Sentinel lymph node biopsy in patients with clinical stage IIB/C cutaneous melanoma: A national cohort study

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Background: Approval of adjuvant anti-programmed cell death protein 1 therapy for pathologic stage IIB/C cutaneous melanoma has led some to question the role of sentinel lymph node (SLN) biopsy in the clinical stage IIB/C disease.

Objective: To determine the prognostic significance of SLN staging on disease-specific survival (DSS) for clinical stage IIB/C primary cutaneous melanoma in the preimmunotherapy era.

Methods: A retrospective cohort study was performed evaluating patients who underwent excision of clinical stage IIB/C cutaneous melanoma using the Surveillance, Epidemiology, and End Results database (2004-2011). Patients who did and did not undergo SLN biopsy were compared using propensity matching, and among those who underwent SLN biopsy, matched patients were further stratified by SLN status (SLN positive [SLN+] or SLN negative [SLN-]).

Results: Of the 8562 patients evaluated, 6021 (70.3%) underwent SLN biopsy. SLN positivity was associated with significantly reduced 5-year DSS among matched patients who underwent SLN biopsy (47.1% SLN+ vs 75.5% SLN-; $P < .001$). Five-year DSS remained significantly different across matched T-stages: T3b (54.2% SLN+ vs 64.8% SLN-; $P = .004$), T4a (55.5% SLN+ vs 71.6% SLN-; $P = .001$), and T4b (38.6% SLN+ vs 60.9% SLN-; $P < .001$).

Limitations: Retrospective study.

Conclusion: For patients with clinical stage IIB/C cutaneous melanoma, SLN status provides essential prognostic information. (J Am Acad Dermatol 2022;87:754-60.)

Key words: adjuvant therapy; immunotherapy; melanoma; prognosis; sentinel node; sentinel lymph node biopsy; survival.

INTRODUCTION

Contemporary effective systemic melanoma therapies, including targeted molecular agents and immune checkpoint inhibitors, have revolutionized the treatment of advanced-stage melanoma, resulting in improved survival for patients diagnosed with stages III and IV.[1-3] Furthermore, based on the results of the recent KEYNOTE-716 study, which demonstrated improved recurrence-free survival for patients with resected and appropriately staged (ie, negative sentinel lymph node [SLN] microstaging) stage IIB/C melanoma, the Food and Drug Administration has granted approval for using pembrolizumab to treat pathologic stage IIB/C melanoma after complete

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resection.[4,5] The results of this study raised the question of whether SLN biopsy is still necessary for the management of all patients presenting with clinical stage IIB/C melanoma who are deemed high-risk for distant metastasis or whether certain patients may be able to forego SLN evaluation to proceed with wide excision of the primary tumor followed by treatment with adjuvant immune checkpoint inhibitors.[6,7] While the importance of SLN staging to provide accurate prognostic information and to guide treatment decisions for patients with ≥T1b melanoma is well studied, the prognostic importance of SLN biopsy for patients specifically with clinical stage IIB/C disease is less well defined.[8,9]

Using data from the Surveillance, Epidemiology, and End Results (SEER) program, the current retrospective observational study sought to determine the prognostic significance of SLN staging on disease-specific survival (DSS) among patients undergoing wide excision for clinical stage IIB/C primary cutaneous melanoma from the preimmune checkpoint therapy era.

CAPSULE SUMMARY

- Adjuvant immune checkpoint blockade therapy improves recurrence-free survival for patients with pathologic stage IIB/C cutaneous melanoma.
- For patients with clinical stage IIB/C cutaneous melanoma, sentinel lymph node status provides essential prognostic information and is an important factor for collective decision-making regarding adjuvant therapy administration based on risk assessment.

MATERIALS AND METHODS

Data source and patient selection

The SEER Research Plus database was used for this study. The SEER program is a clinical database funded by the National Cancer Institute that collects data on cancer incidence, treatment, and survival from population-based cancer registries covering approximately 34.6% of the US population.[10,11] SEER data are deidentified and compliant with the Health Insurance Portability and Accountability Act. Institutional review board approval was obtained for using SEER data (protocol # 53183), but approval was not required for this specific study as no patient, physician, or hospital identifiers were evaluated.

From 2004 to 2011, patients with *American Joint Committee on Cancer* 8th edition[12] clinical stage IIB/C primary cutaneous melanoma (SEER ICD-0-3 histology codes 8720-8723, 8726, 8730, 8740-8746, 8770-8774, 8780; SEER primary site codes C44.0-C44.9) who underwent primary tumor excision were identified. Collaborative stage site-specific factor 3 was used to select patients with clinically negative regional lymph node disease.[13] The study years were chosen to evaluate patients from a preimmunotherapy era to analyze the significance of SLN biopsy status without the results being confounded by immunotherapy treatment for patients with a positive SLN (SLN+) biopsy. Among patients who underwent SLN biopsy, patients with an SLN+ biopsy were compared to those with a negative SLN (SLN-) biopsy to identify factors associated with SLN positivity and evaluate the prognostic significance of SLN status. Additionally, patients who did and did not undergo SLN biopsy were compared to evaluate the prognostic significance of SLN biopsy performance. Patients who did not undergo primary tumor excision had clinical stage III/IV disease at diagnosis or had unknown or inconsistent staging data were excluded. The resulting final cohort consisted of 8562 patients (Supplementary Fig 1, available via Mendeley at https://data.mendeley.com/datasets/5wmd4547sv/1).

Variables and outcomes

The clinical variables evaluated included age, sex, race (White, Black, Asian American/Pacific Islander, or other), and treatment with adjuvant systemic or adjuvant radiation therapy. Tumor variables evaluated included tumor location (head/neck, trunk, extremity, or unknown), histologic subtype (superficial spreading, nodular, acral lentiginous, lentigo maligna, or not otherwise specified), tumor thickness, ulceration status, clinical T-stage, clinical overall stage, the performance of SLN biopsy, and SLN status.[14] Variables with missing data were recorded as unknown. The primary study outcome was 5-year DSS. Secondary study outcomes included the rate of, and annual trends in SLN biopsy performance and the identification of factors associated with SLN positivity among patients undergoing SLN biopsy.

Statistical methods

Univariable analysis was performed using Pearson's χ^2 test for categorical variables and the Wilcoxon rank sum test for continuous variables. Among patients who underwent SLN biopsy, multivariable logistic regression analysis was performed to evaluate factors associated with SLN positivity. Factors with a P value of ≤.10 on univariable analysis were included in this multivariable analysis, and the goodness-of-fit of the model was assessed with the Hosmer-Lemeshow test.[15] Trends in the annual

Abbreviations used:

APC: annual percentage change
DSS: disease-specific survival
IQR: interquartile range
OR: odds ratio
SEER: Surveillance, Epidemiology, and End Results
SLN: sentinel lymph node
SLN+: sentinel lymph node positive
SLN-: sentinel lymph node negative

performance of SLN biopsy were estimated using joinpoint regression analysis (Joinpoint Regression Program, version 4.9.0.0, March 2021; Surveillance Research Program, National Cancer Institute).[16] One-to-one propensity matching using the "nearest neighbor" technique was performed to match patients.[17] Following propensity matching, 5-year DSS was calculated using the Kaplan-Meier method and compared using the log-rank test. The start time for follow-up and survival analyses was the day of diagnosis.[18] All tests were 2 sided. *P* values of <.05 were considered statistically significant. All statistical analyses were performed using Stata version 17.[19]

RESULTS

Patient demographics and rate of SLN biopsy performance

Of the 8562 patients evaluated, 6021 (70.3%; 95% CI, 69.3%-71.3%) underwent SLN biopsy. The median age of the study cohort was 69 years (interquartile range [IQR], 56-80 years), 5621 patients (65.7%) were men, and 8297 patients (96.9%) were White. Baseline descriptive statistics for the study cohort and univariable analysis comparing patients who did and did not undergo SLN biopsy are shown in Table I.

Across the study period, patients with T3b tumors were significantly more likely to undergo SLN biopsy than were patients with T4a or T4b tumors (75.2% T3b vs 68.4% T4a vs 66.2% T4b; $P < .001$). Among the overall cohort, the rate of SLN biopsy performance significantly increased across the study period by an average annual percentage change (APC) of 2.2% ($P = .019$), with an SLN biopsy performance rate of 80.0% (95% CI, 77.0%-82.6%) in the final year of the study. This change was primarily driven by a substantial increase in the rates of SLN biopsy performance for patients with T4a (APC, 3.0%; $P = .011$) and T4b (APC, 2.6%; $P = .010$) tumors across the study period, while the rate of SLN biopsy performance did not significantly increase for patients with T3b tumors (APC, 1.4%; $P = .116$). Compared with T3 patients, T4 patients were significantly older (median age, 70 years for T4 vs 68 years for T3; $P < .001$) and more likely to have head/neck melanomas (29.1% T4 vs 22.9% T3; $P < .001$).

Table I. Patient cohort and univariable analysis comparing patients with clinical stage IIB/C primary cutaneous melanoma who did versus did not undergo SLN biopsy

	SLN biopsy not performed 2541 (29.7%), *N* (%)	SLN biopsy performed 6021 (70.3%), *N* (%)	*P* value
Age, y, median (IQR)	80 (68-86)	65 (53-76)	<.01
Sex			
Male	1621 (63.8)	4000 (66.4)	.02
Female	920 (36.2)	2021 (33.6)	
Race			
White	2458 (96.7)	5839 (97.0)	.03
Black	33 (1.3)	75 (1.3)	
AAPI	24 (0.9)	77 (1.3)	
Other	26 (1.0)	30 (0.5)	
Location			
Head/neck	964 (37.9)	1316 (21.9)	<.01
Trunk	565 (22.2)	1891 (31.4)	
Extremity	1001 (39.4)	2804 (46.6)	
Not reported	11 (0.4)	10 (0.2)	
Histology			
Superficial spreading	286 (11.3)	788 (13.1)	<.01
Nodular	900 (35.4)	2036 (33.8)	
Acral lentiginous	57 (2.2)	215 (3.6)	
Lentigo maligna	66 (2.6)	77 (1.3)	
NOS	1232 (48.5)	2905 (48.3)	
Thickness, mm, median (IQR)	5.0 (3.5-7.0)	4.5 (3.0-6.0)	<.01
Ulceration			
No	704 (27.7)	1523 (25.3)	.02
Yes	1837 (72.3)	4498 (74.7)	
T-stage			
T3b	833 (32.8)	2528 (42.0)	<.01
T4a	704 (27.7)	1523 (25.3)	
T4b	1004 (39.5)	1970 (32.7)	
Clinical stage			
IIB	1537 (60.5)	4051 (67.3)	<.01
IIC	1004 (39.5)	1970 (32.7)	
Adjuvant systemic therapy			
No	2475 (97.4)	5394 (89.6)	<.01
Yes	66 (2.6)	627 (10.4)	
Adjuvant radiation therapy			
No	2443 (96.1)	5775 (95.9)	.62
Yes	98 (3.9)	246 (4.1)	

AAPI, Asian American/Pacific Islander; *IQR,* interquartile range; *NOS,* not otherwise specified; *SLN,* sentinel lymph node.

Factors associated with SLN positivity

Among the 6021 patients who underwent SLN biopsy, 1877 (31.2%; 95% CI, 30.0%-32.4%) had an

SLN+ biopsy (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/5wmd4547sv/1). The median number of lymph nodes removed was significantly higher for those with an SLN+ biopsy compared to those with an SLN- biopsy (13 [IQR, 4-23] SLN+ vs 2 [IQR, 1-4] SLN-; $P < .01$). On multivariable analysis of this cohort who underwent SLN biopsy, younger age (odds ratio [OR], 1.02; 95% CI, 1.01-1.02; $P < .001$), Asian American/Pacific Islander race (OR, 2.64; 95% CI, 1.33-5.25; $P = .005$), truncal (OR, 1.80; 95% CI, 1.51-2.14; $P < .001$) and extremity (OR, 1.61; 95% CI, 1.36-1.90; $P < .001$) tumor location, acral lentiginous histology (OR, 2.89; 95% CI, 1.45-5.77; $P = .003$), increasing tumor thickness (OR, 1.00; 95% CI, 1.00-1.00; $P < .001$), and positive ulceration status (OR, 1.67; 95% CI, 1.44-1.94; $P < .001$) were significantly associated with SLN positivity (Supplementary Table II, available via Mendeley at https://data.mendeley.com/datasets/5wmd4547sv/1). Patients with SLN+ biopsies were also significantly more likely to receive adjuvant systemic (OR, 3.43; 95% CI, 2.86-4.12; $P < .001$) and adjuvant radiation (OR, 2.72; 95% CI, 2.04-3.63; $P < .001$) therapy.

Follow-up and survival analysis

The median follow-up for patients alive at the last follow-up was 130 months (IQR, 110-154 months). Following propensity matching among patients who underwent SLN biopsy, no significant differences in baseline patient or tumor characteristics were observed between these 2 groups (Supplementary Table III, available via Mendeley at https://data.mendeley.com/datasets/5wmd4547sv/1). SLN positivity was associated with significantly lower 5-year DSS rates compared with SLN- disease (47.1% SLN+ biopsy vs 75.5% SLN- biopsy, log-rank $P < .001$) (Fig 1).

Propensity matching was further performed on the subgroups of patients with T3b, T4a, and T4b tumors who underwent SLN biopsy, comparing patients with and without SLN+ disease and matching for the same factors as were matched among the total cohort of patients who underwent SLN biopsy (Supplementary Tables IV-VI, available via Mendeley at https://data.mendeley.com/datasets/5wmd4547sv/1). On these subgroup analyses, 5-year DSS remained significantly different across T-stages based on SLN status. Specifically, for patients with T3b, T4a, and T4b tumors, 5-year DSS rates for patients with positive versus SLN- disease were 54.2% versus 64.8% (log-rank $P = .004$), 55.5% versus 71.6% (log-rank $P = .001$), and 38.6% versus 60.9% (log-rank $P < .001$), respectively (Fig 2).

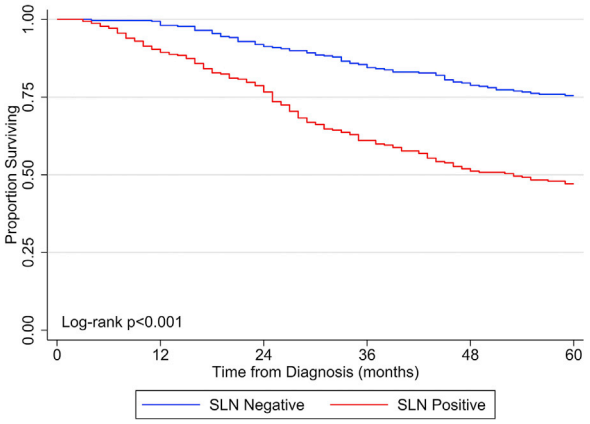

Fig 1. Kaplan-Meier estimate of 5-year disease-specific survival curves among all patients who underwent sentinel lymph node biopsy comparing patients by sentinel lymph node status.

Propensity matching was additionally performed among the entire study cohort, comparing patients who did versus did not undergo SLN biopsy (Supplementary Table VII, available via Mendeley at https://data.mendeley.com/datasets/5wmd4547sv/1). No difference in 5-year DSS rates was observed based on the performance of SLN biopsy (64.6% SLN biopsy performed vs 64.8% SLN biopsy not performed, log-rank $P = .896$).

DISCUSSION

In the current study evaluating patients who underwent wide excision of clinical stage IIB/C primary cutaneous melanoma in a preimmunotherapy era, a 5-year DSS difference of nearly 30% was found between patients with positive versus negative SLN biopsy. Moreover, a significant survival difference persisted based on SLN status when patients were subcategorized by either T3b, T4a, or T4b T-stage. These data demonstrate the prognostic importance of SLN biopsy even in patients with high-risk clinically localized diseases. While these findings are generally consistent with the current *American Joint Committee on Cancer* 8th edition staging criteria, a major advantage of this study is that it evaluates only a preimmune checkpoint therapy population. The long-term survival results are not confounded by the use of modern, effective systemic melanoma therapies, and these results represent an accurate portrayal of the prognostic implications that SLN biopsy has among this high-risk population. Additionally, this study uses propensity matching to adjust for confounding variables, allowing for a more accurate comparison of SLN positive and negative patients. Notably, patients with T3b tumors in the current study were also found to have worse survival

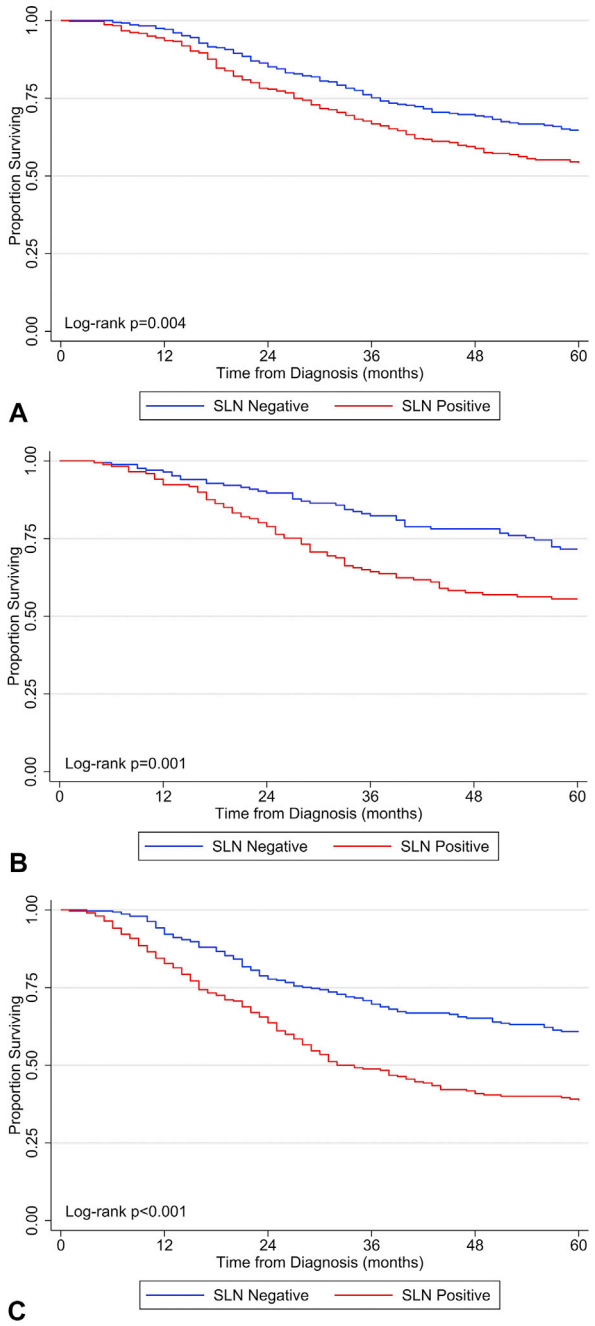

Fig 2. Kaplan-Meier estimates of 5-year disease-specific survival curves among patients who underwent sentinel lymph node biopsy comparing patients by sentinel lymph node status among (**A**) T3b, (**B**) T4a, and (**C**) T4b T-stages.

outcomes than those with T4a tumors. This has also been shown in prior analyses and is likely due to the negative prognostic significance of ulceration status.[20]

Interestingly, patients in the current study with T4a and T4b tumors were less likely to undergo SLN biopsy than patients with T3b tumors. Given the timeframe of the current study, this discrepancy may be because of the results of the Multicenter Selective Lymphadenectomy Trial-1, which found that among patients with intermediate-thickness melanomas with nodal metastases, the 10-year DSS rate was significantly improved for the group of patients who underwent SLN biopsy compared with those in the observation group who did not undergo SLN biopsy. However, no 10-year DSS difference was seen between the SLN biopsy group and observation group for patients with thick melanomas with nodal metastases.[21] Additionally, T4 patients in the current study were older and more likely to have head/neck melanomas than T3 patients. Older patients may be less likely to undergo SLN biopsy due to higher rates of associated comorbidities, and head/neck melanomas are known to have more variable lymphatic drainage and higher false-negative rates, likely impacting the decision to perform SLN biopsy.[22] More contemporary analyses have shown a prognostic benefit for SLN biopsy even among patients with T4 melanomas.[23-26]

In the present study, no advantage in DSS was observed for patients who underwent SLN biopsy compared with those who did not, findings consistent with previously reported results from prospective randomized trials, as discussed above.[21] Although the data on whether SLN biopsy provides a direct therapeutic benefit regarding melanoma DSS remains unclear, its association with regional lymph node basin control is well appreciated.[27,28]

It is imperative to note that all patients in the KEYNOTE-716 study underwent SLN biopsy, so the results of that trial cannot be directly applied to patients who have not undergone complete pathologic regional nodal basin staging.[4] Given the large survival difference between SLN+ and SLN- biopsy patients, even in the high-risk cohort studied here, some patients may be comfortable deferring adjuvant treatment in the setting of an SLN- biopsy. However, without the performance of this procedure, complete and accurate pathologic staging cannot be achieved. Additionally, for patients who are considering receipt of adjuvant immune checkpoint blockade therapy, knowledge of their SLN status also allows them to make a more informed decision regarding the risks versus benefits of adjuvant treatment. For example, in the KEYNOTE-716 trial, 36.2% of patients in the pembrolizumab cohort developed an immune-related adverse event.[4] Although most of these complications were grade 1-2 in severity, this is still clinically a much higher complication rate than the traditionally reported 5% to 10% complication rate associated with SLN biopsy.[29,30] Furthermore, the severity of complications associated with SLN biopsy is generally

benign, most commonly consisting of wound infection or seromas/lymphoceles, and rarely require hospitalization.[29,31] Unlike after a complete lymph node dissection, in which the rates of lymphedema can be upwards of 10% to 15% (or even higher for inguinal disease), development of lymphedema is exceedingly rare after SLN biopsy (~1.5%).[31-33] In contrast, complications related to immunotherapy can be permanent and disabling, including persistent endocrinopathies, something that cannot be overstated.[34,35] For some patients, the risk of complications related to immunotherapy in the setting of unknown SLN status may outweigh the risks associated with determining their SLN status.

There are several limitations that should be considered when interpreting this study. All patients who had at least 1 regional lymph node evaluated were considered to have undergone an SLN biopsy. It is possible that some of these patients underwent lymph node dissection without ever having had an SLN biopsy performed, although this is unlikely given the stage of patients included in the study, the time period over which the study took place, and the traditional management of melanoma at that time. Additionally, it is possible that some patients who had positive regional lymph nodes only had these positive nodes on a lymph node dissection (although this would suggest that these patients either underwent upfront lymph node dissection or had an SLN- biopsy and then underwent subsequent completion lymph node dissection, which would be unlikely). Comorbidity data are not provided within the SEER program and thus were not able to be considered when evaluating rates of SLN performance or included in the propensity-matched models. However, given the primary study outcome of DSS, it is unlikely that this would have majorly impacted the results. The inclusion of patients with unknown results for the variables analyzed could have also confounded the findings of this study. Finally, as a retrospective analysis, it is possible that unknown potential confounding variables were not captured and could have impacted the results in undefined ways.

CONCLUSION

In the current study evaluating patients who underwent wide excision for clinical stage IIB/C primary cutaneous melanoma in the preimmunotherapy era, SLN status was found to be significantly associated with DSS among all included patients, as well as across T-stages. For patients with clinical stage IIB/C cutaneous melanoma, SLN status provides essential prognostic information and can be an important factor for collective decision-making regarding adjuvant therapy administration based on risk assessment. Foregoing SLN biopsy in favor of immediate immune checkpoint blockade treatment in these high-risk patients can result in failure to obtain critical prognostic and staging information.

Conflicts of interest

None disclosed.

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