Current controversies in early-stage melanoma

Questions on incidence, screening, and histologic regression

Laura J. Gardner, MS,[a] Jennifer L. Strunck, BS,[a] Yelena P. Wu, PhD,[b,c] and Douglas Grossman, MD, PhD[b,c]
Salt Lake City, Utah

Learning objectives
After completing this learning activity, participants should be able to discuss the current controversies associated with the epidemiology and diagnosis of early-stage melanoma; explain the potential factors associated with increasing melanoma incidence; discuss the conflicting epidemiologic studies associated with melanoma screening; and classify the controversial aspects of histologic regression of early-stage melanoma and its potential impact.

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In the first article in this continuing medical education series we review controversies and uncertainties relating to the epidemiology and initial diagnosis of localized cutaneous melanoma (ie, stage 0, I, or II). Many of these issues are unsettled because of conflicting evidence. Melanoma incidence appears to be increasing, yet its basis has not been fully explained. Despite the advantages of early detection, the US Preventive Services Task Force does not recommend skin screening for the general population. Occasionally, biopsy specimens of melanoma will show histologic regression, but the prognostic importance of this phenomenon is uncertain. Some practitioners recommend obtaining a sentinel lymph node biopsy specimen for thin melanomas showing regression, although this histologic finding is not part of the staging system for thin melanomas. Our goal is to provide the clinician who cares for patients with (or at risk for) melanoma with up-to-date contextual knowledge to appreciate the multiple sides of each controversy so that they will be better informed to discuss these issues with their patients and their families. (J Am Acad Dermatol 2019;80:1-12.)

Key words: epidemiology; melanoma; nevus; regression; screening; sentinel lymph node biopsy.

From the University of Utah School of Medicine[a] and the Department of Dermatology[b] and Huntsman Cancer Institute,[c] University of Utah Health Sciences Center, Salt Lake City.
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Reprint requests: Douglas Grossman, MD, PhD, Huntsman Cancer Institute, 2000 Circle of Hope, Salt Lake City, UT 84112. E-mail: doug.grossman@hci.utah.edu.
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Abbreviations used:

AJCC:	American Joint Committee on Cancer
SEER:	Surveillance, Epidemiology, and End Results
SLNB:	sentinel lymph node biopsy
USPSTF:	US Preventive Services Task Force
UVR:	ultraviolet radiation

This review focuses on controversial questions relating to the epidemiology and diagnosis of localized, early-stage cutaneous melanoma (ie, stages 0, I, and II). The questions we address are controversial because there is significant disagreement about interpretations of certain population-based data or because they relate to uncertainties about the biologic behavior or prognostic significance of histologic features of a melanoma biopsy specimen. Many of these issues are unsettled because of conflicting evidence. Melanoma incidence in the United States has been increasing at a greater rate than most other cancers.[1] In fact, it has been suggested that in the period from 1930 to the present day, the lifetime risk of developing invasive melanoma in the United States has increased from 0.1% to almost 2%.[2] The basis for this trend has not been fully explained, and multiple potential contributory factors have been suggested and challenged. Although melanoma survival is much greater for lesions diagnosed at earlier stages,[3] the US Preventive Services Task Force (USPSTF) has repeatedly not recommended skin screening for the general population.[4] Nevertheless, routine skin screening may be appropriate for high-risk groups. Occasionally, melanoma biopsy specimens will show immune-mediated regression of part of the tumor, but there are conflicting data on the prognostic importance of this phenomenon which is compounded by lack of consistent pathologic reporting. Some practitioners recommend obtaining a sentinel lymph node biopsy (SLNB) specimen for thin melanomas showing regression, although this histologic finding is not part of the latest American Joint Committee on Cancer (AJCC) staging system[3] for thin melanomas. In the first article in this continuing medical education series we review the controversies and uncertainties relating to these issues. Our goal is to provide the clinician with an understanding of the multiple sides of each controversy so that they will be better informed to address these issues with their patients and their families.

IS THERE A MELANOMA EPIDEMIC?

Key points

- **Melanoma incidence is increasing**
- **Melanoma mortality rates are not increasing as fast as incidence rates**
- **Increased incidence of thick as well as thin lesions**
- **Basis for increasing incidence is unclear**
- **Roles of ultraviolet light exposure, aging, and socioeconomic status**
- **Pathologic overdiagnosis may be a factor**
- **Role of increased awareness and screening**

Overview of melanoma trends: Incidence, mortality and tumor thickness

The National Cancer Institute (NCI) estimates that there will be >91,270 new cases of invasive melanoma in the United States in 2018.[5] There is universal agreement that the incidence of melanoma diagnoses is increasing,[6] and a similar trend has been observed in Europe.[7] Multiple studies using the US Surveillance, Epidemiology and End Results (SEER) Program and National Program of Cancer Registries have consistently reported increasing melanoma incidence between 1973 and 1997.[8-10] More recent studies (1992-2006) reported that melanoma incidence increased 3% to 4% per year across most demographic groups.[11,12] However, a recent study of the Centers for Disease Control and Prevention database suggests that incidence in New England states may be decreasing.[13]

The NCI also estimates that there will be 9320 melanoma deaths in the United States in 2018.[5] Although melanoma mortality has been increasing, multiple studies have concluded that the mortality rate has not been increasing as fast as the incidence rate.[8,9] In fact, melanoma-specific survival was stable[5,12] or improved across all subgroups except in males >65 years of age,[11] nonblack minorities, and patients with nodular and acral lentiginous subtypes. These mortality trends cannot be explained by selective increases in thin melanomas, because multiple studies reported increased incidence of both thin and thick tumors,[9,11,12,14] although median thickness may have slightly decreased.[14]

Roles of ultraviolet radiation, aging, and socioeconomic status

It is likely that multiple factors have contributed to the increased incidence of melanoma seen over the past 50 years[15,16] (Table I). At the heart of the debate is whether the observed increased incidence is "real" or artefactual as a result of various factors that may lead to increased diagnosis. Exposure to ultraviolet radiation (UVR) is the predominant environmental risk factor for melanoma,[17] including both early[24] and later[25] adult-life exposures. It is unclear to what extent population exposure to UVR has increased in recent decades,[26] although a significant component of new melanoma cases is represented by lentigo

Table I. Factors underlying increases in melanoma diagnoses

Cause	Effect
Increased UV exposure, tanning bed use	Melanoma risk increases with UV exposure
Multiple biologic mechanisms linking UV exposure to melanoma risk[17]	
Indoor tanning rate of 20.4% among those 18-29 years of age[18]	
Aging population	Melanoma risk increases with increasing age
Melanoma incidence increases with age[11]	
Among US whites, 79% of increased diagnoses through 2031 will be attributable to rising age-specific rates and 21% to population growth and aging[19]	
Diagnostic shift	Increased tendency to diagnose melanoma; favors increase in early-stage lesions
Average 2.6% annual increases in US melanoma diagnoses, while melanoma in situ diagnoses increased at annual rate of 9.5%[20]	
29 cases of dysplastic nevi with severe atypia and 11 cases of thin radial growth-phase melanoma from 1988-1990 were rereviewed and 18/40 classified as melanoma[21]	
Increased awareness and screening	Earlier melanoma detection; increase in early-stage lesions; may not decrease mortality
Medicare claims and SEER data from 1986-2001 showed average biopsy rate increased 2.5-fold while average melanoma incidence increased 2.4-fold[8]	
"Melanoma paradox" of increased diagnoses not matched by increased mortality[22]	
More biopsy specimens obtained	Increased detection; favors increase in early-stage lesions
Increases in biopsy rates mirror increases in melanoma incidence[17]	
Higher melanoma rates at Lawrence Livermore National Laboratory associated with correspondingly higher biopsy rates[23]	
Increased reporting efficiency	More lesions/information captured
The 20 SEER registries currently represent 28% of the US population (24.9% of US whites), but the 9 registries extant from 1975-1992 only represent 9.4% and 8.7% of the US and US whites, respectively[5]	
Increases in incidence rates reported by NPCR (vs. SEER) registries 1995-1997 may be related to increased case ascertainment and reporting[10]	

NPCR, National Program of Cancer Registries; *SEER*, Surveillance, Epidemiology, and End Results; *UV*, ultraviolet.

maligna,[20] and tanning bed use has been rampant among younger generations.[18] Sunscreens were developed in the 1970s, and some studies show that sunscreen use is associated with reduced melanoma risk.[27,28] On the other hand, a telephone survey covering habits from 1986 to 1996 revealed increases both in sunburns and sunscreen use.[29]

The risk of melanoma, as with most cancers, increases with age.[30,31] The average life expectancy in the United States has increased,[32] but primarily in higher socioeconomic groups.[33] The increased incidence and mortality in older patients[8,11] suggests that this factor is contributory, and it has been estimated that a significant proportion of new diagnoses in the coming decades will be attributable to rising age-specific rates and population growth and aging.[19] The basis for the increased incidence and higher mortality rates observed in more economically advantaged groups,[14,34-36] if separate from the association with aging, is unclear. It is possible that such groups may have more UVR exposure because of increased opportunities for recreational activity.

It is reasonable to consider additional factors that may have contributed to the observed increased melanoma incidence and relatively steady-state mortality. It is notable that melanoma in situ (stage 0) lesions represent an increasingly larger percentage of the overall increase in melanoma incidence. For example, while there have been on average 2.6% annual increases in all US melanoma diagnoses in recent years, melanoma in situ diagnoses have increased at an annual rate of 9.5%.[20] Similar trends have been noted in Europe[37] and Australia.[38] The increased proportion of early-stage lesions suggests that factors related to overdiagnosis, screening, an increased number of biopsy specimens, and incomplete reporting may have contributed to the

increased incidence of melanoma, and these are discussed separately below.

Is melanoma overdiagnosed?

One explanation for increased melanoma incidence with stable mortality is the misclassification by pathologists of biologically benign melanocytic lesions as melanoma. Although the histologic criteria for melanoma have been well-defined, it is not possible to predict the biologic behavior of lesions that share features overlapping with nevi and melanoma.[39] There is diagnostic certainty for lesions initially called melanomas if they ultimately recur as tumors or metastasize; however, the same cannot be said for lesions that do not recur because benign melanocytic lesions would have the same outcome. Given the increasing potential liability of misdiagnosing a melanoma as a benign neoplasm[40] and the costs of such an error,[41] there is substantial pressure on pathologists to call borderline lesions melanoma.

Another consideration is whether over the past decades there has been diagnostic drift, whereby the threshold for rendering a diagnosis of melanoma has changed over time such that lesions that may have been histologically diagnosed as nevi in the past are more likely to be diagnosed as melanoma today. Several studies have addressed this issue, with one finding that a significant fraction of cases originally reported as benign were reviewed as malignant when reexamined decades later,[42] while another reached the opposite conclusion.[21] It has also been noted that in instances where there is disagreement with a previously rendered diagnosis there is a greater tendency to "overcall" rather than "undercall,"[43] and that routine histopathologic error in the diagnosis of borderline lesions is not self-correcting and results in more over- than underdiagnoses of malignancy.[44] On the other hand, it has been suggested that the melanoma "epidemic" is primarily the result of previous underdiagnosis rather than current overdiagnosis, resulting from improved histologic diagnostic criteria that allow melanomas to be recognized more accurately and at earlier stages.[45] Indeed, before the 1980s, biopsy specimens were rarely obtained from small lesions that were not highly suspicious of melanoma, while it has become increasingly common to obtain biopsy specimens from smaller lesions that may represent melanoma earlier in histologic evolution.[43]

Role of screening and increased biopsies

Skin cancer screenings sponsored by the American Academy of Dermatology began in 1985, and since that time increased melanoma awareness has resulted in an increasing fraction of the population being screened for melanoma.[46,47] Several studies have documented a correlation of increasing melanoma incidence with biopsy rates.[8,48] Could the "melanoma paradox" of increased diagnoses not matched by increased mortality be explained by earlier detection, treatment and consequent avoidance of melanoma-related mortality?[22] At the same time, increased screening would be expected to amplify the effects of overdiagnosis and increase the false-positive rate for melanoma.[49] It has been suggested that the vast majority of lesions contributing to the melanoma "epidemic" are biologically benign lesions that most expert pathologists would agree show microscopic features diagnostic of melanoma,[50] analogous to the situation of prostate and thyroid cancer, in which diagnoses have risen dramatically as a result of increased sampling of tissues that contain a reservoir of lesions diagnosed as cytologically malignant but are not biologically malignant, as evidenced by the high rate of these cancers found in autopsy specimens.[51,52] However, although the majority of increased melanoma diagnoses are represented by thin lesions,[20,37,38] diagnosis of thicker lesions has also increased over the past decades.[9,11,12,14,53] In addition, it is worth considering that melanoma incidence has increased without regard to socioeconomic status, which is a surrogate marker for access to care and screening.[12,54] Therefore, while intensified screening efforts and increased biopsy rates are a likely contributor, these factors alone cannot account for the dramatic increase in melanoma diagnoses.

Limitations of reporting

Finally, it has been suggested that the observed increased melanoma incidence may be an artifact of underreporting in earlier decades.[55] Most of the studies cited above relied on SEER and National Program of Cancer Registries data to compare melanoma rates at different time points.[56] The 20 SEER registries currently represent 28% of the US population (24.9% of US whites), but the 9 registries extant from 1975 to 1992 only represent 9.4% and 8.7% of the United States and US whites, respectively.[5] In the past, data collection from hospitals and hospital-based clinics is likely to have been more efficient than from outpatient physician offices.[23] Many previous epidemiologic studies were missing data on tumor thickness,[10,57] many registries did not capture in situ lesions, and there is a significant error rate in SEER for thin melanomas related to decimal point placement.[58] These factors could account for an underrepresentation of thicker

melanomas and overestimation of mortality from thin melanomas.

DOES MELANOMA SCREENING IMPROVE OUTCOMES?

Key points

- **Population-based skin screening is not recommended by the USPSTF**
- **Inconsistent screening/survival results have been reported from Germany**
- **Screening may enable diagnosis at an earlier stage or identify low-grade lesions that are unlikely to metastasize**
- **There may be significant costs of screening**
- **Recommending skin screening for high-risk groups**

In 2016, the USPSTF reviewed the effectiveness of skin screening and concluded, as they did in 2001[59] and 2009,[60] that the "current evidence is insufficient to assess the balance of benefits and harms of visual skin examination by a clinician to screen for skin cancer in (asymptomatic) adults."[4] In their review of skin cancer screening, the USPSTF considered evidence on reducing skin cancer morbidity and mortality, the potential harms associated with screening, differences in screening outcomes when performed by a primary care clinician versus a dermatologist, and whether screening leads to earlier detection.[61] The National Comprehensive Cancer Network recommends skin screening every 6 to 12 months after a melanoma diagnosis but does not address screening for the general population or persons at increased risk.[62] Similarly, the American College of Physicians, American Academy of Family Physicians, American College of Preventive Medicine, American Cancer Society, and the American Academy of Dermatology do not have specific recommendations on skin cancer screening.[63]

Effect of screening on survival

The ultimate question is whether screening improves survival at a population level. Prospective studies are problematic, given the cost and time required for implementation and follow-up and difficulties assembling an appropriate control group. The most notable was the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany (SCREEN) trial, in which 19% (>350,000) of the eligible citizens of Schleswig-Holstein were screened with whole-body skin examination by general physicians and dermatologists from 2003 to 2004, and population data were compared to that for the 2-year period preceding the trial.[64,65] The incidence of invasive melanoma increased by 34% (16% in men, 39% in women) in Schleswig-Holstein, while incidence rates remained constant in other parts of Germany.[64,65] As of 2008, melanoma mortality in the screened area had decreased from 1.9 to 0.79 per 100,000 in males and from 1.4 to 0.66 per 100,000 in females.[64] This declining mortality trend in Schleswig-Holstein was significantly lower than that of adjacent nonscreened regions.[65,66] In 2008, skin screening was extended to the rest of Germany, and Boniol et al[67] evaluated whether melanoma mortality trends decreased in Germany compared with surrounding countries and whether the initial decreasing mortality trend observed in Schleswig-Holstein was maintained upon longer follow-up. They reported that melanoma mortality rates in Schleswig-Holstein from 2008 to 2012 increased by 2.6% in men and 0.02% in women, and from 2009 to 2013 returned to levels observed before screening initiation; moreover, trends of melanoma mortality in Germany from 1980 to 2012 did not differ from those observed in surrounding countries.[67] The basis for the transient decrease mortality in Schleswig-Holstein followed by return to prescreening levels is unclear. It has been suggested that there was a temporal modification in the reporting of death causes[67] and that the method of screening subsequent to the initial trial was less thorough.[68]

Screening reduces melanoma thickness at diagnosis

It has been suggested that there are other valuable endpoints for melanoma screening aside from survival.[69] For instance, decreased melanoma thickness can be a surrogate for reduced mortality. Indeed, the SCREEN trial[70] and other trials not randomized or controlled[71,72] or adequately powered to detect differences in survival[73] also demonstrated reduced melanoma thickness in the screened population. Moreover, multiple case-control studies have shown that skin screening results in earlier (ie, thinner) melanoma detection.[74-76] Use of dermoscopy may further increase the accuracy of detection of melanoma in situ.[77,78] In addition to improved survival, earlier detection of melanoma can result in reduced morbidity from staging and treatment, because thinner lesions are less likely to need SLNB and require smaller margins for excision. Finally, screening provides opportunities for melanoma education, including instruction on skin self-examination and sun protection behaviors to reduce risk and identify family members who may be at increased risk.[69,79,80]

Cost effectiveness of screening and increased biopsy procedures

Is screening cost effective? In the SCREEN trial, 620 people had to be screened to find 1 melanoma[81]; other screening studies have reported that 50 to 100 biopsy specimens were obtained for each melanoma diagnosed.[8,82] Cost effectiveness of screening has also been evaluated in terms of cost per year of life saved, where numbers for one-time screening range from $10,000 to $40,000.[83-85] There is a significant cost savings when melanoma is diagnosed at an earlier stage, with a T4b lesion being >2000% more expensive to treat than an early in situ melanoma and 1000% more expensive than a T1a tumor.[86] In addition to high costs, arguments against the benefit of melanoma screening include the possibility of overdiagnosis and overtreatment of skin cancers (as discussed above) without improving mortality rates. Biopsy specimens obtained from atypical nevi may lead to reexcisions[87] that may not be necessary.[88] In addition, although shave biopsy specimens are associated with minimal scarring,[89] numerous excisions can potentially lead to cosmetic and functional morbidity. However, in a study in which trained primary care physicians were compared to untrained physicians, the trained physicians made 79% more melanoma diagnoses with no substantial increase in skin surgeries or dermatology visits.[90]

Screening is unlikely to impact survival for some melanomas

A subset of melanomas is unlikely to be impacted by screening because they are typically difficult to identify visually or exhibit rapid growth resulting in significant depth upon detection. For example, amelanotic melanomas (representing <2% of melanomas) have minimal melanin and lack other recognizable features of melanocytic lesions.[91,92] Desmoplastic melanomas (representing <4% of melanomas) are also often amelanotic.[93] These melanoma subtypes generally evade early detection and are usually diagnosed at an invasive stage. Nodular melanomas are fast-growing, such that deep invasion has occurred by the time individuals notice bleeding or rapid growth.[94] In addition, melanomas may arise in mucosal or genital sites that are often not included in skin examinations.

Screening recommendations should be tailored to risk

A summary of the potential benefits and costs of melanoma screening is presented in Table II.

Geller et al[95] have advocated for reducing melanoma mortality in individuals at high risk through education and screening. Several algorithms to determine melanoma risk may have utility for identifying others who might benefit most from screening.[96,97] Johnson et al[98] proposed that individuals between 35 and 75 years of age should receive an annual total body skin examination based on comparison of screening age ranges to incidence and mortality rates for colorectal, cervical, breast, and lung cancer. They recommended that individuals receive skin screening on an annual basis if their relative melanoma risk is >1.8—namely those with personal history of melanoma, family history of melanoma, personal history of nonmelanoma skin cancer, ongoing immunosuppression, and those with various physical features associated with increased risk (blonde or red hair, >40 nevi, >2 clinically atypical nevi, freckling, and other signs of UVR overexposure).[98] The USPSTF acknowledged that "benefits of skin cancer screening may be greatest among subgroups most likely to develop fatal melanoma."[61] In particular, older men who continue to exhibit increased incidence of thick lesions[8,11] and traditionally have resisted screening and performing self-skin examinations[99] would be an example of a subgroup to target.

HOW SHOULD HISTOLOGIC REGRESSION IN PRIMARY MELANOMA BE INTERPRETED?

Key points

- **Lack of pathologic reporting consistency**
- **Regression may indicate an antitumor immune response**
- **Conflicting studies on prognostic importance of regression**
- **Histologic regression is not an indication for SLNB in thin melanoma**

Regression is a histopathologic parameter observed in many solid tumor types, including melanoma, that is used to describe spontaneous tumor disappearance.[100] Regression may be appreciated in some melanomas on clinical examination by the presence of depigmentation resulting in blue, pink, white, or gray areas. Under dermoscopic examination, regression structures are typically defined by the presence of white and blue areas within the lesion; however, the presence and nature of such regression structures does not accurately predict melanoma invasion.[101,102] Histologic regression is present in 10% to 35% of melanomas[103] and more commonly associated with the radial growth phase of thin lesions[104] on the trunk.[105] Understanding the prognostic significance of regression has been problematic because of a lack of consistent histopathologic reporting and conflicting

Table II. Potential benefits and costs of skin screening

- Benefits of screening
  - Earlier melanoma detection
    - German SCREEN trial: melanomas diagnosed within 4-24 months were thinner than those diagnosed during pre-SCREEN era[70]
    - Screening program at Lawrence Livermore National Laboratory: melanomas >0.75 mm decreased from 22 to 4.6 cases per 100,000 person-years[71]
    - Screening program in Queensland, Australia: 39% of melanomas were in situ, 55% were <1 mm, and 6% were ≥1 mm compared to respective rates of 36%, 48%, and 16% in the general population of Queensland[72]
  - Reduction in thick melanomas should reduce mortality
    - German SCREEN trial: 5 years later, melanoma mortality decreased from 1.9 to 0.79 per 100,000 in males, and from 1.4 to 0.66 per 100,000 in females, without reduction in surrounding areas[64,66]
    - Screening program at Lawrence Livermore National Laboratory: melanoma-related mortality was 0 (vs 3.4 expected melanoma-related deaths)[71]
  - Treatment of early-stage melanoma less costly than treating advanced-stage melanoma
    - Melanoma expense model estimates cost of treatment and surveillance of melanoma in situ to be $4648 vs $159, 808 for stage IV melanoma[86]
  - May avoid SLNB and lymph node dissection
    - Thin melanomas will not require assessment and treatment of draining lymph nodes[3]
  - Opportunity for education
    - Instructions on skin self-examination and sun-protection behaviors to reduce risk, and identification of family members who may be at increased risk[69,79]
- Costs of screening
  - May increase biopsy rates without reducing mortality
    - Review of Medicare claims from 9 different geographic areas from 1986-2001 showed biopsy rates increased 2.5-fold without a significant reduction in mortality[8]
  - Potential for overdiagnosis
    - Potential liability and costs of misdiagnosing a melanoma as a benign neoplasm[40,41]
    - Potential for diagnostic drift[42]
    - Greater tendency to "overcall" rather than "undercall" melanocytic lesions[43]
  - Screening is expensive
    - University of Pittsburgh Medical Center screening: total cost to detect a single melanoma was $32,594[82]
  - Obtaining biopsy specimens of atypical nevi may lead to reexcisions
    - Majority of dermatologists will reexcise moderately dysplastic nevi with positive margins[87]
    - Reexcision of such nevi may be unnecessary[88]
  - Most biopsy specimens are negative for melanoma
    - German SCREEN trial: 20 excisions were performed to find 1 melanoma in men ≥65 and >50 excisions were required to find 1 melanoma in men 20-49[65]
  - May not reduce mortality for some melanomas
    - Nodular melanomas more likely to be detected by patients than screening and be deeply invasive upon diagnosis[94]
  - Some melanomas may evade screening
    - Amelanotic melanomas may lack recognizable features of melanocytic lesions[91,92]
    - Desmoplastic melanomas are also often amelanotic[93]

SCREEN, Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany; *SLNB*, sentinel lymph node biopsy.

studies correlating regression with clinical outcomes, as discussed below.

Inconsistent histologic reporting of regression

Regression is histologically characterized by a variable decrease in the number of melanoma cells accompanied by ≥1 feature(s) reflecting a host response that includes dermal fibrosis, inflammatory infiltrate, melanophages, neovascularization, epidermal flattening, and apoptosis of keratinocytes or melanocytes.[106] The relative extent of these features depends on the stage of the regression, and the degree

Table III. Evolving guidelines for recommending SLNB for thin (<1 mm) melanoma

Guidelines	Indications
AJCC, 2001	Ulceration or Clark level ≥IV
AJCC, 2009	Ulceration or mitotic rate ≥1 per mm^2 (Clark level removed)
NCCN, 2010	Ulceration or mitotic rate ≥1 per mm^2
NCCN, 2016	Ulceration or mitotic rate ≥1 per mm^2 or thickness ≥0.76 mm
AJCC, 2018	Thickness ≥0.8 mm or ulceration (mitotic rate removed)

AJCC, American Joint Committee on Cancer; *NCCN*, National Comprehensive Cancer Network; *SLNB*, sentinel lymph node biopsy.

to which these individual changes are required for a diagnosis of histologic regression has not been well established. Because regression is interpreted subjectively as a pattern of characteristics rather than as a single finding, the reporting of regression is often inconsistent.[106,107] There is also the problem of consistent quantification of the extent (horizontal and vertical) of regression, based on amount of tumor involved, which (when reported) is subjective and often rounded to the nearest 10% or reported as greater than some quartile (ie, 25%, 50%). In order to determine the clinical significance of histologic regression, there is a compelling need for a universal scheme to objectively define and report it.[108]

Regression may indicate an antitumor response

Tumor regression likely results from an immune-mediated response of activated T lymphocytes directed against tumor antigens.[109] In most cases, however, it is not clear why the antitumor response results in only partial regression rather than complete eradication of the primary tumor. Moreover, studies have not consistently shown that regression is more common in subsequent melanomas in patients with multiple primary melanoma,[110,111] arguing against an "immunization effect." On the other hand, one study of patients who presented with macroscopic nodal disease found that those with unknown primary tumor had significantly better disease-free, distant metastasis–free and melanoma-specific survival after complete lymph node dissection.[112] An alternative explanation is that in some of these patients with unknown primary tumor, their melanoma may not have been metastatic but rather originated from nevus cells in lymph nodes, which may have a more favorable prognosis.

The presence of tumor-infiltrating lymphocytes has been associated both with improved[113,114] and reduced[115] survival. It is important to note that the favorability of the immune response likely depends on the presence of regulatory lymphocytes, because the function of antitumor CD8 lymphocytes is inhibited by the presence of CD4 lymphocytes expressing the Foxp3 transcription factor.[116] Bastian[117] suggested that melanoma tumor regression may be secondary to telomere dysfunction in tumor cells resulting in cellular crisis and increased apoptosis and that the antitumor response may be directed toward apoptotic bodies that are highly antigenic.[118] While immune cell infiltration may enhance clearance of tumor cells, it may also facilitate selection of tumor cells that through acquired genetic variation have developed immune escape mechanisms.[117]

Conflicting studies on prognostic importance of regression

Several studies have shown regression to be a favorable prognostic factor,[119-121] and multiple others found that regression was not significantly associated with either disease-free or overall survival.[105,122-124] By contrast, a number of other studies consistently found that histologic regression was associated with worse clinical outcomes, including recurrence, metastasis, and death.[125-130]

Guidelines for SLNB in thin melanomas

The evolving indications for recommending SLNB for thin melanoma are summarized in Table III. While mitotic rate was previously a consideration, the 8th edition of the AJCC melanoma staging guidelines (implemented in January 2018) no longer include mitotic rate as a staging criteria for stage I melanoma.[3] The net effect over time has been to restrict recommendations for SLNB to a smaller subset of patients in whom the test is more likely to be positive. Primary tumor regression has never been incorporated into AJCC[3] or National Comprehensive Cancer Network[131] guidelines for staging or treatment of early stage melanoma. Nevertheless, because histologic regression theoretically may result in an underestimation of tumor depth (and possibly stage), its presence has been considered a soft indication for SLNB in patients with thin melanoma. It should be noted, however, that one study concluded that regression does not significantly underestimate melanoma thickness.[132] Several studies have shown that patients with thin regressed melanomas are unlikely to have a positive SLNB specimen[122,133] and that the presence of regression is not associated SLNB outcome.[134,135] On the other hand, several studies found that regression was protective against sentinel lymph node metastasis.[120,136,137] Taken together, the data

generally do not support the practice of performing SLNB in thin melanomas with regression (in the absence of additional adverse prognostic features), which is unlikely to be positive.

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