazex-Dupré-Christol syndrome, dys keratosis congenita, and basal cell nevus syndrome (Gorlin syndrome) also increase the incidence of NMSC. Although MCC is also clearly related to UV exposure, age, and immunosuppression, this neural crest–derived cancer also appears to have a viral etiology; an oncogenic Merkel cell polyomavirus (MCPyV) is present in 80% of tumors. In patients with MCPyV-positive tumors, there is inactivation of tumor-suppressor genes, specifically the p53 transcription factor and retinoblastoma protein (Rb). In addition, the viral large T antigen is expressed on tumor cells, and many patients have detectable cellular or humoral immune responses to polyoma viral proteins, although this immune response is insufficient to eradi cate the malignancy. ■ ■CLINICAL PRESENTATION Basal Cell Carcinoma BCC arises from epidermal basal cells or the follicular bulge. The least invasive of BCC subtypes, superficial BCC, consists of often subtle, erythematous scaling plaques that slowly enlarge and are most commonly seen on the trunk and proximal extremities (Fig. 81-3). This subtype may be confused with benign inflammatory dermatoses, especially nummular eczema and psoriasis or premalignant actinic keratoses. BCC also can present as a small, slowly growing, pearly nodule, often with tortuous telangiectatic vessels on its surface, rolled borders, and a central crust (nodular BCC). The occasional pres ence of melanin in this variant of nodular BCC (pigmented BCC) may lead to confusion with melanoma. Morpheaform (fibrosing), infiltrative, and micronodular BCC, the most invasive and potentially aggressive subtypes, manifest as solitary, flat or slightly depressed, indurated whit ish, yellowish, or pink scar-like plaques. Borders are typically indistinct, and lesions can be subtle; thus, delay in treatment is common, and tumors can be more extensive than expected clinically. Squamous Cell Carcinoma Primary cutaneous SCC is a malig nant neoplasm of keratinizing epidermal cells that has a variable clini cal course, ranging from indolent to rapid growth, with the potential to metastasize to regional and distant sites. Commonly, SCC appears as an ulcerated erythematous nodule or superficial erosion on sun-exposed skin of the head, neck, trunk, and extremities (Fig. 81-4). It may also appear as a banal, firm, dome-shaped papule or rough textured plaque. It is commonly mistaken for a wart or callous when the inflamma tory response to the lesion is minimal. Dotted or coiled vessels are a hallmark of SCC when viewed through a dermatoscope. The margins of this tumor may be ill defined, and fixation to underlying structures may occur (“tethering”). A very rapidly growing low-grade form of SCC, called keratoacan thoma (KA), typically appears as a large dome-shaped papule with a central keratotic

crater. Some KAs regress spontaneously without ther apy, but because progression to metastatic SCC has been documented,

A B C FIGURE 81-3 Clinical, dermascopic, and confocal diagnostic findings of basal cell carcinoma. A. Typical basal cell carcinoma with skin-colored, slightly translucent rolled borders and a small central erosion on chronically sun-damaged skin of the lateral posterior shoulder. B. Dermoscopic image of the same lesion as in panel A clearly revealing the central erosion and classic gray, nonreticular globular structures of melanophages that characterize BCC. C. In vivo reflectance confocal microscopy of the same lesion as in panel A showing typical nests of dermal basaloid cells (*) with classic cleft formation around the nests. (Photos courtesy of Dr. Alexander Witkowski and Dr. Joanna Ludzik, © Copyright 2022 Oregon Health & Science University [OHSU].) KAs should be treated in the same manner as other types of cutaneous SCC. KAs occur in 15–25% of patients receiving monotherapy with a BRAF inhibitor. Actinic keratoses and cheilitis (actinic keratoses on the lip), both premalignant forms of SCC, present as hyperkeratotic papules on sun-exposed areas. Malignant transformation occurs in 0.25–20% of untreated lesions. SCC in situ, also called Bowen's disease, is the intraepidermal form of SCC and usually presents as a scaling, ery thematous plaque. SCC in situ most commonly arises on sun-damaged skin but can occur anywhere on the body. Bowen's disease occurring secondary to infection with human papillomavirus can arise on skin with minimal or no prior sun exposure, such as the buttock or poste rior thigh. Treatment of premalignant and in situ lesions reduces the subsequent risk of invasive disease. Merkel Cell Carcinoma MCC, also known as cutaneous apu doma, primary neuroendocrine carcinoma of the skin, primary small-cell carcinoma of the skin, and trabecular carcinoma of the skin, arises from Merkel cells, which are neuroendocrine skin cells that act as pressure receptors. Like other skin cancers, MCCs most commonly arise as visible skin lesions, usually as raised, flesh-colored nodules or masses; they can also be red or blue in color and vary in size from 0.5 to >5 cm in diameter and may enlarge rapidly. Although MCCs may arise almost anywhere on the body, they are most often found in sunexposed areas such as the head, neck, or extremities. They can also be found around the anus and on eyelids. The common clinical features of MCC can be summarized by the acronym AEIOU: asymptomatic/ nontender, expand rapidly, immune suppression, older than 50 years, and ultraviolet-exposed site. ■ ■NATURAL HISTORY Basal Cell Carcinoma The natural history of BCC is that of a slowly enlarging, locally invasive neoplasm. The degree of local destruction and risk of recurrence vary with the size, duration, loca tion, and histologic subtype of the tumor. Location on the central face, ears, or scalp may portend a higher risk. Small nodular, pigmented, cystic, or superficial BCCs respond well to most treatments. Large lesions and micronodular, infiltrative, and morpheaform subtypes may be more aggressive. The metastatic potential of BCC is low (0.1%) in immunocompetent patients, but the risk of recurrence or a new pri mary NMSC is about 40% over 5 years.

CHAPTER 81 Cancer of the Skin Squamous Cell Carcinoma The natural history of SCC depends on tumor and host characteristics. Tumors arising on sun-damaged skin have a lower metastatic potential than do those on non-sun-exposed areas. Cutaneous SCC metastasizes in 0.3–5.2% of individuals, most frequently to regional lymph nodes. Tumors occurring on the lower lip and ear develop regional metastases in 13 and 11% of patients, respec tively, whereas the metastatic potential of SCC arising in scars, chronic ulcerations, and genital or mucosal surfaces is higher. Recurrent SCC has a 30% probability for metastatic spread. Large, poorly differenti ated, deep tumors with perineural or lymphatic invasion, multifocal tumors, and those arising in

immunosuppressed patients often behave aggressively. Merkel Cell Carcinoma MCCs usually present locally yet have a high probability of spread to regional lymph nodes and distant sites. Molecular markers of neuroendocrine origin such as synaptophysin or chromogranin A are useful to diagnose MCC. Unlike other neuroen docrine tumors, such as small-cell lung cancer (SCLC), MCCs are not associated with measurable hormone secretion or endocrine syndromes. Survival with MCC depends on extent of disease: 90% of patients with local disease are cured, whereas 52% with nodal involvement and 10% with distant disease survive. MCC has its own tumor-node-metastasis (TNM) staging system, which incorporates tumor size (<2 cm vs >2 cm), nodal status (which can be determined by SLNB for clinically negative nodes), and the presence of distant metastases. Independent of stage, the prognosis of MCC is improved if the tumor cells contain virus, express RB protein, and exhibit intratumoral CD8+ T lymphocyte infiltration. p63 expression, lymphovascular infiltrative pattern, and concomitant immunosuppression (e.g., organ transplant, HIV infection, and certain cancers) portend a worse prognosis. TREATMENT Basal Cell, Squamous Cell, and Merkel Cell Carcinoma BASAL CELL CARCINOMA Treatment for BCC includes electrodesiccation and curettage (ED&C), excision, cryosurgery, radiation therapy (RT), laser ther apy, MMS, topical 5-fluorouracil, photodynamic therapy (PDT), and topical immunomodulators, such as imiquimod. The choice

PART 4 Oncology and Hematology A B C D E F G H I A B C D E F G H I FIGURE 81-4 Progression of basal cell (BCC) and squamous cell carcinoma (SCC). A. Superficial BCC; note salmon pink color, rolled boarder, erosions, and a gray central globule. B. Nodular BCC; note shiny, slightly pearly character with prominent arborizing vessels. C. Eroded BCC with serous and sanguinous crusting. D. Multiple actinic keratoses; note flat lesions are early, and thicker lesions may require biopsy to discriminate between advanced actinic keratosis versus early SCC. E. Superficial SCC. F. Keratoacanthoma (well-differentiated SCC). G. Mucocutaneous SCC in a high-risk area on the lower lip. H. Cutaneous SCC. I. Large exophytic SCC on the wrist. (Photos courtesy of the Dr. Leonard Swinyer Collection, © Copyright 2020 University of Utah and Oregon Health & Science University.) of therapy depends on tumor characteristics including depth and location, patient age, medical status, and patient preference. ED&C remains the most frequent treatment for superficial, minimally invasive nodular BCCs and low-risk tumors (e.g., a small tumor of a less aggressive subtype in a favorable location without terminal hairs). Wide local excision with standard margins is usually selected for invasive, ill-defined, and more aggressive subtypes of tumors or for cosmetic reasons. MMS, a specialized type of surgical excision that provides the best method for tumor removal while preserv ing uninvolved tissue, is associated with cure rates of >98%. It is the preferred modality for lesions that are recurrent, in high-risk or cosmetically sensitive locations (including recurrent tumors in these locations), and for which maximal tissue conservation is critical (e.g., the eyelids, lips, ears, nose, and digits). RT can cure patients not considered surgical candidates and can be used as a surgical adjunct in high-risk tumors. Imiquimod can be used to treat superficial and smaller nodular BCCs, although it is not FDA approved for nodular BCC. Topical 5-fluorouracil therapy should be limited to superficial BCC. PDT, which uses selective activation of a photoactive drug by visible light, has been used in patients with numerous tumors. Intralesional therapy (5-fluorouracil or interferon) can also be employed. Like RT, it remains an option for selected patients who cannot or will not undergo surgery. Systemic therapy with a targeted hedgehog pathway inhibitor, such as vis modegib or sonidegib, is indicated for patients with metastatic or advanced BCC that has recurred after local therapy and who are not candidates for surgery or RT. Targeted therapy does not cure patients with BCC but induces regression in approximately 50% of patients with a median duration of response of 9–12 months in patients with

metastatic disease and ~2 years in patients with locally advanced disease. Checkpoint immunotherapy using cemiplimab can be offered to BCC patients who progress after targeted therapy. SQUAMOUS CELL CARCINOMA The principles for surgical management of SCC are the same as for BCC. Cemiplimab, a monoclonal antibody targeting PD-1, has become the systemic therapy of choice, inducing tumor regression in 47% of patients with advanced disease. Neoadjuvant cemiplimab has been given in stage II, III and IV SCC and is associated with a

> 50% probability of pathologic complete response and is becoming a standard of care in patients with very-high-risk presentations and/ or who have disease that may be technically difficult to resect. SCC and KAs that develop in patients receiving BRAF-targeted therapy should be excised, after which BRAF therapy can be continued.

MERKEL CELL CARCINOMA The epidemiology, clinical features, and treatments for MCC over lap those for melanoma and NMSC. Early-stage MCCs may be cured with wide local excision of the primary tumor and nodal staging with SLNB. Like SCLCs, MCC is sensitive to radiation, PD1-directed immunotherapy, and platinum-based chemotherapy. RT is often used as postoperative adjuvant therapy at both the primary excision and SLNB sites, although its use may be withheld around sensitive areas such as the eyelids and hands and after a negative SLNB. For nonsensitive areas, RT may allow for primary excision margins smaller than the traditionally recommended 2-cm radial margins. When a positive sentinel node is found, adjuvant RT, close observation, and clinical trials investigating immunotherapy are favored over completion nodal dissection. For patients with metastatic disease, immunotherapy has sup planted chemotherapy. Avelumab (anti-PD-L1) therapy led to objective responses in 33% of patients with advanced MCC; 82% of the responses were durable. Pembrolizumab has an objective response >50% in patients with MCPyV-associated and nonvirus-associated advanced MCC resulting in a median duration of response approaching 2 years. Clinical trials should be offered to MCC patients who progress after checkpoint therapy and whose functional status can support additional treatment. Follow-up of patients with MCC is based on stage and risk. Rou tine skin exams by a dermatologist familiar with MCC and regular examinations of the nodal basins are recommended. Antibody serum titers to MCPyV should be obtained in newly diagnosed MCC patients. The test can be used to follow patients for relapse if the titer is elevated at baseline and returns to normal after A C F D B E G FIGURE 81-5 Other malignant cutaneous tumors. A. Patch stage mycosis fungoides (variant of cutaneous T-cell lymphoma). B. Tumor stage mycosis fungoides. C. Extramammary Paget’s disease. D. Merkel cell carcinoma. E. Dermatofibrosarcoma protuberans. F. and G. Kaposi’s sarcoma. (Parts A, B, and D-G photos courtesy of the Dr. Leonard Swinyer Collection, © Copyright 2020 University of Utah and Oregon Health & Science University. Part C photo courtesy Dr. Justin Leitenberger, © Copyright 2022 Oregon Health & Science University [OHSU].)

treatment. Conversely, if the titer is elevated but does not return to normal after treatment, imaging should be obtained to look for occult metastases.

■ ■PREVENTION The principles for prevention are those described for melanoma earlier. Unique strategies for NMSC include active surveillance for patients on immunosuppressive medications or BRAF-targeted therapy. Chemopro phylaxis using synthetic retinoids and immunosuppression

reduction when possible may be useful in controlling new lesions and managing patients with multiple tumors. Nicotinamide 500 mg BID may be used in patients with large numbers of actinic keratoses and SCCs to reduce the development and/or progression of disease. Field therapy with topi cal 5-fluorouracil (with or without calcipotriol), ingenol mebutate, or imiquimod can reduce transformation to SCC in patients with severely sun-damaged skin and numerous premalignant actinic keratoses. Older, immunosuppressed patients should be managed with the lowest doses of immunosuppression possible and encouraged to be particularly care ful to minimize UV exposure. Earlier biopsy of unusual-appearing skin lesions may lead to better control of aggressive lesions. ■ ■OTHER NONMELANOMA CUTANEOUS MALIGNANCIES Neoplasms of cutaneous adnexae and sarcomas of fibrous, mesenchy mal, fatty, and vascular tissues make up the remaining 1–2% of NMSCs (Fig. 81-5). Lymphomas of B- or T-cell origin can also manifest in the skin and can mimic benign conditions such as psoriasis and eczema. CHAPTER 81 Extramammary Paget’s disease is an uncommon apocrine malig nancy arising from stem cells of the epidermis that is characterized Cancer of the Skin

---

Revision #1
Created 2026-01-06 16:31:47 UTC by Omar Ayman
Updated 2026-01-06 16:31:47 UTC by Omar Ayman