The Melanoma Handbook
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The incidence of melanoma in the United States has been doubling every 15 to 20 years over the past several decades. This is attributable to both a true increase as a result of extensive sun exposure in the last half of the 20th century, as well as greater and more effective surveillance of individuals at risk. Because of increased public awareness of this malignancy, patients are now being diagnosed earlier. Moreover, with the advent of more effective systemic therapies administered to prevent metastatic disease or at the time of diagnosis of distant metastases, overall survival for patients with melanoma is improving.

The Melanoma Unit at Yale Cancer Center, established in 1976, was the first of the multidisciplinary programs and has now expanded to include 35 caregivers and researchers representing surgery, medical oncology, dermatology, diagnostic radiology, nuclear medicine, therapeutic radiation, surgical pathology, dermatopathology, psychiatry, nursing, and basic science research. A major Special Program of Research Excellence (SPORE) grant has provided the opportunity and funding to carry out significant clinical and basic research investigations that have led to better understanding of the mechanisms of cancer genetic mutations and mechanisms of immunologic response in melanoma.

As a result of these collaborations at our institution, as well as several other centers committed to melanoma research, we are now on the threshold of significant new therapeutic interventions that were not possible a decade ago. The understanding of the immune checkpoint blockers and stimulators and the mechanisms of immune evasion have ushered in new and very effective immunotherapies that may now be able to cure patients who have distant organ metastases.

This book represents the work of the present members of the Yale Melanoma Unit. We believe that these authors’ experiences will be relevant to the practice of the reader, and in turn will be beneficial to melanoma patients.

Stephan Ariyan, MD, MBA
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The Melanoma Handbook
INTRODUCTION
Melanoma is a malignant tumor of melanocytes that typically develop in the skin and may, in rare cases, develop in the mouth, intestines, or eyes. The National Cancer Institute tabulates statistics in the Surveillance, Epidemiologic, and End Results (SEER) Program, and according to most recent data, melanoma is the sixth most common invasive cancer in the United States (1). Over the past several decades, the incidence of cutaneous melanoma has increased dramatically among White populations worldwide (2). In addition, melanoma is the most rapidly increasing cancer in Whites; rates have tripled over the past 30 years in the United States and in Central Europe (2). Epidemiologic studies have helped define genetic and environmental risk factors that may contribute to the development of melanoma. This chapter highlights the incidence, patient demographics, and mortality rates of melanoma and reviews the environmental and genetic risk factors. The recommendation practices for screening pigmented lesions will then be summarized.

EPIDEMIOLOGY
Rising Incidence and Patient Demographics
Over the past several decades, the incidence of melanoma has increased significantly. It has been estimated that rates have increased from 6 cases/100,000 in the 1970s to 21.6/100,000 in 2015 in the United States (Figure 1.1) (1–3). According to the most recent SEER database, there was an estimated 73,870 new cases of melanoma of the skin in the United States in 2015 and an estimated 9,940 deaths from melanoma (1). According to the American Cancer Society (ACS), the overall lifetime risk of developing melanoma is about 1 in 40 for Whites, 1 in 1,000 for Blacks, and 1 in 200 for Hispanics (3). The continuous rise in melanoma has been demonstrated in countries predominantly inhabited by Whites, consistent with the higher likelihood of developing melanoma in lighter-skinned individuals (1–3). Australia and New Zealand have the highest reported incidence rates of melanoma.
in the world, followed by the southern United States (2–4). The incidence is generally lower in European countries (2). The southern Mediterranean countries with darker skin types report lower rates than the northern Scandinavian countries with lighter skin types (2).

In contrast to nonmelanoma skin cancers, cutaneous melanoma is commonly diagnosed at an earlier age. The median age is approximately 55 to 64 years of age in the United States (1); however, thicker melanomas are found at higher rates in individuals older than 60 years of age (5). Possible explanations for thicker tumors in older patients include decreased vision, lower likelihood of performing self-examinations, increased seborrheic keratoses complicating the observation of new or changing pigmented lesions, and lower inclination to report changes in color or texture of skin lesions until symptoms of bleeding or ulceration develop (5). Older patients are also more likely to develop melanoma in sites of chronic sun exposure, in particular the head and neck (2,5).

Gender analysis demonstrates that the ratio of male to female incidence may vary based on the country. In countries with higher incidence such as Australia and the United States, melanoma was found more commonly in men (1–3). In countries with lower incidence such as the United Kingdom, a higher ratio of women patients may be found (6). Recent studies suggest that in the United States,
melanoma incidence is rising more steeply among women than men in the younger age groups (<50 years old) (7). This has been attributed to increased tanning bed habits (7). The anatomic site of melanoma varies according to gender, with 55% of tumors in men localized on the trunk (with 39% on the back) whereas in women, 42% are localized on the lower extremities (2).

Whether the increased incidence of melanoma represents a true epidemic remains an area of controversy. Some studies attribute the rising incidence to environmental risk factors with ozone depletion and carcinogenesis from ultraviolet (UV) exposure, while other studies suggest that better screening practices and earlier detection of thinner and less biologically aggressive tumors may contribute to the rising incidence (2,8–10). Others postulate that the rise in melanoma is not fully explained by improved screening practices as low socioeconomic groups with less routine surveillance have increased rates as well, and tumors of both low and high thickness may be on the rise (8,10). Regardless of whether a true epidemic exists, cutaneous melanoma has become one of the most common malignancies in the United States and there is a growing need to identify individuals most at risk.

**Mortality Rates**

Melanoma is one of the most deadly skin cancers; prior estimates suggest that one person in the United States dies every hour from the disease (11). On a global scale, mortality rates increased throughout the 1980s in most European countries as well as in North America, Australia, and New Zealand, then peaked in the late 1980s (1,2,10,11). Different studies report varying trends in mortality, but most recent SEER data suggests that mortality has stabilized over the past few years in the United States (2008–2012) (1,10). The favorable mortality trends may be related to changing patterns of sun exposure and sunburn in younger generations as well as earlier detection of thinner and less biologically aggressive melanomas (2,10).

The mortality risk in individuals with melanoma depends on a number of factors, including age, race, and gender. In general, studies have demonstrated that women and patients younger than 65 years of age have significantly longer survival rates compared with men and older patients, respectively (5). Some studies suggest that mortality from melanoma continues to increase in men aged 65 and older, whereas both men and women under 65 years of age demonstrate decreased mortality rates (8). While incidence rates for melanoma are lower among Hispanic and Black populations compared with non-Hispanic White populations in the United States, these minority groups are more likely to have melanomas that metastasize and have poorer outcomes (8,12). This may be explained by less access to health prevention education and practices in these populations (8,12).
Regarding prognosis, the Breslow depth or vertical tumor thickness is the single most important local prognostic factor in cutaneous melanoma (2,13–15). Tumors that are detected earlier will likely have lower Breslow depth and a favorable prognosis (>95% long-term survival in tumors <1 mm) (15). Unfortunately, patients with deep primary tumors or tumors that metastasize to regional lymph nodes frequently develop distant metastases. The overall 5-year survival for patients with visceral disease is less than 5% (15).

The status of an individual’s immune system is another important clinical factor that affects mortality. Individuals with weakened immune systems, such as those infected with HIV or with AIDS as well as organ transplant recipients on immunosuppressive therapy, have been shown to be at greater risk of dying from melanoma (3).

Risk Factors for Melanoma

*UV exposure*

Epidemiologic studies have consistently demonstrated that sun exposure is the major environmental risk factor for developing cutaneous melanoma (16). The UV spectrum includes UVA (95% of midday solar radiation reaching Earth’s surface), UVB (5% of solar radiation), and UVC (largely removed by stratospheric ozone layer) (17). While the entire UV spectrum is classified as carcinogenic to humans (18), UVA as well as UVB have both been shown to induce melanoma in animal models (17,18). Mouse models have shown UVA (320–400 nm) to cause oxidative DNA damage within melanocytes and UVB (280–320 nm) to cause direct UV DNA damage (17,18). UVB rays, which are the major cause of sunburn, have a more intense effect in equatorial regions where there is a higher incidence of melanoma. UVA rays, with a longer wavelength, penetrate to the deeper layers of skin and likely play a greater role in melanoma incidence from tanning beds, where fluorescent bulbs emit mostly UVA rays with smaller doses of UVB rays (7).

Meta-analyses of epidemiologic studies show that the type of sun exposure that increases melanoma risk is the intermittent pattern of sun exposure (short, intense exposure through leisurely outdoor activities and holidays in sunny climates) (16). Furthermore, 80% of melanomas develop in regions that receive intermittent sun exposure (2). In contrast, lentigo maligna melanoma, which is more common in elderly patients, develops from chronic cumulative sun-damaged skin on the head and neck (2). In addition, sunburns in childhood and adolescence, in particular, were shown to elevate the risk for melanoma development (2,19–21). The proportion of melanoma attributed to sun exposure has been estimated to be as high as 65% to 90% (9,22).

In addition to solar exposure, there is a growing trend of indoor tanning bed use in the United States. Approximately 20% of all female
high school students have reported tanning indoors, and 30% of White female high school students have tanned indoors (23). These trends might explain the steeper increase in melanoma rates in the United States among younger women compared with men (7). A recent population-based case-control study was conducted in Minnesota on 681 patients diagnosed with melanoma between 2004 and 2007. The study demonstrated that women younger than 30 years were six times more likely to be in the melanoma group than in the control group if they tanned indoors (7). In 2009, the International Agency of Research on Cancer (IARC) classified indoor tanning devices as carcinogenic to humans (18). In the United States, many states regulate the use of tanning facilities, precluding minors under age 18 from tanning. The FDA has also increased their regulation of the tanning industry with certification requirements and recommended exposure safety limits. Hopefully, the combination of efforts by the legislature and FDA as well as enhanced patient counseling by providers will reduce the incidence of melanoma from UV exposure.

The use of sunscreen to reduce the risk of melanoma has been widely studied. While there are varying results, one seminal randomized controlled trial of regular sunscreen use among 1,621 people aged 25 to 75 in Queensland, Australia, demonstrated a 50% reduction in melanoma incidence, particularly invasive melanomas, at a 10-year follow-up (24). The ACS recommends counseling patients on use of sunscreen as well as sun protective behavior. This includes avoiding sunlight during midday hours (10 a.m.–4 p.m.), when the sun’s rays are strongest; using sunscreen (SPF 30 or higher) with frequent reapplication; and covering the skin with clothing, hats, and sunglasses (3).

**Nevi and pigmentation factors**

Nevi are common benign melanocytic collections that have been closely studied in association with the development of melanoma. The number of melanocytic nevi has been identified as the most important inherent risk factor for cutaneous melanoma (15,25). Studies have demonstrated that with growing numbers of melanocytic nevi, the melanoma risk increases almost linearly (15). A meta-analysis showed that individuals with more than 100 normal nevi had an approximately seven times greater risk of melanoma than those with less than 15 nevi (25). In addition, atypical nevi are associated with increased melanoma risk such that one atypical nevus confers a 1.6 times greater risk of melanoma and five or more atypical nevi confer a 10-fold increased risk (25). Childhood sun exposure and sunburn are also significantly associated with increased number of nevi and atypical nevi (15,21). While prior histologic studies reported a wide range of melanomas associated with underlying melanocytic nevi
(4%-72%), a recent prospective study of high-risk patients (i.e., multiple nevi or atypical nevi, atypical mole syndrome, or familial atypical mole syndrome) demonstrated 52.4% of primary melanomas were associated with melanocytic nevi (26). The authors suggested that compared with individuals at risk for de novo melanoma, patients with multiple acquired nevi appear to be at higher risk for nevus-associated melanomas (26).

Other pigmentation characteristics have been associated with the development of melanoma including skin type, ability to tan, hair color, eye color, and freckling. In general, individuals with more pigmentation of their eyes, skin, and hair have a lower risk of developing melanoma (4,27). Skin reaction to the sun is also a predictor of melanoma risk, as well as increasing number of sunburns (27). A pooled analysis of 10 case-control studies demonstrated that both fair skin type and a high degree of freckling were associated with a two-fold increased risk of developing melanoma, independent of each other, the hair color, and number of nevi (27). The relative risks for developing melanoma in individuals with light brown, blonde, and red hair were 1.49, 1.84, and 2.38, respectively, compared with individuals with black or dark brown hair (27). Individuals with blue eyes had a risk of 1.55 times, compared with individuals with brown eyes (27). It is important for clinicians to recognize the phenotypic traits that place individuals at risk for developing melanoma and counsel these individuals on screening and prevention.

Genetic risk factors
An estimated 5% to 12% of all melanomas are thought to be caused by inherited, high-penetrance, germline mutations (28). Hereditary melanoma, also known as familial atypical multiple mole melanoma (FAMMM) syndrome, is an autosomal dominant group of disorders characterized by hundreds of dysplastic nevi on individuals with an increased risk of melanoma (28). A number of genes have been implicated including the tumor suppressors cyclin-dependent kinase inhibitor 2A (CDKN2A) and cyclin-dependent kinase 4 (CDK4) and the telomerase complex proteins telomerase reverse transcriptase gene (TERT) and protection of telomeres 1 (POT1) (28). The most common mutation is in CDKN2A, which encodes p16 and p14, which are genes that have a regulatory role on the cell cycle through the retinoblastoma protein and p53 pathways, respectively. Inherited mutations in the CDKN2A, CDK4, POT1, and TERT confer a 60% to 90% lifetime risk of melanoma (28). In addition, individuals with mutations in CDKN2A/p16 may have up to a 20% risk for pancreatic cancer (28). Other associated malignancies with familial melanoma syndrome include nervous system tumors or ovarian, renal, bladder, breast, and lung cancers (28).
There are many other syndromes associated with increased melanoma risk including \textit{BAP1} cancer syndrome (cutaneous and uveal melanoma, renal cancer, and mesothelioma), Li–Fraumeni syndrome (tumor protein 53 [\textit{TP53}] gene with associated cutaneous and uveal melanoma; breast, bone, soft tissue, and central nervous system tumors; and leukemia), xeroderma pigmentosum (\textit{XPC}, \textit{XPD}, \textit{and XPA} genes, with associated cutaneous melanoma and other non-melanoma skin cancers), phosphatase and tensin homolog [\textit{PTEN}] hamartoma tumor syndromes (\textit{PTEN} gene, associated cutaneous melanoma, trichilemmomas, hamartomas, and breast, colorectal, thyroid, kidney, and endometrial cancer), and hereditary breast cancer and ovarian cancer syndromes (breast cancer 1 or 2 [\textit{BRCA 1/2}] genes, cutaneous, and uveal melanoma) (28). There is also an increased susceptibility to melanoma and renal cell carcinoma with mutations in melanogenesis-associated transcription factor (\textit{MITF}) gene (28).

Through continued research, it is likely that more genes will be discovered to play a role in melanocytic growth and proliferation, as well as the development into melanoma. Currently, some notable somatic mutations that may confer increased melanoma risk include melano-cortin-1 receptor (\textit{MC1R}) gene, neuroblastoma RAS viral oncogene homolog (\textit{NRAS}) (nodular subtypes), \textit{BRAF} (superficial spreading melanoma, intermittent sun exposure sites), \textit{KIT} mutations (mucosal, acral, and sun-damaged sites), and G protein subunit alpha Q (\textit{GNAQ}) and G protein subunit alpha 11 (\textit{GNA11}) (uveal and central nervous system [CNS] melanomas) (4,29).

Patients with strong family histories of melanoma should be offered genetic counseling. The risk of melanoma is at least double for first-degree relatives of individuals with melanoma and five-fold higher if two first-degree relatives or more are affected (30). Importantly, regardless of whether genetic tests identify a gene mutation in these individuals, they should be counseled on their increased risk and sun prevention practices as well as the recommendation for full-body skin examinations. Genetics and genomics will continue to be important factors in treating melanoma on an individualized basis and may offer prognostic information. Furthermore, understanding the biological pathways and genetics involved in melanoma development will hopefully translate into new therapeutic targets.

**SCREENING OF PIGMENTED LESIONS**

**Screening Recommendations**

In the United States, there are presently no national screening guidelines for melanoma despite evidence that melanoma is a potentially lethal cancer with rising incidence rates. A screening program entails a balance of benefits and harms. The major benefit is the detection
of a potentially lethal tumor, at a thinner, earlier stage, which may translate into a survival benefit. The potential harms include misdiagnosis, overdiagnosis, false reassurance, anxiety, and cost, as well as complications of skin biopsy and treatments. A comprehensive review of clinical studies and randomized trials are necessary to demonstrate whether screening results in a survival benefit.

The United States Preventive Services Task Force (USPSTF), in 2001, reviewed clinical data for skin cancer screening. They determined that there was insufficient evidence to recommend for or against routine screening with whole-body skin examination for the early detection of cutaneous melanoma, basal cell cancer, or squamous cell cancer in the adult general population (31). The USPSTF based their decision on a lack of high-quality evidence (i.e., randomized trials) demonstrating improved health outcomes, as well as the limited information about the utility of adequate examinations by primary care providers (31). An update by the USPSTF in 2009 re-examined these two issues, but found no new evidence on the effectiveness of skin examination in reducing the morbidity or mortality from melanoma (32). While there remains a paucity of randomized trials, other high-impact studies have explored the utility of melanoma screening.

Evidence for Earlier Detection

Many previous studies have consistently shown that melanoma screening programs identify tumors that are thinner on average than those found during routine care. A screening by dermatologists participating in the American Academy of Dermatology’s skin cancer screening program from 1985 to 1999 demonstrated detection of a higher percentage of thin melanomas less than 1.5 mm (10% of cases), compared with 2% of cases reported in the SEER registry ($p < 0.001$) (33). In another study of 816 patients with melanoma, lesions identified by physicians were thinner than those identified by nonphysicians (0.68 mm vs. 0.90 mm) (34). Furthermore, patients who performed skin self-examinations had significantly thinner melanomas than those who did not (0.77 mm vs. 0.95 mm) (34). Similar findings have been replicated in more recent papers (35,36). These studies support the role of whole-body skin examinations, either by a physician or by the patient, in detecting early staged, thinner melanomas.

The effect of earlier detection of thinner tumors by screening programs on disease morbidity and mortality has been extensively studied. According to recent SEER data, while the incidence rates of melanoma have increased, the overall mortality has not changed substantially, suggesting that detection of less biologically aggressive tumors may not significantly impact overall mortality rates (32). One analysis of 650 cases from the Connecticut Tumor Registry demonstrated that there was no statistically significant association between
a physician screening examination or a patient self-examination and the risk of death from melanoma (37). However, a community-based program conducted at Lawrence Livermore National Laboratory in California found the incidence of thicker melanomas (>0.75 mm) significantly decreased from 22.1 to 4.62 cases/100,000 persons years after screening was initiated, with no melanoma deaths occurring during the screening period (expected number of deaths was calculated to be 3.39 deaths) (38). Another study demonstrated individuals who did not perform skin self-examination had a continuous increased risk of death from melanoma for approximately 20 years after diagnosis, whereas melanoma deaths in skin self-examiners plateaued before 10 years after diagnosis (39). While these results did not reach statistical significance ($p = 0.32$), individuals who were more aware of changes in their skin were significantly less likely to die of their melanoma over 16 years of follow-up (39). Such studies support the role of educating patients on self-examinations.

The largest population-based skin cancer screening project in the world took place in Germany in 2003. The Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) project provided whole-body skin examination to 360,288 patients (40). Melanoma mortality rates were compared before and after screening in the same location, as well as to matched nonscreened areas elsewhere in Germany. Interim analysis in 2008 demonstrated a 47% and 49% reduction in mortality in men and women, respectively (40). The majority (77%) of clinicians performing skin examinations consisted of general practitioners, gynecologists, internists, surgeons, and urologists, with all physicians requiring a training course (40). The striking positive results of this study led to a nationwide screening program in Germany in 2008. Screenings were provided to all people over the age of 35. Unfortunately, mortality data from 2008 to 2013 returned to prescreening levels and mortality rates in Germany did not differ from neighboring countries (40).

### Diagnostic Aids in Melanoma Screening

Various algorithms have been employed to help facilitate the identification of melanoma on physical examination. The ABCDE mnemonic, including asymmetry, border, color, diameter greater than 6 mm, and evolution, delineates worrisome features to look for when evaluating a lesion (Figure 1.2) (41). While the ABCDE criteria have been validated as a useful screening tool, physicians and individuals can miss early melanomas and amelanotic melanomas, which do not usually meet the criteria, and can overdiagnose benign lesions like seborrheic keratoses (41). The EFG criteria (elevated, firm, or growing lesion) can be useful for amelanotic or nodular melanomas. In addition, the “ugly duckling” sign is an important diagnostic pearl, and refers to overall
pattern irregularity or a lesion that is distinct from other lesions on the patient’s body (42). In contrast, the “little red riding hood” sign describes a high-risk patient (fair skin with light-colored hair, a personal history of melanoma, or a large number of atypical-appearing nevi), in whom a melanoma may not stand out as completely different; therefore, a more diligent examination is required (42). The sign may also denote the finding of erythema or inflammation surrounding a cutaneous melanoma (42). Importantly, not all melanomas may present with these aforementioned clinical features; therefore, if a patient is worried about a particular skin lesion, it is important to address his or her suspicion and to lower the threshold to perform a skin biopsy.

Physicians have employed diagnostic aids such as dermoscopy and digital photography to help evaluate and monitor pigmented lesions. Dermoscopy involves an examination with a skin surface microscope, the dermatoscope, to more closely inspect the features of a skin lesion. When performed by a trained clinician, dermoscopy can significantly increase the accuracy and sensitivity for melanoma diagnosis (43). In addition, digital photography with or without dermatoscopic views can allow for improved surveillance of suspicious nevi. Studies support the use of such techniques in a whole-body skin examination, as they may promote the earlier detection of melanoma by identifying lesions that should be biopsied, which remains the gold standard for diagnosis (43).
SUMMARY

Melanoma incidence continues to rise. While the mortality of melanoma has leveled off in many countries, patients who present with thicker tumors are at risk for advanced disease and have a poor prognosis. Therefore, early detection and prevention of melanoma remains an important global health initiative. The predominant environmental risk factor for developing melanoma is UV radiation. The inherent risk factors include increasing number of nevi; atypical nevi; decreased pigmentation of the skin, hair, and eyes; and personal or family history of melanoma, as well as genetic risk factors. Further, characterizing the genetic basis of melanoma will hopefully lead to new insights into the pathogenesis and development of new targeted treatments.

In 2015, an updated draft recommendation from the USPSTF again reached the conclusion that evidence was insufficient to support routine skin cancer screenings (44). However, screenings may lead to the diagnosis of thinner and earlier stage melanomas, with a possible reduction in mortality. The USPSTF recommends counseling children and young adults aged 10 to 24 years of age with fair skin to minimize UV exposure to reduce the risk for skin cancer (44). The ACS encourages educating all people on the risk of UV exposure in an effort to promote skin cancer prevention (3).

Health care providers should be knowledgeable of the epidemiology and screening practices of melanoma in order to better diagnose, treat, and counsel patients with the disease.

REFERENCES


INTRODUCTION

The vast majority of patients newly diagnosed with melanoma do not present with clinically enlarged lymph nodes; however, lymph nodes represent the most frequent sites of metastatic disease for melanoma, and nodal status is a known prognostic factor for melanoma-specific survival (MSS) (1–3). Approximately 15% to 20% of all patients diagnosed with melanoma will develop metastatic disease in the associated draining nodal basin, and the presence or absence of microscopic nodal disease has been found to be the most important prognostic factor for recurrence and death in early stage melanoma (4,5). In addition, microscopic nodal disease that is clinically undetected and left untreated can develop into palpable nodal disease and theoretically may promote the development of distant metastases. Therefore, detection of microscopic nodal disease provides powerful prognostic data and allows for early control of regional disease. Sentinel lymph node biopsy (SLNB) is an efficacious procedure that has emerged as the technique of choice for nodal staging, and plays a critical role in the management of patients diagnosed with localized cutaneous melanoma.

HISTORY OF ELECTIVE LYMPH NODE DISSECTION

When considering nodal staging for melanoma patients who are clinically node negative, several factors need to be considered such as the patient’s risk for nodal metastases, the prognostic and therapeutic benefit of nodal staging, the false-negative rate (FNR) of the technique utilized, and the morbidity associated with the procedure, particularly taking into consideration a patient’s age and comorbidities. Prior to SLNB, patients with melanoma were treated with either elective lymph node dissection (ELND) at the time of wide local excision (WLE) or with clinical observation and lymphadenectomy if nodal metastases later developed. Approximately 20% of patients who underwent nodal observation eventually developed macroscopic nodal recurrences, which could occur as much as 8 to 10 years after the initial diagnosis of melanoma (5,6). ELND was introduced as a way to identify and
potentially treat 20% of patients who may harbor microscopic nodal
disease. Although ELND was a relatively extensive procedure, it was
the only method available at that time to identify clinically occult
nodal metastases. However, ELND was associated with potentially
significant morbidity, with the majority of patients (approximately
80%) being found to have no evidence of nodal metastases (7–9).
These patients saw minimal benefit from the procedure but were
exposed to the increased risks associated with lymphadenectomy.
Furthermore, subsequent prospective randomized trials showed that
ELND provided no survival benefit over nodal observation, and these
data challenged the role of ELND in the management of melanoma
patients (8,9).

**DEVELOPMENT OF SLNB**

Due to these issues with ELND and the recognition that nodal sta-
tus is an important prognostic marker, Morton began extensive
work looking into ways to evaluate draining nodal basins without
unnecessarily exposing patients to the risks of lymphadenectomy.
Dr. Morton subsequently reported on SLNB as a method for nodal
staging in melanoma patients using a technique that was associated
with lower morbidity. SLNB allows for identification and removal of
a select group of lymph nodes, termed *sentinel lymph nodes*, that
are the first to drain the lymphatics of a melanoma primary (10).
Dr. Morton’s work on SLNB was based on three principles: (a) specific
areas of the skin drain to specific lymph nodes; (b) these specific
lymph nodes can be identified and removed; and (c) if these lymph
nodes do not contain tumor, then the remaining nodal basin is
unlikely to contain metastases, thereby making completion lymph
node dissection (CLND) unnecessary (4,10). These sentinel nodes
serve as “gatekeepers” for metastases to the draining nodal basin,
and by identifying, removing, and examining the sentinel nodes,
the nodes most likely to harbor metastatic melanoma could be eval-
uated to determine the status of the entire regional lymph node
basin. SLNB has been shown to predict the negative status of the
remaining regional nodes in at least 96% of negative SLNB patients
(11–13). Alternatively, approximately 20% of patients found to have
metastatic disease in a sentinel lymph node (SLN) are found to have
additional disease in the regional nodes or beyond (14,15). Furth-
more, SLNB is associated with lower morbidity compared with
formal lymph nodes dissection, primarily because SLNB involves
removal of a lower number of lymph nodes and use of smaller
incisions. Of note, the SLNB technique is a complex procedure and
requires expertise and a coordinated multidisciplinary approach
involving nuclear medicine, surgery, and pathology.
TECHNIQUE FOR PREOPERATIVE AND OPERATIVE IDENTIFICATION OF SENTINEL LYMPH NODES

Localization of sentinel nodes utilizes several methods including radiotracer detection with or without the use of intraoperative vital blue dyes. The initial technique of sentinel node mapping described by Morton et al. utilized isosulfan blue dye (lymphazurin) infiltrated intradermally at the site of the primary tumor at the time of WLE (Figure 7.1). The SLN identification rate in the initial report by Morton et al. was 82% when blue dye was used alone. The blue dye was found to have adequate lymphatic uptake while being large enough to become trapped inside of the first lymph nodes encountered (10). As shown in Figure 7.1, surgical exploration of the associated nodal basin allows for identification of the blue-colored lymphatics draining toward the blue sentinel nodes. Vital blue dyes currently utilized include isosulfan blue dye, methylene blue dye, and patent blue dye. Lymphazurin is specifically associated with a very low risk of anaphylactic shock (1%); however, the overall risk of complications from using vital blue dyes, such as mild allergic reactions like local swelling and pruritus, is low and varies in the literature (16,17).

A second method of lymph node mapping utilizes injection of radiolabeled colloid, frequently technetium-99m, also infiltrated at the primary tumor site. Use of preoperative radiotracer allows one to obtain a lymphoscintigraphy to map the location of the draining sentinel nodes (Figure 7.2). Preoperative lymphoscintigraphy is particularly helpful for head/neck melanomas where lymphatic drainage can be complex and vary considerably. Preoperative lymphoscintigraphy is also useful for truncal melanomas that may have more than one draining lymph node basin, may drain cranially and caudally, and may drain across the midline to the contralateral side. In addition,

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**Figure 7.1** Injection of vital blue dye intradermally at the primary melanoma site (image on left) allows for identification of the draining lymphatic channel and sentinel lymph node (image on right) (courtesy of Stephan Ariyan, MD, MBA).
preoperative lymphoscintigraphy may help to identify drainage to epitrochlear nodes or popliteal nodes for extremity melanoma, may help to identify direct drainage to deep pelvic nodes, or may help to identify drainage to interval nodes that are nodes not located in standard nodal basins (18). Radiotracer may be injected several days prior to surgery to perform lymphoscintigraphy with a second radiotracer dose given in the operating room on the day of surgery. Another option is to inject radiotracer as a single dose within 24 hours of surgery (lower dose if injection is done on the day of surgery while a larger dose is used if injection is done the day before surgery) with lymphoscintigraphy and surgery performed on the same day.

Intraoperatively, the radiotracer is then detected using a handheld gamma probe. The surgeon identifies the region with the highest radiotracer uptake, and a small incision is made over this area. Of note, the incision should be fashioned so that it can be potentially incorporated into a CLND incision. Upon entering the nodal basin, the lymph nodes with the highest uptake are found and removed. If vital blue dye was also used, any nodes that are stained blue are also removed. The lymph node with the highest radiotracer count is identified and removed, as well as all associated nodes with ≥10% radioactivity of

Figure 7.2 Injection of radiotracer intradermally at the primary melanoma site on the left forearm allows for identification of the sentinel lymph nodes in the left axilla on lymphoscintigraphy (courtesy of Stephan Ariyan, MD, MBA).
the highest count node. This method optimizes the detection of all nodes that may harbor micrometastases (19). The use of both intraoperative vital blue dye and radiotracer has been found to identify sentinel lymph nodes in 97% to 99% of patients (20,21). Today, the majority of sentinel nodes are identified utilizing intraoperative radiotracer primarily with or without the use of vital blue dye (3,22).

In addition to technetium-99m, other radiotracers have been developed for use during SLNB. Tilmanocept has been Food and Drug Administration (FDA) approved for use during SLNB for patients with melanoma (23,24). Tilmanocept is a radiotracer that binds tightly to both technetium and mannose receptors through its attached mannose molecules. Mannose receptors are expressed in reticuloendothelial cells that are present in lymph nodes. Tilmanocept is readily picked up and retained in these draining lymph nodes. The efficacy of tilmanocept when used for SLNB specifically for melanoma was demonstrated in a phase III study. In this study, tilmanocept identified more sentinel nodes in more patients and also identified more sentinel nodes with melanoma when compared with vital blue dye (23,24).

Single-photon emission computed tomography with integrated CT (SPECT/CT) has also been used as a modality to identify sentinel nodes (25). Radiotracer is injected up to 24 hours preoperatively, and the sentinel nodes are identified using SPECT. The location of these sentinel nodes is then determined by integrating with CT imaging. Several studies have demonstrated a potential benefit of using SPECT/CT for preoperative planning and intraoperative decision making (25–27).

PATHOLOGY EVALUATION OF SENTINEL LYMPH NODES

The gold standard for pathology evaluation for melanoma metastases in a SLN is hematoxylin and eosin preparation (H&E). Metastatic melanoma cells within the SLN commonly resemble the histologic features of the primary lesion and are most frequently located subcapsular as single cells, nests, or clusters of cells and are less frequently located within the parenchyma and fibrous capsule (28).

H&E staining is associated with a FNR of 10% to 15%, and the addition of immunohistochemical staining for melanoma-associated tumor markers increases the sensitivity of detecting microscopic melanoma metastases (28–30). The most widely used immunohistochemistry markers for evaluation of sentinel nodes for melanoma metastasis include S-100, HMB45, MART-1/Melan A, and tyrosinase (see Figure 7.3). S-100 is a highly sensitive marker for melanocyte differentiation; however, it is not specific for melanoma cells as it also stains several other tumor types and normal cells within the lymph node including benign capsular melanocytic nevi and dendritic cells (31). MART-1 antibodies target with high specificity the MART-1/Melan A complex expressed by malignant melanocytes; however, MART-1 can also be expressed by
macrophages (28,32). The antibody HMB45 identifies most melanoma cells within a SLN and usually does not stain macrophages (28,33). The use of reverse transcriptase polymerase chain reaction assay for detection of melanocytic messenger RNA expression remains investigational as studies examining its diagnostic and prognostic value have been conflicting (34,35).

The identification of melanoma in the SLN can be confounded by the presence of nodal nevi, which are collections of benign melanocytes thought to result from the dislodgement of nevocytes into the nodes (36,37). Nodal nevi are most frequently located within the capsule, in contrast to the subcapsular location of melanoma metastases, and can be further distinguished by their different cytologic features compared with metastatic melanoma cells (28,37).

**DISCUSSION**

**Validation of SLNB**

The role of SLNB in the management of patients with primary cutaneous melanomas was validated by the groundbreaking Multicenter Selective Lymphadenectomy Trial I (MSLT-I) (3). MSLT-I was a
prospective, randomized trial designed to determine whether SLNB performed in clinically node-negative patients conferred a survival advantage when compared with patients who underwent nodal observation alone after WLE (2). The trial initially evaluated patients with intermediate thickness melanomas but was later expanded to include patients with thin and thick melanomas. Patients were randomized to either WLE with SLNB or WLE with clinical observation of the nodal basin. For patients in the SLNB arm, a CLND was performed for patients who had a SLN positive for metastatic disease, while patients in the nodal observation arm underwent a therapeutic lymphadenectomy only if there was clinical evidence of a nodal recurrence in the follow-up period.

The final report of MSLT-I was published in 2014 and analyzed a total of 2,001 randomized patients (14). The positive SLN rate was 16% for patients with an intermediate thickness melanoma and was 32.9% for patients with a thick melanoma. Specifically, in the intermediate thickness group, the 10-year disease-free survival (DFS) rates were significantly higher in the SLNB arm when compared with the nodal observation arm (71.3% ± 1.8% vs. 64.7% ± 2.3%, respectively; hazard ratio (HR) = 0.76; 95% CI: 0.62–0.94; \( p = .01 \)), but there were no significant differences in 10-year MSS or overall survival (OS) between the SLNB arm and the nodal observation arm. Similarly, in the thick melanoma group, there was also a significant difference in 10-year DFS between the SLNB arm and the nodal observation arms (50.7% ± 4.0% vs. 40.5% ± 4.7%, respectively; HR = 0.70; 95% CI: 0.50–0.96; \( p = .03 \)), but again there were no significant differences in MSS and OS between the SLNB and nodal observation arms. No survival analyses could be performed in the thin melanoma group due to a low number of patients and events. Although no significant difference was found in the primary endpoint MSS between the treatment arms, it must be remembered that MSLT-I was underpowered to look for differences in survival due to relatively low event rates, and the true effect of performing SLNB on MSS and OS in this population is still unknown.

The most important information to come from MSLT-I was confirming the prognostic value of SLN status. In looking specifically at the SLNB arm, for the intermediate thickness group, positive SLN patients had a significantly lower 10-year MSS (62.1% ± 4.8%) compared with negative SLN patients (85.1% ± 1.5%; HR = 3.09; 95% CI: 2.12–4.49; \( p < .001 \)). Similarly, for the thick melanoma group, positive SLN patients also had a significantly lower 10-year MSS (48.0% ± 7.0%) compared with negative SLN patients (64.6% ± 4.9%; HR = 1.75; 95% CI: 1.07–2.87; \( p = .03 \)). Furthermore, SLN status was found to be the most important independent prognostic factor for melanoma recurrence and melanoma-specific death on multivariable analysis in the intermediate thickness group (3). Therefore, SLN status provides
powerful prognostic information in both the intermediate thickness and thick melanoma groups.

In addition to providing prognostic information, data from MSLT-I showed that SLNB identified patients who would have later developed a macroscopic nodal recurrence due to the presence of nodal micrometastases. This was shown by comparing the total nodal disease rate in the nodal observation and SLNB arms. For the nodal observation arm, the total nodal disease rate would include patients who developed a nodal recurrence during follow-up, while in the SLNB arm the total nodal disease rate would include positive SLN patients and negative SLN patients who later developed a nodal recurrence. In the intermediate thickness group, the total nodal disease rate was 21.9% in the SLNB arm while the nodal recurrence rate was similar at 19.5% in the nodal observation arm. In the thick melanoma group, the total nodal disease rate was 42% in the SLNB arm which was almost identical to the nodal recurrence rate of 41.4% in the nodal observation arm (14). These results demonstrate that SLNB identifies the subset of patients who would recur with nodal disease due to the presence of micrometastases.

**FNR of SLNB**

The effectiveness of any procedure is in part dependent on the number of positive cases missed by that test or what is known as the FNR. For SLNB, true-positive cases consist of patients who have a SLN with metastatic melanoma that has been found on pathology examination. False-negative cases consist of patients with a negative SLNB who later develop a nodal recurrence in the dissected nodal basin. The largest meta-analysis on SLNB analyzed data from 71 studies and included over 25,000 patients. This study demonstrated a FNR ranging from 0% to 34% in the included studies, with a weighted summary estimate of 12.5%. The FNR was associated with increasing length of follow-up and studies found to be of higher quality, although FNR was inversely correlated with successful SLN mapping via lymphoscintigraphy with or without the use of dyes (38).

**Complications of SLNB**

SLNB is a far less morbid procedure when compared with lymph node dissection. Complications after lymph node dissection, including wound separation, cellulitis, hematoma/seroma, nerve injury, and lymphedema, have been reported at rates as high as 65% in some studies, particularly for lymphadenectomies performed in the groin (25,39). Two of the largest melanoma trials to date, MSLT-I and the Sunbelt Melanoma Trial, reported on complication rates for patients after undergoing SLNB and for patients who had a CLND following a positive SLNB. The complication rate after SLNB alone was approximately
12% to 13% in MSLT-I when all of the various complications were added together and was approximately 5% in the Sunbelt Melanoma Trial (14,19). In contrast, patients who had a subsequent CLND for a positive SLN had complication rates ranging from approximately 23% to 40% in these two large trials. The most frequent complications seen after SLNB alone were hematoma/seroma formation and wound infection, while the most frequent complications in the CLND group included lymphedema, wound infection, hematoma/seroma formation, and sensory nerve injury.

**SLNB for Intermediate Thickness Melanoma**

SLN status has been shown to have important prognostic value and is the most important predictor for recurrence and survival in patients with intermediate thickness melanoma. Furthermore, SLNB has a low FNR (12.5%) and also has a low complication rate ranging from approximately 5% to 10%. The overall positive SLN rate for patients with melanomas ≥1 mm in thickness was 19.8% in the Sunbelt Melanoma Trial while MSLT-I showed a positive SLN rate of 16% in patients with intermediate thickness melanomas (14,19). Based on these data, current guidelines recommend SLNB for all patients with intermediate thickness melanomas who are clinically node negative and are deemed medically fit to tolerate the procedure (40,41).

**SLNB for Thick Melanoma**

Thick melanomas (>4 mm Breslow thickness) account for approximately 5% of primary melanomas, but are associated with a worse survival rate of approximately 50% (1,42). Approximately 40% of thick melanoma patients will eventually develop distant disease, and studies have demonstrated an increased risk of occult metastases in this population (43). Therefore, use of SLNB in thick melanoma patients has been debated since the prognosis of many of these patients is ultimately driven by the development of distant metastases. However, approximately 25% to 40% of thick melanoma patients will have nodal disease, and it is this population of thick melanoma patients who may potentially benefit from nodal staging. Recent studies have shown the prognostic value of SLN status in thick melanoma patients and report significant differences in overall and disease-specific survival between negative and positive SLN patients (19,44). Current guidelines state that SLNB may be recommended for staging purposes in thick melanoma patients who are clinically node negative and deemed medically fit to tolerate the procedure (40,41). Furthermore, in this population of patients who are already at relatively high risk for recurrence, detection of SLN metastasis can identify patients for potential systemic therapy, entry into clinical trials, and treatment of nodal disease at a microscopic stage.
SLNB for Thin Melanoma

In the United States, approximately 70% of newly diagnosed melanomas are thin melanomas (≤1 mm Breslow thickness) (42). Although the risk for nodal disease in thin melanoma patients is relatively low, nodal staging may be prognostic in the subset of patients who harbor nodal micrometastasis (45,46). The role of SLNB for patients with thin melanoma is debated, and there is currently no consensus as to which patients with thin melanoma should be offered nodal staging. Current guidelines do not recommend routine use of SLNB in thin melanoma patients, but instead recommend discussion with each patient regarding the risks and benefits (40,41).

SLN metastases are reported in 5% to 10% of thin melanoma patients, although some studies on thin melanoma have shown a positive SLN rate as high as 18% (47–49). Several independent predictive markers for a positive SLN in thin melanoma patients have been described, but factors found to be significant vary in these studies. In addition, the significance of SLN status in thin melanoma patients is inconsistently reported, although the follow-up times in these studies vary widely (47,49,50). Given these issues, no consensus exists as to which factors should be used to select patients who may be at higher risk for nodal metastasis and who may benefit from nodal staging. The most frequently reported predictors for a positive SLN in thin melanoma patients are Breslow thickness, Clark level, ulceration, mitotic rate, and younger age (45,47–50).

The decision to offer nodal staging depends in part on the risk threshold utilized. For SLNB, many surgeons utilize a 5% risk threshold for nodal metastasis as a criterion for potentially offering nodal staging based in part on the low complication rate (approximately 5%–10%) and the low FNR (12.5%) for SLNB. A 5% risk for a positive SLN is generally seen in melanomas ≥0.75 mm in thickness, and this criterion is often used as a threshold for offering SLNB in patients with thin melanoma. In contrast, the positive SLN rate for melanomas <0.75 mm falls below 5% and the prognostic information gained from nodal staging becomes limited in these cases (48,51,52). Clark level is also reported to be prognostic for SLN metastasis, but it is unknown if this is a truly independent predictive marker in the face of Breslow thickness. Ulceration has been shown to predict SLN metastasis in thin melanoma patients, but ulceration is rarely seen in melanomas <0.75 mm, and the vast majority of ulcerated thin melanoma cases already are in melanomas ≥0.75 mm. Mitotic rate has recently been incorporated into the American Joint Committee on Cancer (AJCC) staging system as prognostic for MSS in thin melanoma patients; however, the prognostic value of mitotic rate for predicting SLN metastases in thin melanoma patients is inconsistently reported, possibly due to differences in evaluating and classifying mitotic rate.
across studies (48,50–52). Currently, Breslow thickness ≥0.75 mm appears to be the most consistent factor that independently predicts a >5% risk for a positive SLN. Ultimately, the decision to proceed with SLNB in patients with thin melanoma requires a tailored discussion with each patient regarding the risks and benefits.

**SLNB for Desmoplastic Melanoma**

Desmoplastic melanoma (DM) is a unique subtype of melanoma and represents less than 4% of all cutaneous melanomas. It is most commonly found on the head and neck of older patients, and it is often a thicker tumor at presentation when compared with nonDM (53–55). DM is divided into two histologic subtypes based on the extent of desmoplasia. Pure DM consists of a spindle cell melanoma with ≥90% desmoplasia, while a mixed DM has desmoplasia involving <90% but >10% of the spindle cell melanoma (54,56). The role of nodal staging in the management of DM is debated. The positive SLN rate reported in the literature for DM ranges relatively widely from 0% to 18% (57–62). If one excludes the small studies that report a zero rate of a positive SLN and also exclude smaller studies with less than 50 patients, the positive SLN rate for DM then ranges from 6% to 14%.

Furthermore, clinicopathologic predictors for a positive SLN in DM patients have also been evaluated. Several studies demonstrate a significantly higher SLN metastasis rate in patients with mixed DM compared with pure DM. For patients with mixed DM, the positive SLN rate ranges from 14% to 25% while the positive SLN rate for patients with pure DM is lower at 2% to 9% (57,62). There is some controversy as to whether SLNB should be offered to patients with pure DM. Some institutions offer SLNB for patients with pure DM given a potential positive SLN rate as high as 9%; however, other institutions do not recommend SLNB for patients with pure DM since some studies demonstrate that the SLN metastasis rate falls below 5%.

**SUMMARY**

Approximately 15% to 20% of patients with melanoma will harbor nodal micrometastases. SLNB is a powerful tool for nodal staging that provides critical prognostic information in patients with melanoma. Furthermore, the FNR and morbidity of SLNB are both relatively low. In accordance with current guidelines, SLNB should be recommended to all patients with intermediate thickness melanomas that are clinically node negative and are deemed medically fit to tolerate the procedure. SLNB may also be recommended in patients with thick melanoma for nodal staging purposes, but criteria for selecting thin melanoma patients for SLNB are debated, although a Breslow thickness of ≥0.75 mm appears to be the most consistent factor that predicts a >5% risk for SLN metastases.
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