Melanoma is an aggressive type of skin cancer that carries significant morbidity and mortality. Although increased awareness of melanoma has led to more diligent screening, improved understanding of melanoma tumorigenesis has guided the development of therapeutic options. This article reviews melanoma epidemiology, cause, clinical presentation, diagnosis, prevention, treatment, and prognosis, with particular emphasis on melanoma care in the United States.

**Epidemiology**

**Incidence**

Although overall cancer incidence in the United States has annually declined, melanoma incidence has increased rapidly in the past few decades. In 1973, the incidence of melanoma in the United States was 6.8 per 100,000 people; from 2003 to 2007, incidence increased to 20.1 per 100,000 people. It was estimated that more than 68,000 Americans (38,870 men and 29,260 women) were diagnosed with melanoma in 2010. This number was up from the 54,200 new cases (29,900 men and 24,300 women) of melanoma expected in 2003. In 2010, cutaneous melanoma was estimated to be the fifth and seventh most common cancer diagnosed in men and women, respectively. Based on the US Surveillance, Epidemiology, and End Results (SEER) Program cancer incidence rates collected from 2004 to 2006, men have a 2.67% (1 in 37) lifetime risk of developing melanoma, whereas women are less likely to develop the disease in their lifetime (1.79%, 1 in 56). Overall, in both men and women, the lifetime risk of developing melanoma is 1.93%.

Gender differences seem to exist in melanoma incidence. In the United States, melanoma is more prevalent in men compared with women. In 1975, 9.2 per 100,000 men and 7.4 per 100,000 women were diagnosed with melanoma. In 2003 to 2007, incidence increased to 25.6 per 100,000 in men and 16.2 per 100,000 in women. Despite these current gender differences, melanoma incidence may be increasing in younger women because of increased ultraviolet (UV) radiation exposure and use of tanning beds.

The incidence of melanoma also differs between races. Specifically, the incidence of melanoma is significantly lower in nonwhite populations. According to SEER data, 1.1 black people and 27.8 white people per 100,000 individuals were
diagnosed with melanoma in 2007. However, African Americans were much more likely to be diagnosed with metastatic melanoma compared with white people, a stage characterized by therapy resistance and higher mortality. This disparity in melanoma stage and poorer prognosis at diagnosis was also described in a recent study comparing Hispanic people with non-Hispanic white people.

Researchers have questioned whether the increase in melanoma incidence is a true epidemic or an artifact of increased surveillance and improved screening programs. However, evidence suggests that the current increase in melanoma incidence may be caused by true increases in disease incidence. First, incidence increased faster in the 1970s, before the start of a nationwide early detection initiative in 1985 that helped increase the awareness of skin cancer among health care providers and the general public. Second, a recent report found the highest incidence of melanoma in individuals of lower socioeconomic status, a population with decreased access to health services and therefore less regular screening. Third, behaviors associated with increased risk for melanoma, like sun exposure and tanning bed use, have increased in the past decade.

**Mortality**

Despite more vigilant screening and early detection efforts, melanoma mortality has not appreciably declined. From 1975 to 1989, melanoma mortality annually increased by 1.6%, although this trend seems to be stabilizing. From 2003 to 2007, the median age at death for cutaneous melanoma was 68 years. During this period, the mortality was approximately 0.1% for those less than 20 years old, 2.7% for those between 20 and 34 years old, 6.3% for those between 35 and 44 years old, 14.3% for those between 45 and 54 years old, 19.6% for those between 55 and 64 years old, 20.9% for those between 65 and 74 years old, 24.1% for those between 75 and 84 years old, and 11.9% for those 85 years and older. In 2010, approximately 8700 people (5670 men, 3030 women) were estimated to have died of melanoma.

Based on data from 2003 to 2007, the age-adjusted mortality was 2.7 per 100,000 individuals per year. Within the same age group, mortality caused by melanoma was higher in men compared with women. In men, there was a significant 2.3% annual increase in mortality between the years 1975 and 1989, and a 0.2% annual increase from 1989 to 2007. In women, mortality increased 0.8% annually between the years 1975 and 1988; however, between the years 1988 and 2007, mortality decreased annually by −0.6%.

Five-year survival rates have significantly improved annually since the 1970s. From 1975 to 1977, the 5-year survival rate was 78.1% in men and 86.9% in women. The 5-year survival rate from 1999 to 2006 significantly increased to 91.1% in men and 95.1% in women ($P<.05$). Survival was highest in women, individuals less than the age of 45 years at diagnosis, and those diagnosed with localized melanoma.

**ETIOLOGY**

**Pathogenesis and Tumor Progression**

Primary melanoma is a malignant neoplasm of neural crest–derived melanocytes, specialized pigmented cells predominately found in the basal layer of the epidermis. The normal function of melanocytes is to produce and transfer a dark pigment called melanin to mitotically active keratinocytes, which are also found in the epidermis. The transferred melanin is concentrated in the perinuclear space of keratinocytes and protects the nucleus from UV radiation damage.

The transformation of melanocytes to tumor cells occurs in both genetically normal and predisposed patients. Although melanoma pathogenesis is complex and not completely understood, it likely involves interactions between environmental factors, accumulation of sequential genetic alterations, activation of oncogenes, inactivation of tumor suppressor genes, and impaired DNA repair.

Three distinct pathogenic steps have been proposed in melanoma tumor progression. In an early-stage tumor, the melanoma may be confined to the epidermis and displays only radial (or lateral) growth. When melanoma progresses, it can develop into microinvasive melanoma, in which microscopic extensions invade the superficial papillary dermis. More advanced melanomas can progress to the vertical growth phase, which is characterized by invasive growth with discernable involvement deep into the dermis. In this stage of growth, the melanoma has gained the potential to metastasize.

**Genetic Mechanisms**

Many different genes have been associated with increased risk for melanoma. The more well-characterized mutations involve the highly penetrant gene products of familial melanoma syndromes: p16 (also called cyclin-dependent kinase inhibitor 2A [CDKN2A], or inhibitor of cyclin-dependent kinase 4A, INK4A), alternate
reading frame (ARF), and cyclin-dependent kinase 4 (CDK4). The low-penetrance melanocortin-1 receptor (MC1R) gene has also been associated with increased melanoma risk. In addition, a BRAF mutation has been ascertained in up to 60% of cutaneous melanomas and is the target of new mutation-specific therapies, like RG7204 (also referred to as PLX4032 and RO5185426), which are undergoing clinical testing. The best-characterized mutation involves the p16/ARF locus of chromosome 9p21, and this is discussed in more depth later.21–23

**p16/ARF**

The p16/ARF locus is the best-characterized highpenetrance melanoma gene locus.21–23 This locus encodes 2 tumor suppressor proteins that are essential in the pathways of cell growth regulation and apoptosis.24 The first is p16 and the second is ARF (also called p14).16,25 Germline mutations in 1 or both of these gene products are associated with familial melanoma, and have been ascertained in 25% to 50% of familial melanoma kindreds worldwide and in approximately 10% of patients with multiple primary melanoma.26 Identifying individual contributions of p16 and ARF to melanoma tumorigenesis is difficult because melanoma pedigrees with ARF-only mutations are scarce.27–29

The penetrance of these gene mutations has been estimated in recent studies, but the complexities of genetic analyses have provided variable results. The Melanoma Genetics Consortium analyzed data from 385 high-risk families (defined as having at least 3 confirmed melanoma cases in a family) to calculate p16/ARF penetrance.30 By 50 years of age, p16/ARF penetrance reached 0.13 in Europe, 0.50 in the United States, and 0.32 in Australia. By 80 years of age, penetrance increased to 0.58 in Europe, 0.76 in the United States, and 0.91 in Australia.30 In population-based studies, penetrance estimates were 14% (95% confidence interval [CI], 8.0%–22%) by age 50 years, 24% (95% CI, 15%–34%) by age 70 years, and 28% (95% CI, 18%–40%) by age 80 years.31

**Risk Factors**

Although genetic research on melanoma tumorigenesis is ongoing, numerous other risk factors for melanoma are well documented. Natural and artificial UV radiation, previous and family history, nevi, and several other factors are discussed later.

**Natural UV radiation exposure**

The role of solar radiation in the development of melanoma is well documented. Solar radiation has been classified as carcinogenic to humans by the International Agency for Research on Cancer (IARC), an agency of the World Health Organization that classifies carcinogens.32 Average annual amounts of UV radiation positively correlate with melanoma incidence.33 In addition, latitudinal and altitudinal gradients are observed in melanoma incidence, with the highest incidence occurring in higher altitudes or lower latitudes where UV intensity is greater.34,35

Frequency of sunburn, an indirect measurement of intermittent sun exposure, also confers increased risk for melanoma. Although experts have commonly focused on childhood sunburns as a major risk factor for melanoma development, recent studies have shown that the point in life when UV exposure occurs may not be as important to subsequent cancer risk. A meta-analysis found a positive association of melanoma incidence, with an odds ratio (OR) of 1.91 (95% CI, 1.69–2.17) for those with frequent sunburns compared with those with no or rare sunburns in their lifetime.36 A more recent meta-analysis of 25 studies showed that sunburns, regardless of age, conferred increased melanoma risk.37 In addition, a case-control study found a twofold increase in melanoma risk in individuals who had more than 5 sunburns, regardless of their timing in life.38

**Artificial UV radiation exposure (indoor tanning)**

Almost 30 million people in the United States tan indoors, including 2.3 million adolescents.39 In the Health Information National Trends Study, 18.1% of women and 6.3% of men reported using indoor tanning equipment in the past 12 months.40 Overall, indoor tanning has become increasingly popular in the past decades despite the accumulation of compelling evidence on the dangers of artificial UV radiation in melanoma development.39

Through a landmark meta-analysis, the IARC helped confirm the association between indoor tanning and melanoma. This confirmation also contributed to the designation of UV-emitting tanning devices as a group 1 carcinogen by the World Health Organization. Ever use of indoor tanning equipment was associated with increased risk of melanoma (relative risk 1.15; 95% CI, 1.00–1.31). In addition, first exposure of indoor tanning before 35 years of age was associated with a relative risk of 1.75 (95% CI, 1.35–2.26).41

**Family and personal history**

An association between family history and melanoma risk has been described in numerous studies. Patients who reported at least 1 first-degree relative diagnosed with melanoma had approximately a twofold higher risk of developing
melanoma compared with those without a family history.42,43 Having a parent who had multiple melanomas confers the highest relative risk of 61.78 (95% CI, 5.82–227.19).44

A personal history of either melanoma or non-melanoma skin cancer is also a significant risk factor for developing melanoma. A prospective study found that the 5-year risk of developing a second primary melanoma was 11.4%, with the risk increasing for those with atypical nevi or a family history of melanoma.45 In addition, 30.9% of individuals developed a third primary melanoma within 5 years.45 The relative risk for developing melanoma in individuals with a personal history of nonmelanoma skin cancer, like squamous cell carcinoma, basal cell carcinoma, or premalignant actinic keratoses, was between 2.8 and 17.46–48

Nevi
The number of nevi is positively correlated with UV exposure and is used as a surrogate measurement of UV-induced cutaneous damage.49 Studies have shown that approximately 25% of melanoma cases are attributable to the presence of 1 or more atypical nevi (also known as a dysplastic nevi), whereas 27% of melanoma cases are attributable to a high common nevus count (more than 50 common nevi).50 Patients with greater than 1 atypical nevus have an increased relative risk for melanoma of 3.63 (95% CI, 2.85–4.62).50 In addition, relative risk increases linearly with total body common nevus count.50

Other risk factors
Melanoma risk increases with age and is greater in men.9 It occurs most commonly in white people,5 with risk inversely related to degree of pigmentation.51 Similarly, the redhead phenotype characterized by hair color, fair skin, inability to tan, and propensity to freckle is also associated with increased risk of melanoma.52

Certain medical conditions can increase risk for melanoma. Xeroderma pigmentosum is an autosomal recessive disorder that is characterized by exquisite hypersensitivity to sunlight and the inability to repair UV-induced DNA damage. Affected individuals younger than 20 years have a greater than 1000-fold increased risk for melanoma as well as other cutaneous neoplasms.53

Psoriasis is a common autoimmune disease that causes inflammation of the skin and joints. Psoralen and ultraviolet A (PUVA) therapy has been a widely and successfully used treatment to induce remission in psoriasis. In 2001, the third report of the PUVA Follow-up Study showed that the incidence of invasive melanoma was threefold higher in patients receiving at least 250 treatments and at least 15 years from first PUVA therapy compared with cohort patients exposed to lower doses of PUVA.54

CLINICAL PRESENTATION

Clinical Morphology
Early clinical recognition of melanoma is essential in the successful treatment of this cancer. Pigmented cutaneous lesions can be initially evaluated using the ABCD acronym (asymmetry, border irregularity, color variegation, and diameter).55 Recently, it has been recommended that E for evolving lesions be added to this list of parameters.56 Not all melanomas present with all 5 features; it is the combination of the different ABCDE parameters that makes a cutaneous lesion a suspect for early melanoma.57

Asymmetry
Most early malignant melanomas grow at an irregular rate, resulting in asymmetry. This asymmetry differs from benign pigmented lesions, which are typically round and symmetric.

Border irregularity
The uneven growth rate usually causes malignant melanomas to have an irregular border, unlike benign pigmented lesions, which typically present with regular margins.

Color variegation
Macular melanomas are often variegated, containing variable hues of tan, brown, black, red, and white. Benign lesions are generally uniform in color.

Diameter
Most malignant melanomas have diameters of at least 6 mm at the time of diagnosis.

Evolution
Clinicians should note any evolving nevi, particularly focusing on changes to shape, size, symptoms (itching), surface (bleeding, papular or nodular formation), and pigmentation over time.

The ABCDE criteria can be useful in early melanoma detection, but its clinical usefulness is limited in several ways. First, the criteria are commonly applied to radial growth phase melanomas and are not typically helpful in evaluating melanomas with vertical growth involvement. Second, it is difficult to apply these criteria to amelanotic melanomas, like desmoplastic melanomas, because these lesions are characteristically non-pigmented or have minimal residual pigmentation. However, the ABCDE criteria are often used in conjunction with other methods to improve
diagnostic accuracy. An increasingly used method is dermoscopy, a noninvasive technique that aids in the visualization of subsurface structures and recognition of early melanoma.58

Anatomic Distribution

The anatomic distribution of melanoma lesions seems to differ by sex and age. In men, they are commonly located on the trunk (55%), especially the back (39%).59 Another study calculated a relative tumor density (RTD) value, the ratio of the observed to the expected numbers of cases by site assuming even distribution of melanoma over all body sites.60 The RTD was significantly increased in the back (3.4) and the upper arm (1.7) for men less than 50 years of age.60 Men more than 50 years of age showed a significantly higher RTD for the ear (8.5), face (6.0), neck (3.4), and the back (2.6).60

In women, 42% of melanoma lesions were localized to the lower extremities, with 24% on the lower leg. The second most common site was the trunk (25%), with 17% on the back.59 For women less than 50 years of age, only the back had a significantly raised RTD of 2.3. For those more than 50 years old, the density was significantly higher in the face (5.8), upper arm (2.2), and leg (1.5).60

DIAGNOSIS

Biopsy

Skin biopsy remains the standard of practice for diagnosing cutaneous melanoma. Excisional, incisional, shave, and punch biopsies are common techniques. However, excisional biopsy with a 1 mm to 2 mm margin of adjacent normal-appearing skin is the preferred technique for cutaneous lesions suspicious for melanoma.61 This method helps to ensure that the entire lesion is removed and provides important prognostic information for staging.62,63

Incisional biopsies may be indicated in certain clinical circumstances such as facial or acral involvement, low clinical suspicion, or very large lesion. However, subtotal incisional biopsies for melanoma may be inadequate for accurate staging of melanoma.64

Punch biopsies are commonly used to initially assess suspicious cutaneous lesions, and may also be more appropriate when sampling larger lesions. Properly performed punch biopsies that extend to subcutaneous fat can provide accurate T-stage information. However, punch biopsies are limited in diameter and may not encompass the entire lesion, which hampers the assessment of key pathologic findings like overall size and symmetry. Especially in the case of larger lesions, partial sampling with punch biopsies can also lead to misdiagnosis.63

Shave biopsy is frequently performed for suspected epidermoid carcinoma as well as melanoma because it is efficient and easy to perform. However, shave biopsy should be deep enough to avoid transecting the base of the melanoma.62 This method has been criticized for its potential to compromise accurate diagnosis, staging, and thus optimal treatment decision making.63,65 To explore the appropriateness of shave biopsy in melanoma diagnosis, Zager and colleagues63 retrospectively analyzed a consecutive series of 600 patients undergoing treatment of cutaneous melanoma. They found that only 3% of patients were determined to have a more serious melanoma on wide local excision after a preliminary diagnosis was made with shave biopsy. Nevertheless, although shave biopsy is simple to perform, efficient, and commonly used clinically, it is sometimes debated whether it is an acceptable method for the diagnosis of melanoma.

Major Clinical Subtypes of Melanoma

Four major subtypes of melanoma have been described: superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. The less common melanoma subtypes include nevoid melanoma, desmoplastic melanoma, clear cell sarcoma, and solitary dermal melanoma.

Superficial spreading melanoma

Superficial spreading melanoma is the most common melanoma subtype, accounting for 50% to 80% of all melanoma diagnoses.62 The name is derived from a prolonged radial (lateral) growth phase before invasive (vertical) growth commences. It most likely occurs on sun-exposed areas, such as the back in men and the lower limbs in women, but can occur in any anatomic location. Although these melanomas can arise from a precursor nevus, most occur de novo.

Clinically, a superficial spreading melanoma appears variegated with a sharply margined and irregular border. It typically presents with multiple shades of tan, brown, gray, black, violet, pink, and, rarely, blue or focal areas of hypopigmentation.66 At the time of diagnosis, most superficial spreading melanomas are at least 6 mm in diameter and confined to the radial growth phase, which is associated with a good prognosis.67 Advanced lesions often have a diameter greater than 25 mm and can have palpable nodular areas extending several millimeters above the
skin surface\textsuperscript{66,67} ; at this stage, lesions are commonly invasive (vertical growth) and are associated with poorer prognosis.\textsuperscript{67}

Superficial spreading melanoma is characterized histologically by pagetoid and nested epithelioid cells in the intraepidermal portion. Poor circumcision with variable epidermal thickening is also common. Cytologically, the melanocytes may have 1 or more large nuclei with an abundant cytoplasm that is often amphiphilic, eosinophilic, or finely pigmented with melanin granules.\textsuperscript{66}

**Nodular melanoma**

Nodular melanoma comprises 20\% to 30\% of cases.\textsuperscript{62} By definition, the cancer cells in nodular melanoma have an early onset of the vertical growth phase.\textsuperscript{68} They are more common in men, and usually found on the trunk in men and legs in women.\textsuperscript{67} Clinically, they are thick on palpation and pigmented a dark brown, black, or blue-black color in a uniform manner. Histologically, there is no intraepidermal nested melanocytic proliferation beyond the edges of the dermal component (usually no more than 3 rete lateral to the dermal tumor).\textsuperscript{66}

**Lentigo maligna melanoma**

Lentigo maligna melanoma commonly occurs in older individuals with sun-damaged skin and has a predilection for sun-exposed areas such as the malar region, temple, nose, forehead, neck, and forearms.\textsuperscript{67}

Clinically, lentigo maligna melanoma commonly presents as a gradually enlarging tumor that is flat and variably pigmented a tan, brown, and black color. In addition, the tumor is typically asymmetrical with irregular borders. Lentigo maligna begins as a small lesion, but can reach several inches in diameter if neglected.\textsuperscript{65} However, transformation is slow and it may take 10 to 50 years before invasive growth becomes apparent.\textsuperscript{69} Although the tumor is mostly flat, a slightly raised focus of vertical growth may be palpated or detected with tangential lighting.\textsuperscript{66}

Histologically, atypical melanocytes proliferate in a lentiginous manner in sun-damaged skin that exhibits epidermal atrophy, solar elastosis, and dermal thinning. The nuclei commonly appear large and hyperchromatic.\textsuperscript{68} Multinucleated giant cells, also known as star-burst giant cells, containing as many as 30 nuclei, may be present in the basal layer of the epidermis.\textsuperscript{70} Lesion progression frequently presents with the confluence of melanocytes, nesting, and pagetoid epidermal invasion.\textsuperscript{66}

**Acral lentiginous melanoma**

Acral lentiginous melanoma is the least common subtype, accounting for less than 5\% of all melanomas.\textsuperscript{67,71} However, this subtype accounts for 70\% of melanomas seen in African Americans,\textsuperscript{62} and is the predominate form of melanoma in other nonwhite populations.\textsuperscript{72} They are distinguished by their involvement of hairless areas like subungual, palmar, and plantar regions.\textsuperscript{67,73}

Clinically, an acral lentiginous melanoma usually begins as a variably colored macule that develops irregular borders and variegation in pigment, usually brown or black, as it increases in size with time.\textsuperscript{67} The surface may have a papule or nodule that is associated with the vertical growth phase; however, flat lesions may have dermal involvement as well.\textsuperscript{67} Histologically, early acral lentiginous melanomas show diffuse lentiginous proliferation of atypical melanocytes along the basal layer.\textsuperscript{73} As the lesion progresses, it typically presents with confluent lentiginous and nested growth with some pagetoid epidermal invasion.\textsuperscript{74}

Subungual melanoma typically presents as a brown or black longitudinal band that extends from the nail bed epithelium to the proximal nail fold and cuticle. The involvement of the proximal nail fold is known as Hutchinson sign and serves as a clue to distinguish melanoma from other types of lesions such as subungual hematoma.\textsuperscript{67} Subungual melanoma may or may not cause nail dystrophy; however, it sometimes presents as a subungual mass with variable degrees of pigmentation, ulceration, and nail plate destruction.\textsuperscript{73}

**Staging**

Staging of melanoma is based on the tumor-node-metastasis (TNM) staging criteria. The TNM categories described by the American Joint Committee on Cancer (AJCC) consider histopathologic factors such as primary tumor thickness, ulceration status, and rate of mitosis. Mitotic rate has recently emerged as an important prognostic factor and is expressed as the number of mitoses per square millimeter of primary tumor. The AJCC no longer recommends using the Clark level as a staging criterion because it is not an independent prognostic factor when mitotic rate is included in the analysis. In addition, as the TNM acronym implies, the number of metastatic nodes and presence of metastases is also important.\textsuperscript{61}

**Primary tumor**

The primary tumor (T) is based on thickness, with T1 being less than 1 mm, T2 from 1.01 to 2.00 mm, T3 from 2.01 to 4.00 mm, and T4 being greater than 4 mm.
**Regional lymph nodes**

Nodal metastases are rated from N0 meaning no regional lymph node (N) involvement, N1 meaning 1 regional lymph node involvement, N2 meaning 2 to 3 regional lymph node involvement, to N3 meaning 4 or more regional lymph node involvement or matted nodes.

**Distant metastasis**

The absence of distant metastases (M) is signified by M0 and the presence of distant metastases is signified by M1.

TNM combinations correspond to 1 of 5 stages.\(^6^1\) An accurate staging system facilitates the grouping of patients based on similar risk in terms of disease progression and natural history. In turn, this helps physicians with treatment decision making for a specific patient population.\(^6^2\)

- **Stage 0:** carcinoma in situ (TisN0M0)
- **Stage I A/B:** includes lesions up to 2 mm with no nodal or distant metastases (T1aN0M0, T1bN0M0, T2aN0M0).
- **Stage II A/B/C:** includes larger lesions, greater than 2 mm without positive nodes or distant metastases (T2bN0M0, T3aN0M0, T3bN0M0, T4aN0M0, T4bN0M0).
- **Stage III:** includes lesions of any size with positive lymph nodes (TxN1M0, TxN2M0, TxN3M0).
- **Stage IV:** includes lesions of any size with distant metastases (TxNxM1).

**PREVENTION**

Because research suggests that UV light exposure contributes to the development of nonmelanoma skin cancers and possibly melanoma, limiting UV light exposure may prevent the development of skin cancers.\(^7^6,7^7\) The United States Preventive Services Task Force currently recommends that primary care physicians counsel patients on sun-protective strategies, including regular application of sunscreen and avoidance of indoor tanning.\(^7^8\)

Although sun protection has been shown to reduce rates of nonmelanoma skin cancers, increasing evidence suggests that regular use of sunscreen may also confer a protective effect on the development of melanoma.\(^7^9,8^0\) The American Academy of Dermatology (AAD), American Cancer Society, and American Academy of Family Physicians all recommend sun-protective behaviors.\(^7^9,8^1,8^2\) Avoidance of ultraviolet light exposure may be especially beneficial in individuals with a genetic predisposition to melanoma development.\(^7^7\)

Various other strategies to prevent melanoma are also being investigated.\(^8^3,8^4\) To date, no pharmacotherapy has been definitively shown to prevent the development of melanoma. Medications that have been studied in small, early-stage clinical trials include antilipidemics, nonsteroidal antiinflammatory drugs, immune modifiers, and retinoids.\(^8^3\) Certain natural products have also been investigated, including resveratrol, lycopene, selenium, green tea, ginseng, and other botanicals.\(^8^4\) Most of these supplements have not been shown to decrease the risk of melanoma, but case-control studies have found that vitamin D and vitamin E supplementation may be associated with a reduction in the severity of disease.\(^8^4,8^5\)

Secondary prevention of melanoma involves the early detection of melanoma. The United States Preventive Services Task Force does not recommend for or against regular screening in the general population because studies have yet to show definitive benefit of screening melanoma in asymptomatic individuals in the general population.\(^8^6\) However, the AAD recommends that high-risk individuals be examined regularly by a dermatologist. The AAD also recommends monthly self-examinations and annual physician examinations for persons older than 40 years.\(^1^2\) Skin self-examinations seem to have high specificity (83%–97%) but low sensitivity (25%–93%) in detecting melanoma in high-risk individuals.\(^8^7\)

**TREATMENT**

Surgical excision is the cornerstone of melanoma treatment. Wide excision is generally recommended, but the recommended surgical margin varies in the literature. A meta-analysis in the Cochrane Library defines a narrow margin as 1 to 2 cm and a wide margin as 3 to 4 cm; they found a statistically insignificant difference in overall survival between narrow and wide margins.\(^8^8\) The meta-analysis included all participants (all ages, all ethnic groups) with early-stage (stage I and II) invasive melanoma.\(^8^8\) Current national guidelines from the National Comprehensive Cancer Network recommend surgical excision margins up to 2 cm.\(^8^8\) For lesions less than 1 mm in thickness (stage T1), a margin of 1 cm is recommended. For lesions 1 to 4 mm in thickness (stage T2 and T3), a margin of 2 cm is recommended. For lesions greater than 4 mm in thickness (stage T4), a 2-cm margin of resection is generally considered adequate, but more research is necessary to determine optimal surgical margins for varying depths of melanoma.\(^8^9,9^0\) For melanoma in situ, a surgical margin of 5 mm is deemed adequate.\(^9^0,9^1\)
Mohs micrographic surgery has emerged as another surgical option in cases in which tissue preservation is important, such as melanomas of the head and neck. This method makes use of immediate frozen or paraffin sections to ensure that the tumor is adequately excised. Mohs surgery has been used successfully in cases of lentigo maligna in which the borders are often poorly defined. Mohs surgery may also confer an additional treatment advantage in desmoplastic melanoma, which has a high propensity for perineural invasion.

Sentinel lymph node biopsy is important in melanoma staging, and results from sentinel lymph node biopsy can confer important prognostic information. It is usually recommended for melanomas that are more than 1 mm deep. Some studies also suggest that a survival benefit may exist from sentinel lymph node biopsy procedures for lesions less than 1 mm. However, survival benefit for regional lymphadenectomy following positive sentinel lymph node biopsy is equivocal.

Adjuvant systemic therapies have limited success in the treatment of advanced-stage melanoma. Interferon-α is an adjuvant treatment that is approved by the US Food and Drug Administration (FDA) for stage III melanoma. Meta-analysis studies by the National Cancer Institute have found limited efficacy of interferon-α. Specifically, adjuvant treatment with interferon-α increased 5-year survival by only 3%, although this was statistically significant. A study by the European Organization for Research and Treatment of Cancer yielded similar results. The investigators found that, although interferon-α reduced relapse rate, the overall survival rate remained largely unchanged. Interleukin-2 is another immunotherapeutic that has recently been approved by the FDA for the treatment of metastatic melanoma. High-dose recombinant interleukin-2 has been found to induce remission in 6% of cases of metastatic melanoma.

In 2011, the FDA approved ipilimumab for the treatment of advanced-stage melanoma. Ipilimumab is a monoclonal antibody against cytotoxic T-lymphocyte–associated antigen 4 that incites a T-cell–mediated response against the tumor. In clinical trials, ipilimumab was found to improve patient survival by 4 months in patients with stage III and IV melanoma.

Other new drug therapies, including drugs that target biologic receptors, are currently in development. Among these are bevacizumab, an endothelial growth factor antibody, and sorafenib, a BRAF cellular pathway inhibitor. These agents have shown some efficacy in early clinical trials. In particular, BRAF inhibitor therapy has shown an initial response in 70% to 80% of patients, but disease relapsed within a median time of 9 months in all patients. Thus, it seems that overall survival is not significantly altered by BRAF inhibitor treatment, and further studies are necessary to evaluate efficacy.

Radiotherapy plays a limited role in the treatment of melanoma because melanoma is radio-resistant compared with other cancers. The response rate is typically dose dependent. However, because very high doses of radiation are needed to eradicate tumors, radiotherapy is less optimal as primary treatment of melanoma because of its associated adverse effects. However, radiotherapy may be used as an adjuvant therapy when adequate surgical margins cannot be achieved, such as with lesions on the head and neck.

PROGNOSIS

Prognosis is usually good for thin melanomas. Stage I melanoma has a 5-year survival of 91% to 95% and a 10-year survival of 83% to 88%. Stage II melanoma has a 5-year survival of 45% to 79% and a 10-year survival of 32% to 64%. Ulceration is a poor prognostic sign and lowers the survival rate by about 5%. Stage III melanoma has a 5-year survival of 30% to 70%, depending on the degree of node spread. Stage IV melanoma has a 5-year survival of 10% to 20%. Palliative radiation therapy can extend survival to about 6 months in patients with stage IV melanoma.

Metastatic melanoma has a well-known predilection for distant spread and has a median survival time of 6 to 9 months. In advanced regional disease, it commonly metastasizes hematogenously to other skin regions, soft tissues, the lung, the liver, and the brain. The brain is the most common site of metastases in stage IV melanoma and is associated with poorer prognosis compared with other visceral sites. A retrospective review of 6953 patients found that the median survival time of patients with brain metastases from malignant melanoma was 3 to 4 months after diagnosis, and the brain metastases eventually contributed to the death of 94.5% of patients in this group. Lungs are the second most common sites of metastatic disease, after lymph node involvement. In patients who have visceral metastatic disease, the liver is the most common site involved.

NEEDS IN MELANOMA DETECTION AND CARE

Melanoma represents a significant public health concern. Despite substantial research, melanoma
incidence is rising faster than any other type of cancer and melanoma mortality has not appreciably declined. However, addressing certain unmet needs may help reduce the public health burden of melanoma.

Potential opportunities are available to improve screening of melanoma. As stated earlier, melanoma is one of the few cancers for which the United States Preventive Services Task Force does not recommend regular screening. Under such guidelines, the detection of early lesions relies heavily on self-screening by patients and general practitioners. This self-screening is a practice that can be highly inefficient and risks delaying a melanoma diagnosis until later stages that are associated with poorer prognosis. Considering current melanoma screening guidelines, the need for effective and user-friendly screening tests for patients and general practitioners is urgent.

Addressing disparities in melanoma prevention strategies targeting underserved communities, particularly African American communities, may be of value as well. Although melanoma incidence is low in African Americans, melanoma diagnoses are typically made at more advanced stages and associated with poorer outcomes. As such, there is an important need for melanoma prevention interventions that are culturally relevant, linguistically accessible, and provide information on the melanoma subtypes (eg, acral lentiginous melanoma) most prevalent in the targeted community.

SUMMARY

Melanoma is a skin cancer that arises from the malignant transformation of melanocytes. Although it is typically considered a pigmented lesion, the clinical presentation of melanoma can vary greatly. With increased efforts in screening and detection of early-stage melanoma, researchers and clinicians hope to improve clinical outcomes for patients with melanoma. Novel immunotherapies directed at specific molecular targets in the pathogenesis of melanoma usher in a new era of treatment of advanced melanoma.

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REFERENCES


