Five-year survival in patients with nodular and superficial spreading melanomas in the US population

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Background: Although superficial spreading melanomas (SSM) are diagnosed as thinner lesions, nodular melanomas (NM) have a more rapid growth rate and are biologically more aggressive compared with other histologic subtypes.

Objective: To determine the difference in 5-year relative survival in patients with NM and SSM at the same Breslow depth and TNM stage.

Methods: A population-based cross-sectional analysis compared the 5-year relative survival of patients with NM and SSM using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)*Stat software (version 8.2.1-8.3.5). Chi-square tests compared the proportions, and Kaplan-Meier method with Z-score compared 5-year relative survival.

Results: For patients receiving a diagnosis between 2004 and 2009, 5-year relative survival was lower in NM compared with SSM (53.7% vs 87.3%; Z score, −41.35; $P < .001$). Similarly, for patients receiving a diagnosis between 2010 and 2015, 5-year relative survival was lower in NM compared with SSM (61.5% vs 89.7%; Z score, −2.7078; $P < .01$). Subgroup analyses showed inferior survival in NM in T1b, and survival differences remained significant after excluding patients with nodal or distant metastases.

Conclusions: Five-year relative survival is worse in NM compared with SSM especially in T1b, T2a, and T2b melanomas. Melanoma subtype should be taken into consideration when making treatment recommendations. (J Am Acad Dermatol 2021;84:1015-22.)

Key words: 5-year survival; nodular melanoma; overall survival; superficial spreading melanoma.

INTRODUCTION

Several key pathologic characteristics impact the prognosis of melanoma, including tumor thickness, ulceration status, mitotic rate, and lymphovascular invasion.[1-4] The primary determinants of the clinical stage of melanoma are Breslow depth of invasion and ulceration status.[1] Histologic subtypes of melanoma include superficial spreading melanoma (SSM), lentigo maligna melanoma, nodular melanoma (NM), desmoplastic melanoma, and spindle cell melanoma, among others.[5] NMs account for a significant portion of deaths attributable to melanoma, and at diagnosis are characterized by increased thickness, higher likelihood of ulceration, and increased mitotic rate compared with other subtypes.[6-11]

Previous analysis of 17,600 patients of the American Joint Committee on Cancer (AJCC) Melanoma Staging Database identified increasing tumor thickness with decreasing 5- and 10-year

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survival. The 10-year survival was 92% in the 11,841 patients with T1 melanomas (<1.00 mm), 80% in the 8,046 patients with T2 melanomas (1.01-2.00 mm), 63% in the 5,291 patients with T3 melanomas (2.01-4.00 mm), and 50% in the 2,461 patients with T4 melanomas (>4.00 mm).[3] This survival data is incorporated into the staging criteria for localized melanomas (stage I and stage II); however, it is not further subdivided according to histologic subtype.

The impact of histologic subtype on melanoma prognosis and treatment has been relatively limited given that staging according to the AJCC does not incorporate histologic subtype.[12] This finding is largely due to the assumption that increased risk with nodular histology is confounded by increases in thickness and ulceration.[13,14]

Our study aims to determine whether there is a difference in 5-year relative survival for melanoma patients with the same T stage but differing histologic subtypes. By analyzing melanomas with the same TNM stage, we are able to remove other prognostic factors such as thickness, ulceration, and mitotic rate from our analysis and analyze survival in similarly staged melanomas according to subtype. A statistically significant difference in 5-year relative survival could argue for incorporation of melanoma subtype into the AJCC guidelines, which may affect management, staging, and surveillance.

CAPSULE SUMMARY

- Nodular melanoma has been identified as an indicator of poor survival in melanoma. Our findings support this phenomenon, particularly in comparing 5-year survival across a particular T stage.
- These findings should be taken into consideration when deciding on optimal therapy and counseling patients regarding prognosis.

METHODS

We conducted a population-based cross-sectional analysis based on the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) *Stat Software, version 8.2.1-8.3.5.[15] The SEER program is a population-based registry for incident cancers in the United States. Survival sessions were conducted using the SEER-18 registry, which represents approximately 28% of the US population.[16] To assess 5-year survival, data was restricted to the period from 2004 to 2009, during which the sixth edition of the AJCC was implemented, and 2010 to 2015, during which the seventh edition was implemented. Survival was ascertained at 60 months after diagnosis. The International Classification of Disease for Oncology, Third Edition (ICD-0-3) histology and site codes 8721 and 8743 were used to define cases of NM and SSM, respectively. Breslow thickness was measured on a 0.01- to 9.89-mm scale.

Criteria for TNM staging were as follows: per AJCC sixth edition, T1a lesions were defined as having a depth less than or equal to 1 m, Clark level less than 4, and were nonulcerated; T1b lesions were less than or equal to 1 mm, Clark level IV or V, or ulcerated; T2a lesions were 1.01 to 2 mm nonulcerated; T2b lesions were 1.01 to 2 mm ulcerated; T3a lesions were 2.01 to 4 mm nonulcerated; T3b lesions were 2.01 to 4 mm ulcerated; T4a lesions were greater than 4 mm nonulcerated; and T4b lesions were greater than 4 mm with ulceration.[17] The AJCC seventh edition criteria were published in 2010 with significant changes, including the addition of mitotic rate to ulceration as a differentiating factor for T1a and T1b melanomas. We examined age at diagnosis (less than 65 years, ≥65 years), gender, N stage (N0 and N1-N3, excluding NX), and M stage (M0 and M1-3, excluding MX). Melanoma-specific survival curves were created using the Kaplan-Meier product-limit method and compared using the log-rank test. Z score was calculated using (SEER)*Stat and SAS software.

RESULTS

We identified 5,011 patients with NM and 22,490 patients with SSM in the AJCC 6 data set and 2,249 patients with NM and 11,375 patients with SSM in the AJCC 7 data set. In both datasets, compared with patients with SSM, patients with NM were more likely to be older (mean age, 62.5 vs 55; $P < .001$), male (62% vs 51.5%; $P < .0001$), staged at T3/4 (65% vs 7%; $P < .0001$), N1-3 (26% vs 5.5%; $P < .0001$), and M+ (4.5% vs 0.25%; $P < .0001$) (Tables I and II).

For the AJCC 6 data set, 5-year relative survival was lower in NM compared with SSM (53.7% vs 87.3%; Z score, −41.35; $P < .001$). Subgroup analyses showed inferior survival in NM in T1b (55.7% vs 85.5%; Z score, −12.1928; $P < .0001$), T2a (76.1% vs 83.3%; Z score, −3.8909; $P < .0001$), and T2b (56.6% vs 72.4%; Z score, −4.3106; $P < .001$). Survival differences remained significant after adjusting for age in T1b (hazard ratio [HR], 3.057; 95% confidence interval [CI] [2.56, 3.65]; $P < .0001$ [log-rank $P < .0001$]), T2a (HR, 1.392; 95% CI [1.16, 1.67]; $P = .0004$ [log-rank $P < .0001$]), and T2b (HR, 1.774; 95% CI [1.38, 2.28]; $P < .0001$ [log-rank, $P < .0001$]). Survival difference also remained significant after excluding patients with nodal or distant metastases at

Abbreviations used:

AJCC: American Joint Committee on Cancer
CI: confidence interval
HR: hazard ratio
NM: nodular melanoma
SEER: Surveillance, Epidemiology, and End Results
SLN: sentinel lymph node
SLNB: sentinel lymph node biopsy
SSM: superficial spreading melanoma

diagnosis in T1bN0M0 (60.3 % vs 86.2%; Z score. −9.4022; $P < .001$; Fig 1); T2aN0M0 (78.7% vs 84.5%; Z score, −2.9598; $P < .01$; Fig 2); and T2bN0M0 (61.8% vs 74%; Z score, −2.9645; $P < .01$; Fig 3). No significant survival difference was observed for thicker melanomas such as T3a (63.1% vs 63.8%; Z score, −0.2444; $P = .8070$), T3b (46.8% vs 49.1%; Z score, −0.6929; $P = .4884$), T4a (44.8% vs 46.9%; Z score, −0.4397; $P = .6601$), or T4b (29.0 % vs 27.9%; Z score, 0.3146; $P = .7530$).

These trends were also observed for patients receiving a diagnosis between 2010 and 2015 according to the AJCC seventh edition TNM staging criteria: 5-year relative survival was lower in NM compared with SSM (61.5% vs 89.7%; Z score, −2.7078; $P < .01$). Subgroup analyses showed inferior survival in NM in T1b (64.4% vs 91.8%; Z score, −4.8815; $P < .0001$). Survival difference remained significant after adjusting for age in T1b (HR, 4.256; 95% CI [2.92, 6.21]; $P < .0001$ [log-rank $P < .0001$]). Survival difference also remained significant after excluding patients with nodal or distant metastases at diagnosis in T1bN0M0 (72% vs 92%; Z score, −3.4964; $P < .001$; Fig 4). Thick ulcerated melanomas also demonstrated a statistically significant difference in survival including T3b (50.5% vs 65.2%; Z score, −2.3730; $P < .02$) and T4b (40.9 % vs 21.8%; Z score, 2.5307; $P < .02$) compared with those that were nonulcerated including T3a (75.9% vs 72.8%; Z Score, 0.5597; $P = .5757$) and T4a (53.9% vs 67.0%; Z Score, −1.2357; $P = .2166$). Differences in survival in T3b and T4b did not remain significant after adjusting for age: T3b (HR, 1.31, 95% CI [0.94, 1.85]; $P = .1161$ [log-rank $P = .0364$]), T4b (HR, 0.93; 95% CI [0.69, 1.27]; $P = .6630$ [log-rank $P = .3991$]).

Table I. AJCC 6 characteristics of cohorts

	NM (N = 5011)	SSM (N = 22,420)
Age (y)		
< 65	2781 (55.5%)	16,466 (73.4%)
≥ 65	2230 (44.5%)	5954 (26.6%)
Gender		
Male	3138 (62.6%)	11,734 (52.3%)
Female	1873 (37.4%)	10,686 (47.7%)
Race recorded		
White	4859 (97.0%)	21,005 (93.7%)
Black	23 (0.5%)	51 (0.2%)
Other (American Indian/AK Native, Asian/Pacific Islander)	63 (1.2%)	143 (0.6%)
Unknown	66 (1.3%)	1221 (5.4%)
N stage*		
N0	3586 (73.7%)	20,667 (95.3%)
N1-3	1277 (26.3%)	1024 (4.7%)
M stage*		
M0	4659 (95.9%)	21,703 (99.6%)
M1-3	201 (4.1%)	74 (3.4%)

*Excluding NX and MX.

Table II. AJCC 7 characteristics of cohorts

	NM (N = 2249)	SSM (N = 11,375)
Age in years		
< 65	1209 (53.8%)	7917 (69.6%)
≥ 65	1040 (46.2%)	3458 (30.4%)
Gender		
Male	1362 (60.6%)	5808 (51.1%)
Female	887 (39.4%)	5567 (48.9%)
Race recorded		
White	2181 (96.9%)	10,847 (95.4%)
Black	17 (0.8%)	15 (0.1%)
Other (American Indian/AK Native, Asian/Pacific Islander)	26 (1.2%)	119 (1.0%)
Unknown	25 (1.1%)	394 (3.5%)
N stage*		
N0	1592 (73.0%)	10,123 (94.0%)
N1-3	590 (27.0%)	648 (6.0%)
M stage*		
M0	2145 (95.4%)	11,348 (99.8%)
M1-3	104 (4.6%)	27 (0.2%)

*Excluding NX and MX.

DISCUSSION

Our study aimed to determine whether there was a difference in survival of similarly staged melanomas according to histologic subtype. Our analysis found a statistically significant difference in survival of T1b, T2a, and T2b melanomas. Implications of this difference in 5-year survival are particularly profound for the T1 cohort, which historically have an excellent prognosis and in which key decisions are made regarding further staging and surveillance, such as sentinel lymph node biopsy (SLNB).

The incidence of thin melanoma in the United States is increasing.[18,19] Although patients with thin melanomas are found to have a 10-year melanoma-specific survival rate greater than 95%, the absolute number of patients with fatal T1 melanomas is

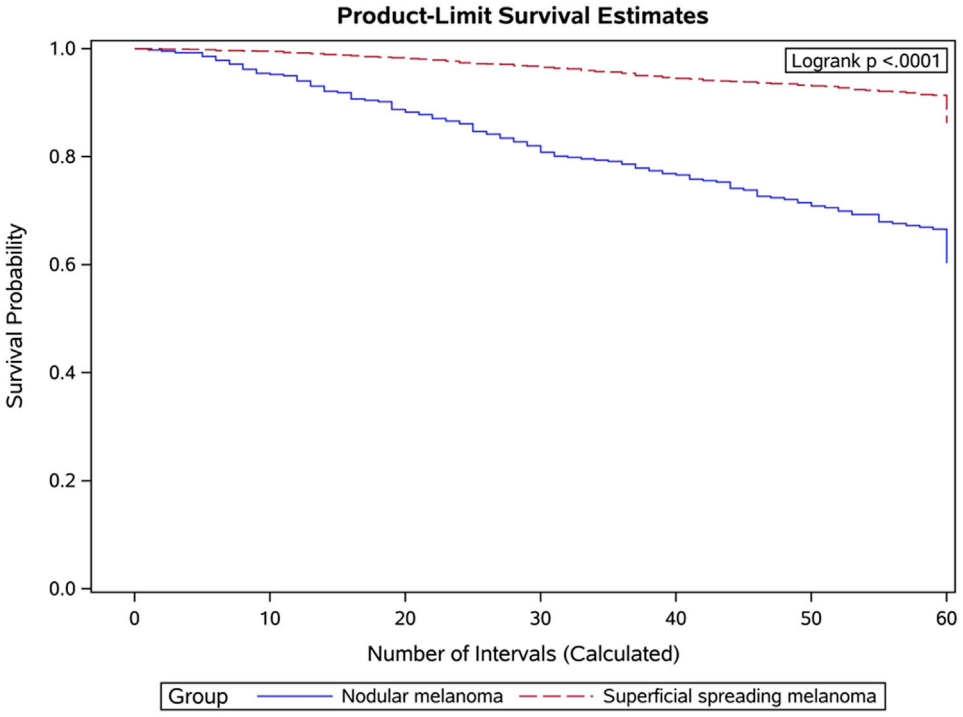

Fig 1. Five-year survival difference in nodular versus superficial spreading melanoma after excluding patients with nodal or distant metastases at diagnosis in T1bN0M0, AJCC 6 data set.

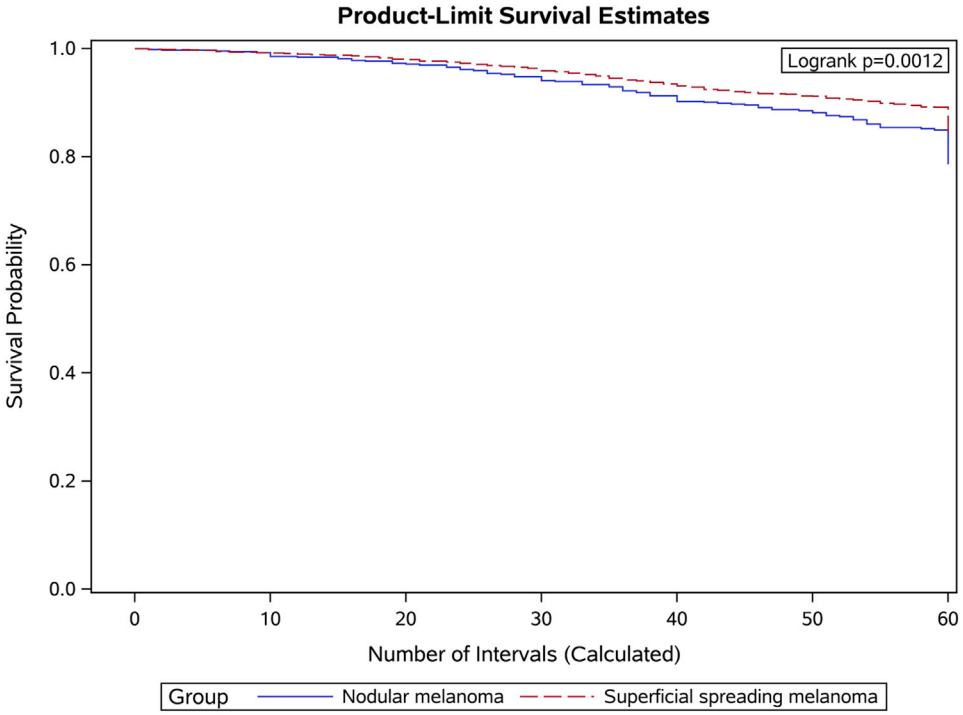

Fig 2. Five-year survival difference in nodular versus superficial spreading melanoma after excluding patients with nodal or distant metastases at diagnosis in T2aN0M0, AJCC 6 data set.

greater than the number of patients with fatal T4 melanomas because most melanoma patients present with early-stage disease.[20-24] The nodular subtype has been identified as an independent predictor of poor survival in thin melanomas.[25,26] Our findings support this phenomenon, and

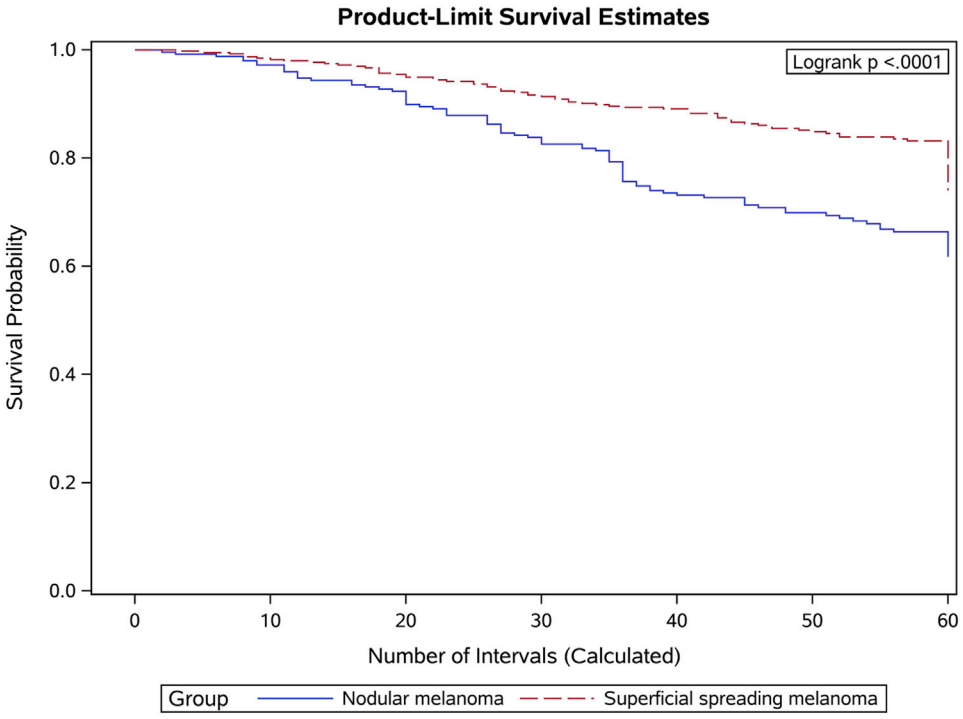

Fig 3. Five-year survival difference in nodular versus superficial spreading melanoma after excluding patients with nodal or distant metastases at diagnosis in T2bN0M0, AJCC 6 data set.

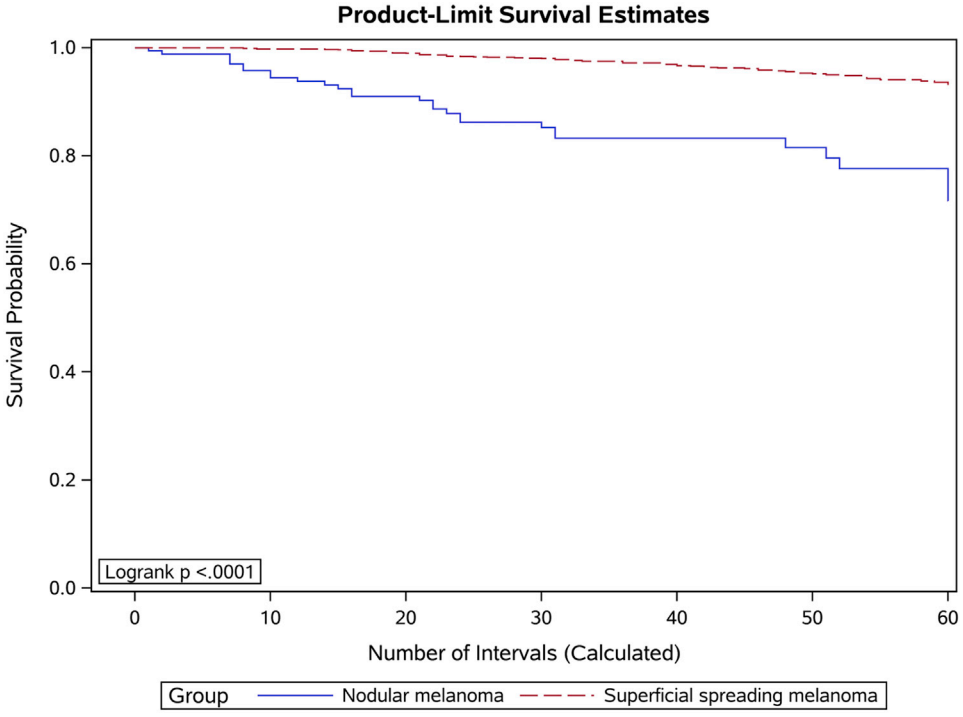

Fig 4. Five-year survival difference in nodular versus superficial spreading melanoma after excluding patients with nodal or distant metastases at diagnosis in T1bN0M0, AJCC 7 data set.

difference in survival remained significant after removing nodal and distant metastases at time of diagnosis, indicative of a worse outcome in NM. The nodular subtype also appears to be associated with a greater risk of recurrence. In a review of patients who underwent SLNB between 1996 and 2015, Faut

et al[27] identified in univariate analysis that nodular subtype was significant for recurrence with a *P* value less than .0001. The authors also found in multivariate analysis that the nodular subtype was associated with recurrence (*P* = .0196), even in node-negative patients.

Although controversies exist in the use of SLNB and its significance in melanoma,[28] it remains the most important staging tool in patients with primary cutaneous melanoma. SLNB is the most sensitive and specific staging test for the identification of micrometastatic melanoma in regional lymph nodes.[29,30] Currently, SLNB should be considered in patients with melanoma greater than 1 mm but is not recommended for patients with melanoma in situ or T1a melanoma.[31,32] SLNB should be discussed in tumors that are between 0.8 mm and 1.0 mm or any tumor between 0.1 mm and 1.0 mm that is ulcerated. SLNB should generally not be considered in tumors less than 0.8 mm unless ulceration or other adverse features are present.[33] These guidelines are based on a B-level strength of evidence, including data from the AJCC Melanoma Staging Database indicating that SLN metastases are infrequent (<5%) in melanomas less than 0.8 mm in thickness but occur in approximately 5% to 12% of patients with primary melanomas from 0.8 to 1.0 mm in thickness.[34] These data do not stratify rates of survival according to histologic subtype, yet the nodular subtype has been found to be an independent factor that correlates with positive SLNB.[35,36]

Given the decreased 5-year survival in the patients we analyzed with thin NM, it would be prudent to record this feature as recommended by various guidelines.[32,33,37,38] Reporting histologic subtype is recommended but not mandatory, as guidelines cite that the prognostic value of subtype has not been established. However, this work and others showed otherwise, particularly in the nodular subtype. Although studies have found that there is poor concordance among dermatopathologists even in the classification of melanoma, efforts should be made to include histologic subtype in reporting, particularly in the era of molecular genetics.[39-44]

The treatment algorithm for melanoma is dictated by AJCC staging at diagnosis. However, it has become increasingly clear that the inherent biologic and histologic characteristics of tumors play an important role in cancer prognosis. In solid tumors, such as lung and breast cancer, the impact of histologic subtype has been found to dictate clinical decision making and correlate with genetic aberrations that may be susceptible to targeted regimens.[45,46] In SSM and NM, molecular studies have found differences in expression between these 2 subtypes. Jaeger et al[47] identified 67 genes differentially expressed in SSM and NM. Increased expression of genes involved in tissue invasion, proliferation, and adhesion were more often found in nodular melanomas.[47] Further research into the inherent biological differences between these two subtypes could assist in the development of novel approaches to therapy.

It is important to acknowledge the inherent limitations of current prognostic factors for melanoma, including SLNB. Molecular testing of the primary tumor may refine prognosis beyond the current factors. One method of evaluating primary tumors is via gene expression profiling (GEP). Data are accumulating that GEP may supplant the routine use of SLNB in the future.[48,49] In the latest version of the National Comprehensive Cancer Network guidelines for melanoma,[50] there is acknowledgment of the potential value of GEP to differentiate between low versus high risk of metastasis. However, the guidelines state that the currently available prognostic molecular techniques should not replace SLNB and that the use of GEP according to specific melanoma stage requires further prospective study in large data sets.

CONCLUSIONS AND RELEVANCE

Five-year survival is worse in NM than in SSM, especially in T1 and T2 melanomas. Consideration should be given to incorporate these factors into the AJCC staging system, particularly so that patients diagnosed with thin NM can be more accurately staged. Additionally, patients with thin NMs may warrant more intense surveillance with clinical examination, imaging, and possibly adjuvant therapy. Research into the genomic differences in NM should also be sought to develop specific treatment regimens and improve survival. We believe the power in this analysis is that the nodular subtype was shown to have a statistically significant independent effect on overall survival across 2 independent data sets over a 10-year period.

Conflicts of interest

None disclosed.

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