Sentinel lymph node biopsy in patients with T1a cutaneous malignant melanoma: A multicenter cohort study

Adrienne B. Shannon, MD,[a] Cimarron E. Sharon, MD,[a] Richard J. Straker III, MD,[a] Michael J. Carr, MD, MS,[b,c] Andrew J. Sinnamon, MD, MSCE,[b] Kita Bogatch, BA,[d] Alexandra Thaler, BA,[a,e] Nicholas Kelly, BA,[a,e] John T. Vetto, MD,[f] Graham Fowler, BS,[f] Danielle DePalo, MD,[b] Vernon K. Sondak, MD,[b] John T. Miura, MD,[a] Mark B. Faries, MD,[g] Edmund K. Bartlett, MD,[d] Jonathan S. Zager, MD,[b] and Giorgos C. Karakousis, MD[a]

Background: Sentinel lymph node biopsy is not routinely recommended for T1a cutaneous melanoma due to the overall low risk of positivity. Prognostic factors for positive sentinel lymph node (SLN^+) in this population are poorly characterized.

Objective: To determine factors associated with SLN^+ in patients with T1a melanoma.

Methods: Patients with pathologic T1a (<0.80 mm, nonulcerated) cutaneous melanoma from 5 high-volume melanoma centers from 2001 to 2020 who underwent wide local excision with sentinel lymph node biopsy were included in the study. Patient and tumor characteristics associated with SLN^+ were analyzed by univariate and multivariable logistic regression analyses. Age was dichotomized into ≤42 (25% quartile cutoff) and >42 years.

Results: Of the 965 patients identified, the overall SLN^+ was 4.4% (N = 43). Factors associated with SLN^+ were age ≤42 years (7.5% vs 3.7%; odds ratio [OR], 2.14; P = .03), head/neck primary tumor location (9.2% vs 4%; OR, 2.75; P = .04), lymphovascular invasion (21.4% vs 4.2%; OR, 5.64; P = .01), and ≥2 mitoses/mm^2 (8.2% vs 3.4%; OR, 2.31; P = .03). Patients <42 years with ≥2 mitoses/mm^2 (N = 38) had a SLN^+ rate of 18.4%.

Limitations: Retrospective study.

Conclusion: SLN^+ is low in patients with T1a melanomas, but younger age, lymphovascular invasion, mitogenicity, and head/neck primary site appear to confer a higher risk of SLN^+. (J Am Acad Dermatol 2023;88:52-9.)

From the Division of Endocrine and Oncologic Surgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania[a]; Department of Cutaneous Oncology, Moffitt Cancer Center, Tampa, Florida[b]; Department of Surgery, University of Louisville, Louisville, Kentucky[c]; Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, New York[d]; Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania[e]; Division of Surgical Oncology, Department of Surgery, Oregon Health & Science University, Portland, Oregon[f]; and Division of Surgical Oncology, The Angeles Clinic and Research Institute, Cedars-Sinai Medical Center, Los Angeles, California.[g]

Drs Zager and Karakousis contributed equally to this article as senior authors.

Drs Shannon and Sharon contributed equally to this article as first authors.

Funding sources: Sondak's relevant financial activities outside the submitted work include BMS, Eisai, Iovance, Novartis, and Regeneron, and he receives research support from Neogene and Turnstone. Bartlett receives institutional research support from SkylineDx and discloses an honorarium from Excite International.

IRB approval status: Reviewed and determined to be exempt by the University of Pennsylvania IRB, protocol # 843609.

Patient consent: No identifiable material, including photographs or identifiable medical information, is included in this manuscript. All included data are de-identified, and as such, this manuscript has been determined to be exempt by the IRB.

Accepted for publication September 26, 2022.

Reprints not available from the authors.

Correspondence to: Cimarron E. Sharon, MD, Department of Surgery, Hospital of the University of Pennsylvania, 3400 Spruce St, Maloney 4, Philadelphia, PA 19104. E-mail: cimarron.sharon@pennmedicine.upenn.edu.

Published online September 30, 2022.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2022.09.040

Key words: melanoma; prognosis; sentinel lymph node biopsy; surgery; survival; wide local excision.

INTRODUCTION

Most newly diagnosed melanomas present with localized disease, of which the majority are T1 lesions (≤1 mm).[1,2] According to National Comprehensive Cancer Network guidelines,[3] sentinel lymph node biopsy (SLNB) should not be routinely recommended for patients with T1a melanomas but may be considered for T1b lesions (0.80-1.0 mm Breslow's depth with or without ulceration or <0.8 mm with ulceration).[4] Past studies have identified high-risk features associated with positive sentinel lymph node (SLN^+) in thin (≤1 mm) melanoma, including younger age, presence of lymphovascular invasion (LVI), mitogenicity, and a higher Clark level.[1,5-12] To what extent these factors confer an increased risk of SLN^+ in otherwise low-risk T1a lesions has not been well defined. Data from prior studies evaluating SLNB in T1 melanomas have generally been weighted toward T1b lesions,[7-10,12] and therefore, data specific to T1a melanomas are largely lacking.

CAPSULE SUMMARY

- Factors associated with sentinel node positivity in patients with T1a melanoma are uncharacterized.
- Patients who are younger in age, with lymphovascular invasion, a high mitotic rate, and a head/neck tumor have a higher risk of node positivity, prompting consideration of sentinel lymph node biopsy.

A previous single-institution study by our group investigated predictors of SLN^+ in T1a cutaneous melanoma and found that younger age (<40 years) and mitotic rate ≥1 mitosis/mm^2 conferred an increased risk of SLN^+, with a rate of 5.3% for younger patients alone and 12.8% when both factors were present.[13] A SLN^+ rate of at least 5% is typically accepted as the threshold to support the performance of SLNB,[1,14,15] suggesting there may be subgroups of patients with T1a (eg, younger age with mitogenic tumors) for whom selective use of SLNB may be justified. The study was limited by its relatively small number of SLN^+ patients (N = 13) and by virtue of its single-center nature.

The purpose of the current study was therefore to evaluate prognostic factors for SLN^+ and outcomes of patients with T1a cutaneous melanoma undergoing SLNB in a large multicenter study population. The findings could help better inform clinicians and patients with these otherwise low-risk melanomas in decision-making for careful and selective consideration of SLNB.

MATERIALS AND METHODS

Data source and patient selection

Adult patients over 18 years of age who underwent wide local excision (WLE) of T1a (<0.80 mm and nonulcerated) cutaneous melanoma and SLNB between January 1, 2001, and December 31, 2020, were identified from 5 high-volume melanoma institutions in the United States. Only patients with no residual disease found on the WLE specimen were included in the study population. All centers obtained institutional review board approval and performed independent data abstraction from the medical records, which were provided to the primary center for analysis. Of the 965 patients included, 490 (51%) were from a single institution and comprised data which have been previously published.[13]

Variables

Patient variables evaluated included age and sex. Tumor characteristics included anatomic site (extremity, axial/trunk, and head/neck), Clark's level, tumor thickness (analyzed as both a continuous and binary variable and separately dichotomized into <0.7 mm [75% quartile cutoff] and ≥0.7 mm), histology (superficial spreading, nodular, lentigo maligna, acral lentiginous, and unclassified), vertical growth phase, tumor-infiltrating lymphocytes (absent, brisk, nonbrisk, and unknown), regression, satellitosis, LVI, perineural invasion (PNI), and mitotic count (0, 1, and ≥2 mitosis/mm^2). Mitotic rate was categorized in this fashion as mitotic rate >2 mitosis/mm^2 is considered as an adverse feature by the National Comprehensive Cancer Network for SLN^+ in thin melanomas.[16] Age was analyzed continuously and was also dichotomized into ≤42 years (25% quartile cutoff) and >42 years. Deep margin status of the original biopsy specimen was classified as positive, negative, or unknown. The

Abbreviations used:

DSS: disease-specific survival
LVI: lymphovascular invasion
OR: odds ratio
PNI: perineural invasion
SLN: sentinel lymph node
SLN−: negative sentinel lymph node
SLN+: positive sentinel lymph node
SLNB: sentinel lymph node biopsy
WLE: wide local excision

patients were divided into cohorts based on negative sentinel lymph node (SLN^-) and SLN^+ SLNB results.

Statistical methods

Descriptive statistics are presented as frequencies for categorical variables and as medians and IQRs for continuous variables. Univariable analyses were performed using the Pearson's chi-square test for categorical variables and the Wilcoxon's rank sum test for continuous variables. Patient and tumor characteristics associated with SLN^+ were analyzed by univariate and multivariable logistic regression analyses. The goodness-of-fit of the model was assessed with the Hosmer-Lemeshow test.[17] A classification and regression tree utilizing a recursive partitioning algorithm developed a decision tree of patients to risk-stratify patients for SLN^+. Only patients without LVI ($N = 952$) were included in the classification and regression tree analysis due to the very low incidence of this histologic characteristic in T1a melanomas. Five-year recurrence-free survival was defined as the interval [in months] from WLE and SLNB to disease recurrence. Five-year disease-specific survival (DSS) was defined as the interval from WLE and SLNB to melanoma-related death. All tests were two-sided, and a P value less than .05 was considered statistically significant. Statistical analyses were performed in Stata version 16 (Statacorp LLC).

RESULTS

Characteristics of the cohort

Of the 965 patients with T1a melanoma, the SLN^+ rate was 4.5% ($N = 43$). The overall median age and tumor thickness were 53.6 (IQR, 43-63) years and 0.60 (IQR, 0.50-0.70) mm, respectively. Approximately 82% of lesions were greater than 0.5 mm ($N = 787$). Most tumors were superficial spreading in histology ($N = 584$, 60.5%), and approximately half were located on the extremities ($N = 475$, 49.2%). The number of SLNs removed did not differ between tumor primary sites, with a median of 2 nodes removed for extremity, axial/truncal, and head/neck tumors ($P = .45$). Of the 420 patients for whom deep margin status of the original biopsy was available, 157 (37.4%) had a positive deep margin, although none of these patients had residual disease at the time of WLE. No SLN^- patients and 1 SLN^+ received adjuvant immunotherapy following SLNB. Patient and tumor characteristics are shown in Table I.

Predictors of SLN^+

On univariate analysis, factors associated with SLN^+ included age less than 42 years (age ≤42 SLN^+: 7.5% vs age >42 SLN^+: 3.7%, $P = .024$), head or neck location (head/neck SLN^+: 9.2% vs non-head/neck SLN^+: 4.0%, $P = .025$), LVI (LVI present SLN^+: 21.4% vs no LVI SLN^+: 4.2%, $P = .002$), PNI (PNI present SLN^+: 25.0% vs no PNI SLN^+: 4.4%, $P = .046$), and mitotic count ≥2 mitoses/mm^2 (≥2 mitoses/mm^2 SLN^+: 8.2% vs <2 mitoses/mm^2 SLN^+: 3.4%, $P = .003$). (Table I). Following multivariable analysis, factors that remained associated with SLN^+ were age <42 years (odds ratio [OR], 2.14; $P = .03$), head/neck primary tumor location (OR, 2.75; $P = .04$), LVI (OR, 5.64; $P = .01$), and ≥2 mitoses/mm^2 (OR, 2.31; $P = .03$) (Table II). The Hosmer-Lemeshow test demonstrated that the multivariate model had appropriate goodness-of-fit ($P = .23$). Among patients without LVI, patients ≤42 years old ($N = 184$) had a SLN^+ of 7.6% (95% CI, 4.2%-12.4%), and if the mitotic rate of the primary tumor was ≥2 mitoses/mm^2 ($N = 38$), the SLN^+ rate was 18.4% (95% CI, 7.8%-34.3%). Patients with these characteristics in addition to a head/neck primary tumor site ($N = 6$) had an SLN^+ rate of 33% (95% CI, 4.3%-77%) compared to those without a head/neck primary site with a rate of 15.6% (95% CI, 5.3%-32.8%) (Fig 1).

Survival and recurrence analyses stratified by SLN status

The median follow-up time of the cohort was 73 (IQR, 31-138) months. Five-year DSS in SLN^+ versus SLN^- patients was 90.7% versus 99.5% ($P < .0001$), and 5-year recurrence-free survival in SLN^+ versus SLN^- patients was 81.4% versus 95.6% ($P < .0001$), respectively (Fig 2). SLN^+ patients were more likely to have a recurrence compared to SLN^-patients (30.0% vs 7.8%, $P < .001$). Of the patients who recurred ($N = 37$), 49% presented with a distant recurrence ($N = 18$) and 38% with regional disease ($N = 14$). The remainder of patients ($N = 5$) presented with both local and locoregional disease. There was no significant difference in patterns of recurrence between SLN^+ versus SLN^- patients ($P = .36$). Patients with head and neck melanomas had a higher recurrence rate overall (19% [$N = 15$] vs 7% [$N = 22$], $P = .001$). The majority of these recurrences (73%) for

Table I. Patient and tumor characteristics of patients with T1a cutaneous melanoma who underwent sentinel lymph node biopsy at 5 institutions from 2001 to 2020

	SLN^- (N = 922, 95.5%) N (%)	SLN^+ (N = 43, 4.5%) N (%)	P value
Age (median, y, IQR)	54 (44-63)	50 (40-64)	.26
Age (y)			.024*
≤42	172 (18.7)	14 (32.6)	
>42	750 (81.3)	29 (67.4)	
Sex			.37
Male	472 (51.2)	19 (44.2)	
Female	450 (48.8)	24 (55.8)	
Site of melanoma			.033*
Extremity	452 (49.0)	23 (53.5)	
Axial or trunk	391 (42.4)	12 (27.9)	
Head or neck	79 (8.6)	8 (18.6)	
Clark's level			.073
2	118 (12.8)	7 (16.3)	
3	356 (38.6)	11 (25.6)	
4	396 (43.0)	19 (44.2)	
Unknown	52 (5.6)	6 (14.0)	
Median tumor thickness: mm (IQR)	6 (5-7)	6.1 (5-7)	.91
Tumor thickness (median, mm, IQR)	0.6 (0.5-0.7)	0.61 (0.5-0.7)	.91
Tumor thickness (mm)			.50
<0.7	583 (63.2)	25 (58.1)	
≥0.7	339 (36.8)	18 (41.9)	
Histology			.13
Superficial spreading	563 (61.1)	21 (48.8)	
Nodular	33 (3.6)	2 (4.7)	
Lentigo maligna	35 (3.8)	0 (0)	
Other/unclassified	291 (31.6)	20 (56.5)	
Vertical growth phase			.074
Absent	347 (37.6)	22 (51.2)	
Present	575 (62.4)	21 (48.8)	
Tumor-infiltrating lymphocytes			.004*
Absent	193 (20.9)	5 (11.6)	
Brisk	79 (8.6)	2 (4.7)	
Non-brisk	457 (49.6)	17 (39.5)	
Unknown	193 (20.9)	19 (44.2)	
Regression			.412
Absent	677 (73.4)	34 (79.1)	
Present	245 (26.6)	9 (20.9)	
Satellitosis	4 (0.43)	1 (2.33)	.091
Lymphovascular invasion			.002*
Positive	11 (1.2)	2 (4.7)	
Negative	776 (84.2)	29 (67.4)	
Unknown	135 (14.6)	12 (27.9)	
Perineural invasion			.046*
Positive	3 (0.6)	1 (2.9)	
Negative	386 (71.4)	18 (52.9)	
Unknown	152 (28.1)	15 (44.1)	
Mitotic count/mm^2			.013*
0	429 (46.5)	15 (34.9)	
1	303 (32.9)	11 (25.6)	
≥2	190 (20.6)	17 (39.5)	
Deep margin status			.13
Positive	154 (16.7)	3 (7.0)	
Negative	253 (27.4)	10 (23.3)	
Unknown	515 (55.9)	30 (70.0)	

SLN^-, Negative sentinel lymph node; SLN^+, positive sentinel lymph node.
*Indicates significance.

Table II. Multivariable analysis of factors associated with positive sentinel lymph node for patients with T1a cutaneous melanoma who underwent sentinel lymph node biopsy at 5 institutions from 2001 to 2020

	Odds ratio [OR] (95% CIs)	*P* value
Age (y)		
>42	1 [reference]	
≤42	2.14 (1.09-4.20)	.027*
Site of melanoma		
Axial or trunk	1 [reference]	
Extremity	1.65 (0.80-3.39)	.18
Head or neck	2.75 (1.06-7.14)	.035*
Lymphovascular invasion		
Absent/unknown	1 [reference]	
Present	5.64 (1.42-22.31)	.014*
Mitotic count/mm^2		
0	1 [reference]	
1	0.99 (0.45-2.21)	.98
≥2	2.31 (1.11-4.80)	.025*

*Indicates significance.

patients with head and neck tumors occurred in SLN$^-$ patients, wherein the recurrence rate was 14% (11/79), compared to 50% for SLN$^+$ (4/8, $P < .001$). By comparison, the recurrence rate for SLN$^-$ patients with non-head and neck melanomas was 2% (17/843). There was no difference in regional recurrence rates for SLN$^-$ patients with head/neck and non-head/neck primaries (2.5% and 0.9%, $P = .14$). Most patients with head/neck tumors who recurred overall did so distantly (60%, $N = 9$).

DISCUSSION

In this study, we identify high risk factors for SLN$^+$ in patients with T1a melanomas using a large multicenter cohort. To our knowledge, this is the largest study addressing this particular topic. As T1 melanomas account for up to 25% of melanoma deaths,[18] identification of high-risk patients for SLN$^+$ with T1a lesions, for whom SLN$^+$ is not routinely recommended, could have profound public health implications in how we care for these patients.

Factors found to be associated with SLN$^+$ in this study included age ≤42 years, LVI, mitotic rate ≥2/mm^2, and head and neck primary tumor site. These data are largely concordant with previously published studies. Prior investigations on thin melanomas have identified younger age as a risk factor for SLN$^+$, including a previous institutional study by our group on T1a lesions.[1,13,19-21] In a prior study by Sondak et al,[20] younger age, particularly in the context of a high mitotic rate, conferred a high risk for SLN$^+$, irrespective of tumor thickness, in thin melanomas. Our study corroborates these results for T1a lesions, even though tumor thickness and Clark's level were not found to carry a higher risk of SLN$^+$ in the present study. This inverse relationship of age with SLN metastasis has been well-documented and may relate to differences in tumor biology or lymphatic permeability.[22-24]

Additionally, head/neck primary tumor location was associated with SLN$^+$ for T1a melanomas. Previous institutional studies have identified the axial location as a risk factor for SLN$^+$ in thin melanomas,[25,26] while a meta-analysis of SLN$^+$ in thin melanoma (<1 mm) performed by Warycha et al[27] did not find primary tumor anatomic location to be a high risk factor for nodal metastases, although there was significant heterogeneity among the included studies. Prior studies across melanoma thickness lesions have demonstrated head and neck site may be associated with lower rates of SLN$^+$ compared to truncal or extremity location, but this is felt to be driven by increased false-negative results.[28-30] This is in line with our results, as most patients with head and neck tumors who recurred were SLN$^-$, suggesting that these may have been false negatives. In our cohort, patients with head and neck melanomas did not have a significantly different number of SLNs removed compared to the patients with melanomas of other anatomic sites. Further investigation is needed to better understand the higher rates of SLN$^+$ and recurrence rates observed in the current study among T1a melanomas of the head and neck, specifically.

The results of our survival analysis highlight the importance of nodal staging for accurate prognostication. There is little information regarding survival outcomes for T1 melanomas stratified by SLN status. The eighth edition of the American Joint Committee on Cancer melanoma staging system reported a 99% 5-year melanoma-specific survival for T1aN0 cutaneous melanomas, but the majority of these patients were likely clinically staged.[31] While patients in our cohort who were SLN$^-$ similarly demonstrated a 99% 5-year DSS, patients who were SLN$^+$ had a DSS of 90.7%. This is concordant with data for melanoma-specific survival from the eighth edition American Joint Committee on Cancer staging criterion among patients with stage IIIA disease, which additionally includes patients with T2a lesions.[4] Notably, our study found that SLN$^+$ T1a patients had a 5-year recurrence-free survival of 81%. These results call attention to the importance of appropriate surveillance of patients with T1a melanomas with high-risk features who may not have undergone SLNB and

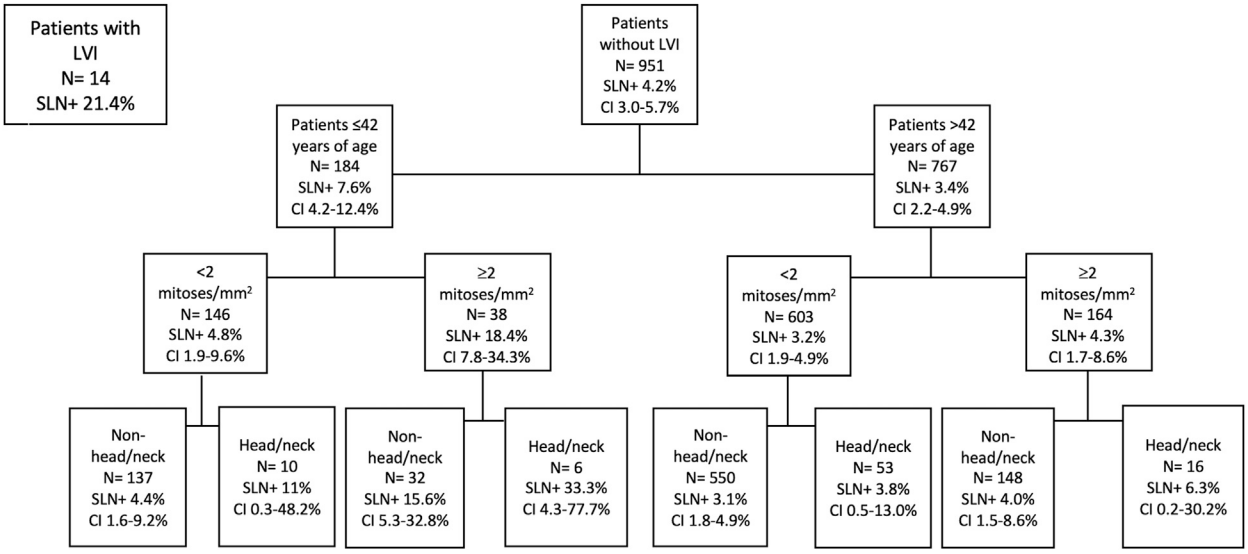

Fig 1. Rate of positive sentinel lymph node among patients with T1a cutaneous melanoma following definitive wide local excision and sentinel lymph node biopsy based on patient and tumor characteristics identified as associated with positive sentinel lymph node.

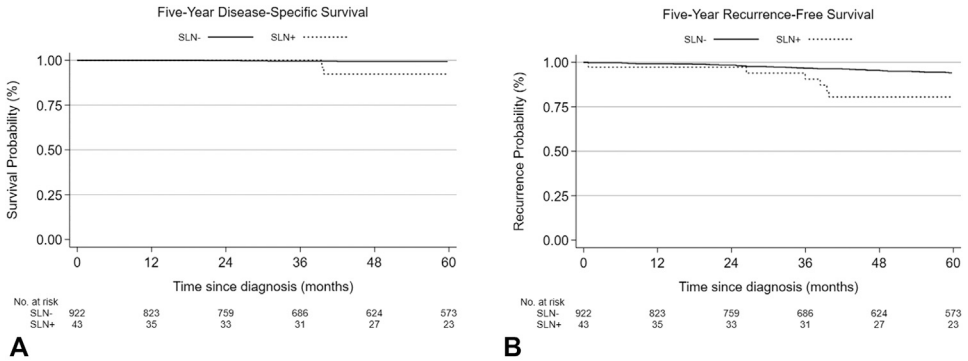

Fig 2. Kaplan-Meier survival curves demonstrating 5-year (**A**) disease-specific survival and (**B**) recurrence-free survival for patients with T1a cutaneous melanoma with a negative sentinel lymph node and positive sentinel lymph node biopsy.

who might otherwise be lost to follow-up due to their perceived favorable prognosis.

There are notable limitations to the current study, many of which are inherent to its retrospective study design. One major limitation is that of selection bias for the performance of SLNB. As SLNB is not generally recommended for this cohort of patients, it is unclear what factors were considered in aggregate in the decision-making to perform this procedure among individual clinicians. For instance, the thickness of the lesion likely contributed significantly, as only a minority of patients had lesions <0.5 mm in thickness. However, the relative importance of the various tumor and patient factors captured in the final decision-making and the possibility of other factors not captured (eg, family history of melanoma, patient's level of concern, etc.) is not discernible from the current data set. The authors acknowledge that the study population represents a highly selective cohort of patients. As this study only included patients who had a SLNB performed, we were unable to compare patient and tumor characteristics among patients with T1a lesions who did and did not undergo staging of the nodal basin. Follow-up of all T1a lesions irrespective of receipt of SLNB could provide meaningful data with respect to predictors of regional nodal metastasis. Another limitation is that the deep margin status of the original specimen was not available for analysis for a significant number of patients. As many T1 melanomas are diagnosed by shave biopsy, there is the possibility of transected specimens which

could underestimate the true depth of the melanoma and impact the likelihood of SLN metastasis. Even so, deep margin status was not found to be significantly associated with SLN status in patients with this data field available, and all patients included in the study had no residual disease noted on WLE, likely mitigating any significant impact of possible tumor upstaging from a transected biopsy specimen. Results from a paper on T1 melanomas studying the impact of deep margin status on biopsy similarly suggest that the presence of positive deep margin on original biopsy does not appear to substantially increase the risk of SLN^+ in the absence of deeper lesion being identified on the wide excision specimen.[32] Lastly, of the 965 patients included, 490 were from one institution and represent previously published data.[13] As 51% of patients were from a single institution, this may bias the results and not reflect that of other centers.

CONCLUSION

The SLN^+ rate for T1a melanomas is low overall, and consistent with National Comprehensive Cancer Network guidelines, SLNB should not be routinely recommended for patients with these early lesions.[3] However, younger age, LVI, mitotic rate $\geq 2/mm^2$, and head/neck tumor location confer a higher risk for SLN^+ in this subgroup of patients, and when present, particularly in combination, should be considered in the decision-making for SLNB.

The authors wish to acknowledge Dale Han, MD, who contributed data to this study and died prior to submission.

Conflicts of interest

Faries serves on the advisory boards for Novartis, Bristol Myers Squibb, Merck, Sanofi, Array Bioscience, and Nektar Biofarma. Shannon, Sharon, Straker, Carr, Sinnamon, Bogatch, Thaler, Kelly, Vetto, Fowler, DePalo, Miura, Zager, and Karakousis have no conflicts of interest to declare.

REFERENCES

1. Sinnamon AJ, Neuwirth MG, Yalamanchi P, et al. Association between patient age and lymph node positivity in thin melanoma. *JAMA Dermatol*. 2017;153(9):866-873. https://doi.org/10.1001/jamadermatol.2017.2497
2. Trotter SC, Sroa N, Winkelmann RR, Olencki T, Bechtel M. A global review of melanoma follow-up guidelines. *J Clin Aesthet Dermatol*. 2013;6(9):18-26.
3. Coit DG, Thompson JA, Albertini MR, et al. Cutaneous melanoma, version 2.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2019;17(4):367-402. https://doi.org/10.6004/jnccn.2019.0018
4. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. Nov 2017;67(6):472-492. https://doi.org/10.3322/caac.21409
5. Bartlett EK, Gimotty PA, Sinnamon AJ, et al. Clark level risk stratifies patients with mitogenic thin melanomas for sentinel lymph node biopsy. *Ann Surg Oncol*. 2014;21(2):643-649. https://doi.org/10.1245/s10434-013-3313-y
6. Piñero-Madrona A, Ruiz-Merino G, Cerezuela Fuentes P, Martínez-Barba E, Rodríguez-López JN, Cabezas-Herrera J. Mitotic rate as an important prognostic factor in cutaneous malignant melanoma. *Clin Transl Oncol*. 2019;21(10):1348-1356. https://doi.org/10.1007/s12094-019-02064-4
7. Ranieri JM, Wagner JD, Wenck S, Johnson CS, Coleman JJ. The prognostic importance of sentinel lymph node biopsy in thin melanoma. *Ann Surg Oncol*. 2006;13(7):927-932. https://doi.org/10.1245/ASO.2006.04.023
8. Murali R, Haydu LE, Quinn MJ, et al. Sentinel lymph node biopsy in patients with thin primary cutaneous melanoma. *Ann Surg*. 2012;255(1):128-133. https://doi.org/10.1097/SLA.0b013e3182306c72
9. Lowe JB, Hurst E, Moley JF, Cornelius LA. Sentinel lymph node biopsy in patients with thin melanoma. *Arch Dermatol*. 2003;139(5):617-621. https://doi.org/10.1001/archderm.139.5.617
10. Cecchi R, Buralli L, Innocenti S, De Gaudio C. Sentinel lymph node biopsy in patients with thin melanomas. *J Dermatol*. 2007;34(8):512-515. https://doi.org/10.1111/j.1346-8138.2007.00323.x
11. Kunte C, Geimer T, Baumert J, et al. Prognostic factors associated with sentinel lymph node positivity and effect of sentinel status on survival: an analysis of 1049 patients with cutaneous melanoma. *Melanoma Res*. 2010;20(4):330-337. https://doi.org/10.1097/CMR.0b013e32833ba9ff
12. Durham AB, Schwartz JL, Lowe L, et al. The natural history of thin melanoma and the utility of sentinel lymph node biopsy. *J Surg Oncol*. 2017;116(8):1185-1192. https://doi.org/10.1002/jso.24765
13. Shannon AB, Wood C, Straker RJ, et al. Age and mitogenicity are important predictors of sentinel lymph node metastasis in T1a melanoma. *Ann Surg Oncol*. 2021;28(9):4777-4779. https://doi.org/10.1245/s10434-021-09929-5
14. Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg*. 2005;242(3):302-311; discussion 311-3. https://doi.org/10.1097/01.sla.0000181092.50141.fa
15. Roaten JB, Pearlman N, Gonzalez R, McCarter MD. Identifying risk factors for complications following sentinel lymph node biopsy for melanoma. *Arch Surg*. 2005;140(1):85-89. https://doi.org/10.1001/archsurg.140.1.85
16. Swetter SM, Thompson JA, Albertini MR, et al. NCCN Guidelines® insights: melanoma: cutaneous, version 2.2021. *J Natl Compr Canc Netw*. 2021;19(4):364-376. https://doi.org/10.6004/jnccn.2021.0018
17. Lemeshow S, Hosmer DW. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol*. 1982;115(1):92-106. https://doi.org/10.1093/oxfordjournals.aje.a113284
18. Hieken TJ, Grotz TE, Comfere NI, Inselman JW, Habermann EB. The effect of the AJCC 7th edition change in T1 melanoma substaging on national utilization and outcomes of sentinel lymph node biopsy for thin melanoma. *Melanoma Res*. 2015;25(2):157-163. https://doi.org/10.1097/CMR.0000000000000143
19. Conic RRZ, Ko J, Damiani G, et al. Predictors of sentinel lymph node positivity in thin melanoma using the National Cancer Database. *J Am Acad Dermatol*. 2019;80(2):441-447. https://doi.org/10.1016/j.jaad.2018.08.051
20. Sondak VK, Taylor JM, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. *Ann Surg Oncol*. 2004;11(3):247-258. https://doi.org/10.1245/aso.2004.03.044

21. Kupferman ME, Kubik MW, Bradford CR, et al. The role of sentinel lymph node biopsy for thin cutaneous melanomas of the head and neck. *Am J Otolaryngol*. 2014;35(2):226-232. https://doi.org/10.1016/j.amjoto.2013.12.004
22. Balch CM, Thompson JF, Gershenwald JE, et al. Age as a predictor of sentinel node metastasis among patients with localized melanoma: an inverse correlation of melanoma mortality and incidence of sentinel node metastasis among young and old patients. *Ann Surg Oncol*. 2014;21(4):1075-1081. https://doi.org/10.1245/s10434-013-3464-x
23. Hanna AN, Sinnamon AJ, Roses RE, et al. Relationship between age and likelihood of lymph node metastases in patients with intermediate thickness melanoma (1.01-4.00 mm): a National Cancer Database study. *J Am Acad Dermatol*. 2019;80(2):433-440. https://doi.org/10.1016/j.jaad.2018.08.022
24. Ecker BL, Kaur A, Douglass SM, et al. Age-related changes in HAPLN1 increase lymphatic permeability and affect routes of melanoma metastasis. *Cancer Discov*. 2019;9(1):82-95. https://doi.org/10.1158/2159-8290.CD-18-0168
25. Naruns PL, Nizze JA, Cochran AJ, Lee MB, Morton DL. Recurrence potential of thin primary melanomas. *Cancer*. 1986;57(3):545-548. https://doi.org/10.1002/1097-0142(19860201)57:3<545::aid-cncr2820570323>3.0.co;2-k
26. Guitart J, Lowe L, Piepkorn M, et al. Histological characteristics of metastasizing thin melanomas: a case-control study of 43 cases. *Arch Dermatol*. 2002;138(5):603-608. https://doi.org/10.1001/archderm.138.5.603
27. Warycha MA, Zakrzewski J, Ni Q, et al. Meta-analysis of sentinel lymph node positivity in thin melanoma (<or=1 mm). *Cancer*. 2009;115(4):869-879. https://doi.org/10.1002/cncr.24044
28. de Rosa N, Lyman GH, Silbermins D, et al. Sentinel node biopsy for head and neck melanoma: a systematic review. *Otolaryngol HeadNeck Surg*. 2011;145(3):375-382. https://doi.org/10.1177/0194599811408554
29. Gibbs P, Robinson WA, Pearlman N, Raben D, Walsh P, Gonzalez R. Management of primary cutaneous melanoma of the head and neck: the University of Colorado experience and a review of the literature. *J Surg Oncol*. 2001;77(3):179-185; discussion 186-7. https://doi.org/10.1002/jso.1091
30. Fadaki N, Li R, Parrett B, et al. Is head and neck melanoma different from trunk and extremity melanomas with respect to sentinel lymph node status and clinical outcome? *Ann Surg Oncol*. 2013;20(9):3089-3097. https://doi.org/10.1245/s10434-013-2977-7
31. Keung EZ, Gershenwald JE. The eighth edition American Joint Committee on Cancer (AJCC) melanoma staging system: implications for melanoma treatment and care. *Expert Rev Anticancer Ther*. 2018;18(8):775-784. https://doi.org/10.1080/14737140.2018.1489246
32. Herbert G, Karakousis GC, Bartlett EK, et al. Transected thin melanoma: implications for sentinel lymph node staging. *J Surg Oncol*. 2018;117(4):567-571. https://doi.org/10.1002/jso.24930