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ORIGINAL ARTICLE – MELANOMA

Practice Patterns and Prognostic Value of Sentinel Lymph Node Biopsy for Thick Melanoma: A National Cancer Database Study

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ABSTRACT

Background. Sentinel lymph node biopsy (SLNB) has been somewhat controversial for patients with a diagnosis of thick (> 4 mm) melanoma. This study aimed to characterize the national practice pattern in performing SLNB for this patient population and to determine the predictors and prognostic value of nodal positivity using population-level data.

Methods. Patients with a diagnosis of clinically node-negative, thick melanoma (2010–2015) were identified using the National Cancer Database. Factors associated with performing regional nodal evaluation were characterized. Predictors of nodal positivity were determined using multivariable logistic regression. Overall survival (OS) was estimated using standard statistical methods.

Results. Of 9847 study patients, 7513 (76.3%) underwent SLNB. The patients who underwent nodal evaluation were younger (median age, 66 vs 81 years; $P < 0.001$), less likely to have comorbid conditions (19.6% vs 26.0%; $P < 0.001$), more often privately insured (40.4% vs 16.4%; $P < 0.001$), and more frequently treated at an academic center (49.5% vs 43.9%; $P < 0.001$). Among those who underwent nodal evaluation, 25.5% had metastatic nodes. Multivariable regression identified age, Charlson-Deyo score, primary location, ulceration, mitoses, vertical growth phase, and lymphovascular invasion as independent predictors of nodal positivity, but with only moderate predictive accuracy (optimism-adjusted area under the curve, 0.684). Furthermore, compared with node negativity, node positivity was significantly associated with decreased OS (hazard ratio, 2.05; $P < 0.001$).

Conclusion. Although nodal status provides important prognostic information, at a national level, nearly one fourth of patients with clinically node-negative, thick melanoma do not undergo SLNB. Appropriate pathologic staging would allow these high-risk patients to be candidates for effective adjuvant therapy.

In 2018, the United States had more than 90,000 cases of newly diagnosed cutaneous melanoma and more than 13,000 deaths from the disease.[1] Survival outcomes for clinically localized melanoma are highly dependent on primary tumor Breslow thickness, among other prognostic factors. Patients with a diagnosis of thin melanoma (≤ 1 mm) experience 10-year melanoma-specific survival (MSS) rates exceeding 90%, whereas those with a diagnosis of thick melanoma (> 4 mm) have a 10-year MSS of only 50%.[2]

For patients with no clinically evident lymph node (LN) metastases, sentinel lymph node biopsy (SLNB) is a sensitive method for evaluating the regional nodal basin. The Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) compared SLNB with nodal observation among patients with melanomas more than 1.20 mm in Breslow thickness.[3] In a subgroup analysis, the trial did not identify a survival advantage of biopsy-based management for patients with melanoma more than 3.50 mm in thickness (SLN positivity vs observation with nodal recurrence:

Yun Song and Feredun S. Azari have contributed equally to the completion of this study.

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10-year MSS, hazard ratio [HR], 0.92; $P = 0.78$).[3] In contrast, for patients with melanomas 1.20 to 3.50 mm thick, earlier detection and treatment of regional LN metastasis was associated with improved 10-year MSS, even by latent subgroup analysis (HR, 0.68; $P = 0.05$).[3] These results formed the basis of the American Society of Clinical Oncology and Society of Surgical Oncology guidelines for performing SLNB, which recommend the performance of SLNB for patients with intermediate-thickness melanoma, but only consideration of SLNB for those with thick melanoma.[4]

Because the risk of hematogenous metastasis is substantial for patients with thick melanoma, the role of regional nodal staging has been called into question.[5] However, although studies have not shown an association between nodal evaluation and survival in this high-risk population, MSLT-1 and retrospective studies have demonstrated that SLNB nonetheless provides important prognostic information even for patients with thick melanoma. Compared with SLN-negative patients, those with nodal micrometastases experience a significant decrease in disease-free survival,[6–11] MSS,[3,6,7,11] and overall survival (OS).[7,8,10,12]

Most retrospective studies to date have been single-institutional series with several hundred patients. The current study aimed to further define the value of nodal evaluation in a nationally representative, large contemporary cohort of nearly 10,000 patients with a diagnosis of clinically node-negative, thick melanoma. Using the National Cancer Database (NCDB), we sought to characterize the current national practice patterns in regional nodal evaluation, identify clinicopathologic predictors of SLN positivity, and determine the prognostic value of SLN status with respect to OS in this patient population.

METHODS

Data Source and Patient Selection

Study patients were identified from the cutaneous melanoma participant use file of the NCDB. As a collaborative effort between the American Cancer Society and the American College of Surgeons' Commission on Cancer, the NCDB includes de-identified data from more than 1500 Commission on Cancer-accredited facilities and encompasses more than 70% of new cancer diagnoses in the United States.[13] All data are compliant with the Health Insurance Portability and Accountability Act. Due to the retrospective nature of the study and inability to identify individual patients or facilities, institutional review board approval was not required.

Patients 18 years of age or older who underwent wide excision of melanoma more than 4 mm in Breslow thickness were identified (Fig. S1). The diagnosis years were limited to 2010 through 2015 for consistency in the reporting of pathologic variables according to the American Joint Committee on Cancer, 7th edition.[2] Only patients who had no clinically evident nodal or distant metastases were included in the study. Additionally, patients were excluded if it was unknown whether regional nodal evaluation was performed, palliative resection was performed, or inconsistent data coding was present (e.g., coded as pathologic N0 but ≥ 1 metastatic LN listed). For patients who underwent SLNB and had vital status and follow-up data available, OS was estimated.

Variables

The primary variables analyzed were performance of SLNB and SLN status. The NCDB identifies only the performance of regional LN surgery and does not categorize LNs removed during SLNB separately from those resected during completion lymphadenectomy. However, it was assumed that more than 18 years after the introduction of SLNB by Morton et al.,[14] patients with clinically node-negative melanoma would not be offered elective lymphadenectomy up front, but would rather undergo SLNB for pathologic nodal staging. Therefore, these clinically node-negative study patients were categorized as having undergone SLNB if one or more LNs were resected, regardless of the total LNs ultimately removed in combination with subsequent completion lymphadenectomy. Patients who underwent SLNB were defined as SLN-negative if they had no metastatic nodes and SLN-positive if one or more metastatic LNs were identified.

Among the patients who underwent SLNB, the secondary outcome evaluated was OS, defined as the interval (in months) between diagnosis and death. Patients alive at the last follow-up visit were censored. Additional variables considered in analyses were patient demographics (age [< 50, 50–59, 60–69, 70–79, ≥ 80 years], sex, race [white, other], ethnicity [Hispanic, non-Hispanic], Charlson-Deyo Comorbidity Index, insurance status [private, Medicare/medicaid, self-pay], residence [metropolitan, urban, or rural county], income quartile), hospital characteristics (type [academic, other], region [Northeast, South, Midwest, West]), and primary tumor characteristics (location [head/neck, trunk, extremity, overlapping/not specified], Breslow thickness, ulceration, mitoses [≥ 1 or < 1 per mm^2], regression, vertical growth phase, lymphovascular invasion [LVI]). In multivariable analyses of factors associated with OS, receipt of radiation and systemic therapies (immunotherapy and chemotherapy) also were considered. Novel immune checkpoint inhibitors could not be distinguished from traditional immunotherapies, such as interferon, in the NCDB.

Statistical Analysis

Descriptive statistics are presented as frequencies for categorical variables and as medians with interquartile ranges (IQRs) for continuous variables. Statistical analyses were performed using Pearson's Chi square and Wilcoxon rank-sum tests, respectively.

To determine factors associated SLN positivity, uni- and multivariable logistic regressions were performed. A backward elimination approach was used to develop the final multivariable model. All patient and tumor characteristics were entered into the initial model, and nonsignificant variables ($P > 0.05$) were sequentially removed to arrive at the final model.

Model performance was assessed using the receiver operating characteristic (ROC) and area under the curve (AUC). Internal validation of the model was performed using bootstrapping with 500 resamples. Risk groups for SLN positivity (low: $< 5\%$; medium: 5–20%; high: $\geq 20\%$) were derived using the multivariable model. Overall survival was estimated using the Kaplan–Meier method, and comparisons were made using the log-rank test.

Factors associated with OS were determined using Cox proportional hazards analyses. The multivariable Cox regression analysis included variables that either were associated with OS or differed between the SLN-positive and SLN-negative patients by univariable analyses with a P value less than 0.10. All tests were two-sided, and P values less than 0.05 were considered statistically significant. Statistical analyses were performed using R version 3.5.3.[15]

RESULTS

Patient Characteristics

Of 9847 study patients, 7513 (76.3%) underwent SLNB. As shown in Table 1, the patients who underwent SLNB were significantly younger (median, 66 years; IQR, 56–76 years vs 81 years; IQR, 71–87 years; $P < 0.001$), less likely to have comorbid conditions (19.6% vs 26%; $P < 0.001$), more often privately insured (40.4% vs 16.4%; $P < 0.001$), and more frequently treated at an academic center (49.5% vs 43.9%; $P < 0.001$). Additionally, patients who had melanoma of the head/neck were less likely to undergo SLNB (67%) than those with a truncal (82.5%) or extremity (79.4%) primary tumor ($P < 0.001$).

Predictors of Lymph Node Positivity

The patients who underwent nodal evaluation had a median of 3 (IQR, 2–6) LNs resected. Of the 7513 SLNB patients, 5598 (74.5%) had no metastatic LNs (SLN-negative patients) and 1915 (25.5%) had one or more metastatic LNs (SLN-positive patients). Among the patients who had no metastatic nodes, the median number of LNs examined was 2 (IQR, 1–4) compared with 12 (IQR, 3–23) among those who were node-positive ($P < 0.001$), which included LNs that may have been resected during subsequent completion lymphadenectomy. The SLN-positive patients had a median of one (IQR, 1–2) metastatic LN.

In the univariable analyses, the demographic and tumor factors associated with SLN positivity were age and primary tumor characteristics such as location, ulceration, mitoses, vertical growth phase, and LVI (Table 2). A multivariable logistic regression model was developed, which identified the following factors as independent predictors of SLN positivity: younger age (every decade after 50 years: odds ratio [OR], 0.81; 95% confidence interval [CI], 0.77–0.84; $P < 0.001$), increased comorbidities (OR, 1.16; 95% CI, 1.01–1.33; $P = 0.037$), head/neck location versus truncal (OR, 1.88; 95% CI, 1.61–2.19; $P < 0.001$) or extremity (OR, 1.74; 95% CI, 1.50–2.01; $P < 0.001$) location, presence of ulceration (OR, 1.63; 95% CI, 1.45–1.83; $P < 0.001$), mitoses (OR, 1.72; 95% CI, 1.30–2.32; $P < 0.001$), vertical growth phase (OR, 1.27; 95% CI, 1.11–1.45; $P < 0.001$), and LVI (OR, 3.17; 95% CI, 2.75–3.67; $P < 0.001$). The AUC of the model's ROC curve was 0.687 (optimism-adjusted AUC, 0.684) (Fig. S2).

Using the multivariable model, patients were stratified by low ($< 5\%$), medium (5–20%), and high ($\geq 20\%$) predicted risk of SLN positivity (Table 3). Only 18 (0.2%) of the 9847 study patients had a low predicted risk. All 18 patients were 80 years of age or older with no high-risk tumor features (e.g., ulceration, mitoses, vertical growth phase, LVI).

Treatments by Sentinel Lymph Node Status

Adjuvant radiation therapy was used for 457 patients (6.1%) who underwent nodal surgery. The rate of radiation therapy was somewhat higher in the SLN-positive patients than in the SLN-negative patients (7.2% vs 5.7%; $P = 0.058$), but this difference was not statistically

TABLE 1 Demographic and clinicopathologic characteristics of 9847 patients with newly diagnosed clinically node-negative, thick melanoma (> 4 mm), stratified by receipt of sentinel lymph node biopsy (SLNB)

Variable	No SLNB (n = 2334, 23.7%) n (%)	SLNB (n = 7513, 76.3%) n (%)	P value
Median year of diagnosis (IQR)	2013 (2011–2014)	2013 (2011–2014)	0.82
Demographics			
Median age: years (IQR)	81 (71–87)	66 (56–76)	< 0.001
Sex			0.023
Male	1502 (64.4)	5029 (66.9)	
Female	832 (35.6)	2484 (33.1)	
Race			0.56
White	2280 (97.7)	7321 (97.4)	
Non-white	54 (2.3)	192 (2.6)	
Ethnicity			0.11
Non-Hispanic	2249 (96.4)	7228 (96.2)	
Hispanic	31 (1.3)	141 (1.9)	
Not reported	54 (2.3)	144 (1.9)	
Charlson-Deyo Comorbidity Index			< 0.001
0	1726 (74.0)	6037 (80.4)	
≥ 1	608 (26.0)	1476 (19.6)	
Insurance status			< 0.001
Private	383 (16.4)	3034 (40.4)	
Medicare/medicaid	1895 (81.2)	4106 (54.7)	
Self-pay	26 (1.1)	288 (3.8)	
Not reported	30 (1.3)	85 (1.1)	
Patient residence			0.36
Metropolitan	1869 (80.1)	6019 (80.1)	
Urban (≥ 2500 population)	349 (15.0)	1157 (15.4)	
Rural (< 2500 population)	44 (1.9)	153 (2.0)	
Not reported	72 (3.1)	184 (2.5)	
Income quartile			0.004
0–25th	304 (13.0)	1033 (13.7)	
26–50th	540 (23.1)	1710 (22.8)	
51–75th	595 (25.5)	2145 (28.6)	
76–100th	884 (37.9)	2608 (34.7)	
Not reported	11 (0.5)	17 (0.2)	
Hospital type			< 0.001
Academic	1025 (43.9)	3721 (49.5)	
Non-academic	1309 (56.1)	3792 (50.5)	
Hospital region			< 0.001
Northeast	666 (28.5)	1642 (21.9)	
South	634 (27.2)	1980 (26.4)	
Midwest	649 (27.8)	2198 (29.3)	
West	356 (15.3)	1258 (16.7)	
Not reported	29 (1.2)	435 (5.8)	
Primary tumor characteristics			
Location			< 0.001
Head/neck	1013 (43.4)	2053 (27.3)	
Trunk	495 (21.2)	2334 (31.1)	

TABLE 1 continued

Variable	No SLNB (n = 2334, 23.7%) n (%)	SLNB (n = 7513, 76.3%) n (%)	P value
Extremity	801 (34.3)	3093 (41.2)	
Overlapping/not specified	25 (1.1)	33 (0.4)	
Median Breslow thickness: mm (IQR)	6.00 (5.00–8.50)	5.80 (4.75–8.00)	< 0.001
Ulceration			0.31
Absent	960 (41.1)	3217 (42.8)	
Present	1335 (57.2)	4185 (55.7)	
Not reported	39 (1.7)	111 (1.5)	
Mitoses			< 0.001
Absent (< 1per mm^2)	165 (7.1)	433 (5.8)	
Present (≥ 1 per mm^2)	1885 (80.8)	6418 (85.4)	
Not reported	284 (12.2)	662 (8.8)	
Regression			0.002
Absent	1587 (68.0)	5369 (71.5)	
Present	174 (7.5)	550 (7.3)	
Not reported	573 (24.6)	1594 (21.2)	
Vertical growth phase			0.011
Absent	689 (29.5)	2079 (27.7)	
Present	873 (37.4)	3071 (40.9)	
Not reported	772 (33.1)	2363 (31.5)	
Lymphovascular invasion			0.17
Absent	1634 (70.0)	5371 (71.5)	
Present	306 (13.1)	995 (13.2)	
Not reported	394 (16.9)	1147 (15.3)	

IQR interquartile range

significant. The patients with node-positive melanoma were more likely to receive adjuvant systemic therapies. Immunotherapy, including immune checkpoint inhibitors or interferon, was used for 22.2% of the SLN-positive patients compared with 8.2% of the SLN-negative patients ($P < 0.001$), and chemotherapy was administered to 4% of the SLN-positive patients compared with only 1.7% of those without metastatic nodes ($P < 0.001$).

Survival by SLN Status

Overall survival was estimated for 6056 patients who underwent SLNB and had known survival outcomes. The median follow-up time for this cohort was 31.6 months (IQR, 20.4–47.4 months). The Kaplan–Meier OS curves differed significantly by SLN status ($P < 0.001$, log-rank; Fig. 1a). The SLN-negative patients had a longer median OS time (median, 80.7 months; 95% CI, 80.7–not determined, months) than the SLN-positive patients (median, 49.0 months; 95% CI, 43.6–57.1 months). The 5-year OS rates were 62.5% (95% CI, 60.5–64.6%) and 44.7% (95% CI, 41.4–48.3%), respectively.

After adjustment for patient, tumor, and treatment factors, SLN status remained significantly associated with OS (HR, 2.05; 95% CI, 1.85–2.27; $P < 0.001$; Fig. 1b; Table 4). Furthermore, SLN positivity was associated with decreased OS for all levels of Breslow thickness greater than 4 mm (Fig. 1b). Other factors associated with OS in the patients who underwent nodal evaluation were age (every decade: HR, 1.39; 95% CI, 1.32–1.46; $P < 0.001$), sex (female vs male: HR, 0.87; 95% CI, 0.78–0.96; $P = 0.007$), Charlson-Deyo Comorbidity Index (≥ 1 vs 0: HR, 1.31; 95% CI, 1.18–1.46; $P < 0.001$), hospital type (nonacademic vs academic: HR, 1.15; 95% CI, 1.05–1.28; $P = 0.005$), primary tumor location (extremity vs head/-neck: HR, 0.78; 95% CI, 0.69–0.88; $P < 0.001$), Breslow thickness (per 1 mm: HR, 1.09; 95% CI, 1.06–1.12; $P < 0.001$), LVI (HR, 1.37; 95% CI, 1.20–1.55; $P < 0.001$), and receipt of immunotherapy (HR, 0.76; 95% CI, 0.64–0.89; $P < 0.001$; Table 4).

TABLE 2 Predictors of sentinel lymph node (SLN) positivity by univariable and reduced multivariable logistic regression models for 7513 patients with clinically node-negative, thick melanoma (> 4 mm) who underwent SLN biopsy

Variable	Univariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Age, every 10 years	0.81 (0.78–0.84)	< 0.001	0.81 (0.77–0.84)	< 0.001
Sex				
Male	Reference			
Female	1.11 (0.99–1.24)	0.065		
Race				
White	Reference			
Non-white	1.12 (0.80–1.53)	0.50		
Ethnicity				
Non-Hispanic	Reference			
Hispanic	1.16 (0.79–1.66)	0.44		
Not reported	0.77 (0.50–1.14)	0.20		
Charlson-Deyo Comorbidity Index				
0	Reference		Reference	
≥ 1	1.04 (0.92–1.19)	0.52	1.16 (1.01–1.33)	0.037
Location				
Head/neck	Reference		Reference	
Trunk	2.21 (1.91–2.56)	< 0.001	1.88 (1.61–2.19)	< 0.001
Extremity	1.93 (1.68–2.22)	< 0.001	1.74 (1.50–2.01)	< 0.001
Overlapping/not specified	1.61 (0.68–3.45)	0.25	1.63 (0.66–3.61)	0.25
Breslow thickness, per mm	1.02 (0.98–1.05)	0.31		
Ulceration				
Absent	Reference		Reference	
Present	1.93 (1.73–2.16)	< 0.001	1.63 (1.45–1.83)	< 0.001
Not reported	0.62 (0.34–1.06)	0.10	0.78 (0.42–1.36)	0.41
Mitoses				
Absent (< 1 per mm^2)	Reference		Reference	
Present (≥ 1 per mm^2)	2.41 (1.83–3.23)	< 0.001	1.72 (1.30–2.32)	< 0.001
Not reported	1.35 (0.96–1.90)	0.090	1.15 (0.80–1.65)	0.45
Regression				
Absent	Reference			
Present	1.18 (0.97–1.44)	0.087		
Not reported	0.89 (0.78–1.01)	0.068		
Vertical growth phase				
Absent	Reference		Reference	
Present	1.29 (1.14–1.48)	< 0.001	1.27 (1.11–1.45)	< 0.001
Not reported	0.94 (0.82–1.08)	0.40	0.95 (0.82–1.10)	0.51
Lymphovascular invasion				
Absent	Reference		Reference	
Present	3.51 (3.05–4.04)	< 0.001	3.17 (2.75–3.67)	< 0.001
Not reported	1.13 (0.97–1.32)	0.10	1.23 (1.05–1.45)	0.011

OR odds ratio, *CI* confidence interval

DISCUSSION

Melanoma is an aggressive cutaneous malignancy that despite accounting for only 1% of all skin cancers diagnosed in the United States, results in the most skin cancer-related deaths.[16] Primary tumor Breslow thickness, ulceration status, and the presence of LN, intralymphatic, or distant metastases are strongly associated with survival outcomes.[2,17] Therefore, proper staging is paramount for prognostication and for ensuring appropriate treatment. To

TABLE 3 Observed and predicted rates of sentinel lymph node (SLN) positivity for patients with clinically node-negative, thick melanoma (> 4 mm) who underwent sentinel lymph node biopsy, stratified by patient age

Age (years)	Predicted risk category[a,b]	Patients n (%)	Rate of SLN positivity (%)	
			Actual	Predicted
All patients	Low	18 (0.2)	5.6	4.6
	Medium	2911 (38.6)	13.9	14.1
	High	4584 (60.8)	32.9	32.8
18–49	Low	0 (0)	N/A	N/A
	Medium	162 (2.2)	19.8	16.7
	High	951 (12.6)	38.0	37.0
50–59	Low	0 (0)	N/A	N/A
	Medium	285 (3.8)	13.7	15.1
	High	1138 (15.1)	33.7	33.9
60–69	Low	0 (0)	N/A	N/A
	Medium	645 (8.6)	14.4	14.5
	High	1219 (16.2)	31.7	31.6
70–79	Low	0 (0)	N/A	N/A
	Medium	949 (12.6)	12.1	13.9
	High	834 (11.1)	28.2	30.3
≥ 80	Low	18 (0.2)	5.6	4.6
	Medium	870 (11.5)	14.6	13.0
	High	442 (5.9)	32.4	29.2

SLN sentinel lymph node, *N/A* not applicable

[a]Low: < 5%; medium: 5–20%; high: ≥ 20%

[b]Low-risk patient characteristics: median age, 84 years (interquartile range [IQR], 81–88) years; 89% with no comorbidities, head/neck primary with no ulceration, mitoses, vertical growth phase, or lymphovascular invasion

our best knowledge, the current study, which included nearly 10,000 patients, is the largest retrospective study to evaluate the national practice patterns and value of SLNB for patients with thick melanoma.

The study identified an appreciable rate of nodal positivity in this patient population (25.5%), with less than 1% of the patients having a low risk (< 5%) of nodal metastasis, suggesting that routine recommendation of SLNB for this patient population may be warranted. Furthermore, SLN status was an independent predictor of OS, further highlighting the importance of accurate pathologic staging for thick melanoma.

The rate of nodal positivity among the study patients who underwent SLNB was 25.5%, slightly lower than the previously reported rate of 30% to 50% for thick melanoma.[7,9,12,18–22] Unlike the current study, many of these cited studies included very few or no head/neck lesions,[8,9,12] for which SLNB has been associated with a higher false-negative rate.[23] Similar to our findings, other studies have found lower rates of nodal positivity among patients with head/neck melanoma.[7,19] Unfortunately, the NCDB does not provide data on recurrence patterns, and thus does not allow formal assessment of the false-negative rate.

Identifying draining basins using conventional planar lymphoscintigraphy can be challenging in head/neck lesions, for which the anatomy of LN drainage is complex and radiotracer injection sites lie in close proximity.[24,25] Use of single-photon emission computed tomography (SPECT) with integrated computed tomography (CT) may improve SLN identification for patients with head/neck melanomas.[26]

The rate of nodal positivity for patients with thick melanoma was significantly higher than for thin and intermediate-thickness melanomas. Using the NCDB, Sinnamon et al.[27] found that only 3.8% of patients with thin melanoma had positive SLNs. In MSLT-1, the rate of SLN positivity in patients with melanoma with a thickness of 1.2 to 3.5 mm was 16%.[3]

Similar to the literature, the current study found ulceration[8] and LVI[20] to be associated with SLN positivity. Yamamoto et al.[7] further identified desmoplastic histology and absence of microsatellites to be associated with a lower rate of nodal involvement in this patient population. Unlike studies of thin and intermediate-thickness melanoma, in which sizeable subgroups of patients at low risk (< 5%) of SLN positivity were identifiable,[27,28] virtually no patients with thick melanoma in the current study had a risk of

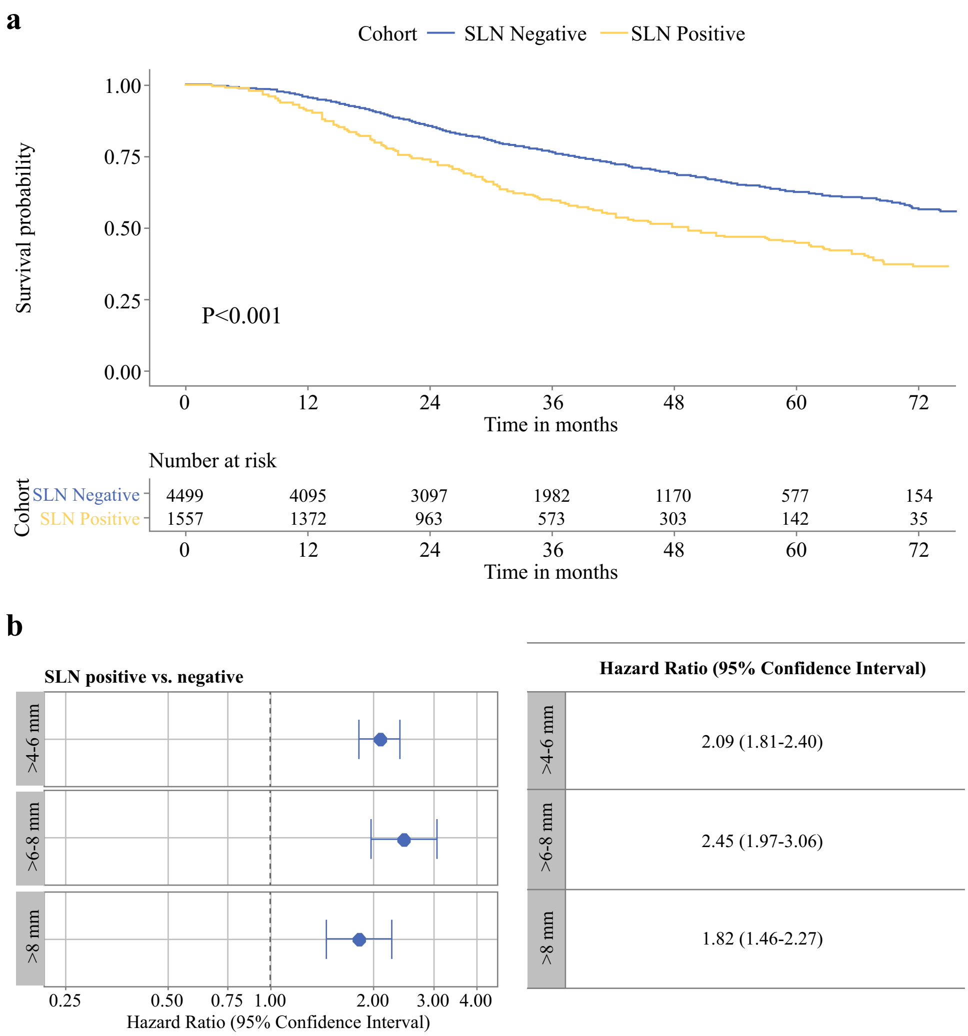

FIG. 1 Overall survival (OS) of patients with newly diagnosed clinically node-negative, thick melanoma (> 4 mm) who underwent nodal evaluation, stratified by sentinel lymph node (SLN) status (6056 patients with survival outcomes). **a** Kaplan–Meier estimates of OS curves. **b** Adjusted hazard ratios comparing OS in SLN-positive versus SLN-negative patients, stratified by Breslow thickness. Hazard ratios < 1 are favorable, and those > 1 are unfavorable. Error bars indicate 95% confidence intervals

nodal involvement < 5%. Moreover, despite use of data from more than 7500 patients, the AUC of the prediction model was moderate at best, making it difficult to predict SLN status accurately based on commonly available clinicopathologic factors. Inclusion of additional tumor characteristics such as histology and satellitosis, which were not available in the NCDB, could potentially improve model performance.

In addition to a high risk of node positivity in this patient population, our study determined that SLN status was an independent predictor of OS irrespective of tumor thickness beyond 4 mm. The available data for 5-year OS rates in the literature for thick melanoma are 32% to 49% for SLN-positive patients and 44% to 68% for SLN-negative patients, comparable with the findings in the current study.[7,12,18,19,22,29] In MSLT-1 and other retrospective studies, SLN positivity has been consistently associated with decreased disease-free survival,[6–11] MSS,[3,6,7,11] and OS.[7,8,10,12,18,19,22]

Approximately 23.7% of the patients in the current study did not undergo SLNB. The patients who did not undergo nodal evaluation were significantly older, with a median age of 81 versus 66 years, and more likely to have comorbidities. They possibly were high-risk surgical candidates, and a rational decision was made to forego nodal surgery. Nonetheless, because of the association between SLN positivity and decreased OS in patients with thick melanoma, SLNB should be strongly considered for patients who are appropriate surgical candidates.

Microscopic nodal involvement is integral to accurate pathologic staging and guides adjuvant therapy. In both the current and other retrospective studies,[7] findings have shown that patients with thick melanoma and positive

TABLE 4 Uni- and multivariable Cox regression analyses of overall survival for patients with newly diagnosed clinically node-negative, thick melanoma (> 4 mm) (6056 patients with survival outcomes)

Variable	Univariable HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
SLN status				
Negative	Reference			
Positive	1.88 (1.71–2.07)	< 0.001	2.05 (1.85–2.27)	< 0.001
Age, every 10 years	1.40 (1.35–1.45)	< 0.001	1.39 (1.32–1.46)	< 0.001
Sex				
Male	Reference		Reference	
Female	0.81 (0.73–0.90)	< 0.001	0.87 (0.78–0.96)	0.007
Race				
White	Reference			
Non-white	0.96 (0.72–1.30)	0.81		
Ethnicity				
Non-Hispanic	Reference			
Hispanic	0.74 (0.51–1.09)	0.13		
Not reported	0.93 (0.67–1.30)	0.69		
Charlson-Deyo Comorbidity Index				
0	Reference		Reference	
≥ 1	1.57 (1.41–1.75)	< 0.001	1.31 (1.18–1.46)	< 0.001
Insurance status				
Private	Reference		Reference	
Non-private/self-pay	1.86 (1.68–2.06)	< 0.001	1.15 (1.02–1.30)	0.023
Patient residence				
Metropolitan/urban	Reference			
Rural	1.07 (0.85–1.34)	0.57		
Income quartile				
0–25th	Reference		Reference	
25–50th	0.88 (0.76–1.02)	0.093	0.88 (0.75–1.02)	0.098
50–75th	0.89 (0.77–1.03)	0.11	0.91 (0.78–1.05)	0.20
75–100th	0.72 (0.62–0.83)	< 0.001	0.76 (0.65–0.88)	< 0.001
Not reported	1.17 (0.43–3.13)	0.76	0.93 (0.34–2.52)	0.89
Hospital type				
Academic	Reference		Reference	
Non-academic	1.08 (0.99–1.19)	0.088	1.15 (1.05–1.28)	0.005
Hospital region				
Northeast	Reference		Reference	
South	1.11 (0.98–1.26)	0.11	1.09 (0.95–1.25)	0.22
Midwest	1.10 (0.97–1.25)	0.15	1.12 (0.98–1.28)	0.098
West	0.84 (0.72–0.98)	0.027	0.91 (0.77–1.07)	0.24
Not reported	0.50 (0.38–0.66)	< 0.001	1.08 (0.79–1.47)	0.63
Primary location				
Head/neck	Reference		Reference	
Trunk	0.96 (0.85–1.08)	0.47	0.94 (0.83–1.07)	0.37
Extremity	0.89 (0.79–0.99)	0.040	0.78 (0.69–0.88)	< 0.001
Overlapping/not specified	1.50 (0.83–2.73)	0.18	1.72 (0.94–3.13)	0.079
Breslow thickness, per mm	1.09 (1.06–1.12)	< 0.001	1.09 (1.06–1.12)	< 0.001

TABLE 4 continued

Variable	Univariable HR (95% CI)	*P* value	Multivariable HR (95% CI)	*P* value
Ulceration				
Absent	Reference		Reference	
Present	1.81 (1.64–2.00)	< 0.001	1.63 (1.48–1.81)	< 0.001
Not reported	0.90 (0.58–1.41)	0.65	0.89 (0.56–1.41)	0.62
Mitoses				
Absent (< 1 per mm^2)	Reference		Reference	
Present (≥ 1 per mm^2)	1.46 (1.17–1.82)	< 0.001	1.14 (0.91–1.43)	0.24
Not reported	1.18 (0.91–1.53)	0.22	1.02 (0.78–1.34)	0.86
Regression				
Absent	Reference		Reference	
Present	1.23 (1.04–1.45)	0.014	1.05 (0.89–1.24)	0.58
Not reported	1.11 (0.99–1.25)	0.068	1.16 (0.99–1.36)	0.062
Vertical growth phase				
Absent	Reference		Reference	
Present	1.18 (1.05–1.32)	0.005	1.09 (0.97–1.23)	0.14
Not reported	1.10 (0.97–1.24)	0.14	1.05 (0.90–1.23)	0.51
Lymphovascular invasion				
Absent	Reference		Reference	
Present	1.69 (1.50–1.91)	< 0.001	1.37 (1.20–1.55)	< 0.001
Not reported	0.98 (0.86–1.12)	0.77	1.04 (0.90–1.19)	0.60
Radiation				
No	Reference		Reference	
Yes	1.08 (0.90–1.30)	0.40	1.03 (0.85–1.25)	0.77
Not reported	0.95 (0.43–2.12)	0.90	0.80 (0.35–1.82)	0.59
Immunotherapy				
No	Reference		Reference	
Yes	0.67 (0.57–0.78)	< 0.001	0.76 (0.64–0.89)	< 0.001
Not reported	0.89 (0.61–1.30)	0.54	0.86 (0.58–1.28)	0.46
Chemotherapy				
No	Reference		Reference	
Yes	1.21 (0.93–1.57)	0.16	1.34 (1.03–1.75)	0.031
Not reported	1.08 (0.83–1.41)	0.55	1.18 (0.90–1.55)	0.24

HR hazard ratio, *CI* confidence interval, *SLN* sentinel lymph node

SLNs are more likely to receive adjuvant systemic therapy, which may be even more important in the current era of immune checkpoint and BRAF/MEK inhibitors.[30–33] Currently, these agents are approved in the adjuvant setting for stage 3 disease, but not lower-stage melanoma. Early recognition of nodal disease and commencement of adjuvant therapies instead of waiting for disease progression and recurrence may yield improved outcomes.

Several study limitations should be noted, including potential biases inherent to a retrospective study design. Although the multivariable analyses accounted for many demographic, hospital, clinicopathologic, and treatment factors, unobserved differences between groups likely persisted. As such, only potential associations, and not causal relationships, could be determined. Although LNs resected by SLNB could not be separately identified from LNs removed during completion lymphadenectomy using the NCDB, the definitions of SLNB and SLN status used in this study are likely reliable because it would be highly unusual for patients with a diagnosis of clinically node-negative melanoma in the years 2010–2015 to undergo elective lymphadenectomy.

Additionally, analyses using large databases may be subject to coding misclassification, but the volume of data provided by the databases used in this study was immensely valuable. Several smaller institutional studies of SLNB in thick melanoma have been conducted, but the current study represents, to our knowledge, the largest evaluation of SLNB in this patient population at a national level. Finally, recurrence data and cause of death are not provided in the NCDB, and thus, disease-free and melanoma-specific could not be estimated.

Using a large national database, we demonstrated that patients with clinically node-negative, thick melanoma have an appreciable risk of SLN positivity, which is independently associated with decreased OS. Furthermore, commonly available clinicopathologic factors cannot reliably identify groups with a low risk for nodal metastasis in this population. A significant proportion of patients with thick melanoma (nearly one fourth) do not undergo SLNB, and further study is needed for better delineation of the underlying reasons for this. Nodal staging is an integral component of accurate prognostication for melanoma and facilitates initiation of adjuvant treatment for node-positive patients in a timely manner. Therefore, SLNB should be strongly recommended and offered to patients with clinically node-negative, thick melanoma.

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