Predictors of sentinel lymph node positivity in thin melanoma using the National Cancer Database

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Background: Sentinel lymph node biopsy (SLNB) specimens are often obtained from patients for further staging after these patients have undergone melanoma excision. Limited data regarding predictors of SLNB positivity in thin melanoma are available.

Objective: We sought to evaluate predictors of SLNB positivity in thin melanoma.

Methods: Patients with cutaneous melanoma with a Breslow thickness ≤1.00 mm who received a SLNB were identified from the National Cancer Database between 2004 and 2014 (n = 9186). Predictors of SLNB positivity were analyzed using logistic regression.

Results: In a multivariate analysis, patients <60 years of age ($P < .001$) and Breslow thickness >0.8 mm ($P = .03$) were at increased risk for positive sentinel lymph node (SLN). Moreover, on multivariate analysis, the presence of dermal mitoses increased the odds of SLN positivity by 95% (odds ratio [OR] 1.95 [95% confidence interval {CI} 1.53-2.5], $P < .001$), ulceration by 63% (OR 1.63 [95% CI 1.21-2.18], $P < .001$), and Clark level IV to V by 48% (OR 1.48 [95% CI 1.19-1.85]). Patients without ulceration but with dermal mitoses had 92% (OR 1.92 [95% CI 1.5-2.48], $P < .001$) increased SLN positivity.

Limitations: Limited survival data are available.

Conclusions: Younger age, a Breslow thickness >0.8 mm, the presence of dermal mitoses, ulceration, and Clark level IV to V are positive predictors of positive SLN. While the new American Joint Committee on Cancer system has removed dermal mitotic rate from staging, continued evaluation of dermal mitotic rate could be valuable for guiding surgical decision making about SLNB. (J Am Acad Dermatol 2019;80:441-7.)

Key words: Clark level; melanoma; mitotic rate; National Cancer Database; sentinel lymph node biopsy; thin.

Melanoma is the third most common cancer and the most deadly skin cancer.[1] The incidence rate of melanoma has increased 15-fold in the last 40 years, more than any other cancer.[1,2] Within melanoma, the highest rate of rise is seen in thin melanomas (≤1 mm), which account for approximately 70% of new melanoma cases in the United States.[3-5] Sentinel lymph node (SLN) positivity in patients with thin melanoma is approximately 5%.[5-7]

The current National Comprehensive Cancer Network (NCCN) guidelines based on American Joint Committee on Cancer (AJCC) 8th edition staging state that for melanomas <0.8 mm in thickness

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Funding sources: None.
Conflicts of interest: None disclosed.
Accepted for publication August 29, 2018.
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Published online September 18, 2018.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.08.051

without ulceration, wide local excision alone is recommended. For melanomas <0.8 mm with ulceration or between 0.8 mm and 1 mm in thickness with or without ulceration, consideration of a SLNB is recommended.[8] In addition, the AJCC 8th edition melanoma staging manual recently removed dermal mitoses entirely; however, the AJCC acknowledges the prognostic value of dermal mitoses and recommends continuing to report them. Under the new guidelines, stage T1a now consists of tumors <0.8 mm without ulceration, and T1b consists of tumors <0.8 mm with ulceration or ≥0.8 to 1.0 mm regardless of ulceration.[9]

A meta-analysis and various studies attempted to evaluate the numerous predictors of SLNB positivity in thin melanoma; however, these studies are largely single-institution and retrospective in nature. Some have focused on clinical characteristics like age and sex, while others focused on histopathologic characteristics, including ulceration, dermal mitotic rate, Clark level, and regression. Therefore, the criteria for SLNB in thin melanomas remain in question. To this end, the National Cancer Database (NCDB) was reviewed to evaluate the importance of dermal mitotic rate, Clark level, and other factors as predictors of SLN positivity in thin melanomas.

CAPSULE SUMMARY

- The presence of dermal mitoses and invasion to Clark level IV to V are important factors in predicting sentinel lymph node positivity, even when accounting for ulceration and Breslow thickness.
- Continued evaluation of possible predictors of sentinel lymph node positivity is necessary to establish clear guidelines when to proceed with obtaining a sentinel lymph node biopsy specimen in patients with thin melanomas.

METHODS AND MATERIALS

The NCDB is a joint, facility-based, clinical oncology database established by the Commission on Cancer and the American Cancer Society. This database contains patients ≥18 years of age who received all or part of their first course therapy at a reported cancer program, covering approximately 48.4% of all US melanoma cases.[10] The authors received these data from the NCDB in a deidentified file following previous approval from the Cleveland Clinic Institutional Review Board.[11]

Patients with a diagnosis of malignant melanoma from 2012 to 2014 were identified using *International Classification of Diseases* codes (Fig 1). Patients were excluded if the form of SLNB was nodal aspiration, if regional lymph nodes were removed but SLNB was not performed, or if no data on SLN outcome were available, leaving a cohort of 9186 patients.

Statistical methods

The main outcome was SLN status classified as positive or negative. Covariates included in the analysis were age, gender, Charlson/Deyo comorbidity score, tumor site, laterality, Breslow thickness, Clark level, histologic type, dermal mitotic rate, ulceration, and regression. A subgroup analysis was performed on patients with SLNB without ulceration. Age at diagnosis was categorized into <30, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥70 years. The Charlson/Deyo comorbidity score was designated as 0 if patients had no comorbidities, 1 if there was 1 comorbidity, and 2 if there were ≥2 comorbidities with comorbidities defined as previously published.[12] Tumor site was designated as head and neck, upper extremities, trunk, lower extremities, or not specified. Tumor laterality was left, right, midline, or unknown. Breslow thickness was categorized into <0.75 mm and ≥0.75 mm. According to the new AJCC guidelines, Breslow thickness will be rounded to the tenth of a millimeter, meaning that patients with a ≥0.75-mm thickness are now be in the 0.8-mm category. Clark level was grouped into I to III, IV to V, and unknown. Ulceration, regression, and dermal mitoses were classified as present, absent, or unknown.

Categorical variables are presented as frequencies and percentages, while continuous variables are presented as medians and interquartile ranges. Chi-square and *t* tests were used for inferential statistics. Analysis for the probability of SLN positivity was performed using multivariate logistic regression. The data were analyzed using R software (v 3.4.1, available at: http://www.R-project.org/).

RESULTS

Cohort characteristics

In total, 9186 patients with cutaneous melanoma who met the study criteria were identified. Of these, 457 (5%) had positive SLNB specimens and 8729 (95%) had negative SLNB specimens (Table I). Patients who were younger were more likely to have positive SLNB specimens, with a median age at diagnosis for positive SLN of 54 years (interquartile range 39-53 years) while for those with negative SLN the median was 57 years (range 44-67 years;

Abbreviations used:

AJCC:	American Joint Commission on Cancer
CI:	confidence interval
NCCN:	National Comprehensive Cancer Network
NCDB:	National Cancer Database
OR:	odds ratio
SLN:	sentinel lymph node
SLNB:	sentinel lymph node biopsy

$P = .002$). In the patients who received SLNB, highest SLN positivity was found in lower extremity melanoma (6.1%) followed by truncal melanoma (5.4%). No differences were found regarding gender ($P = .35$) or comorbidities ($P = .23$).

Predictors of SLN positivity

In a multivariate analysis, patients 40 to 49 years of age had 36% (OR 0.63 [95% CI 0.43-0.96], $P = .03$) lower odds of positive SLN compared with those <30 years of age, while those 50 to 59 years of age had 37% (OR 0.63 [95% CI 0.43-0.92], $P = .02$) lower odds, 60- to 69-year-olds had 48% (OR 0.52 [95% CI 0.35-0.77], $P < .001$) lower odds, and those ≥70 years of age had 44% (OR 0.56 [95% CI 0.38-0.84], $P = .005$) lower odds.

Male sex (OR 1.32 [95% CI 1.07-1.63], $P < .001$), a Breslow thickness between 0.8 and 1.0 mm (OR 1.24 [95% CI 1.04-1.81], $P = .03$), and Clark levels IV to V (OR 1.47 [95% CI 1.19-1.85], $P < .001$) were associated with higher odds of SLN positivity (Table II). In addition, the presence of ulceration increased the odds of SLN positivity by 63% (OR 1.63 [95% CI 1.21-2.18], $P < .001$). Finally, the presence of dermal mitoses increased SLN positivity by 95% (OR 1.95 [95% CI 1.53-2.5], $P < .001$). The number of comorbidities, location of tumor, laterality, and histologic type did not impact SLN positivity. In addition, we attempted to study predictors of SLN positivity among patients with eyelid melanoma; however, there were not enough cases for statistical analysis.

Predictors of SLN positivity in patients without ulceration

Next, we explored predictors of SLN positivity in patients without ulceration (n = 8207, 89%) in an effort to determine if there were any "high-risk" patient characteristics among this subgroup. There were 387 (4.7%) patients with positive SLN. Ages 50 to 59 (OR 0.65 [95% CI 0.44-0.98], $P = .04$), 60 to 69 (OR 0.54 [95% CI 0.35-0.82], $P = .004$), and ≥70 (OR 0.63 [95% CI 0.41-0.98], $P = .04$) were associated with reduced odds of SLN positivity. Breslow thickness between 0.8 and 1.0 mm and Clark levels IV to V were associated with a 34% increased odds of positive SLN (OR 1.34 [95% CI 1.09-1.65], $P < .01$ and OR 1.34 [95% CI 1.06-1.7], $P = .01$, respectively), while dermal mitoses increased the odds of SLN positivity by 92% (OR 1.92 [95% CI 1.5- 2.48]). Male sex, location of tumor, laterality, and histologic type did not impact SLN positivity. We were unable to identify a specific cut point at which SLN positivity increased or decreased in melanoma <0.8 mm thick, likely because of a low SLN positivity rate in melanomas of this thickness.

DISCUSSION

In this cohort, we found that men and patients <60 years of age with thin melanomas were more likely to have a positive SLN on multivariate analysis.

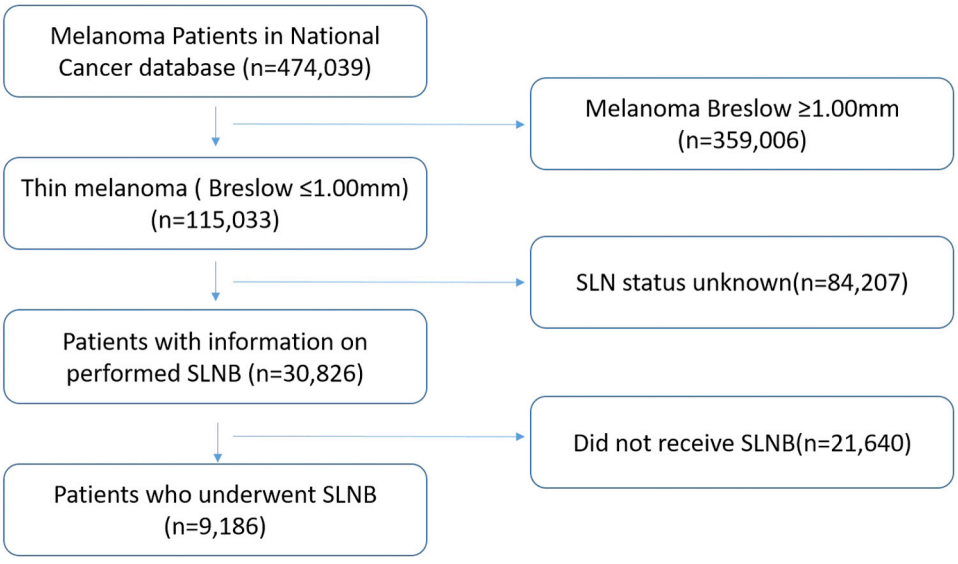

Fig 1. Cohort selection. *SLN*, Sentinel lymph node; *SLNB*, sentinel lymph node biopsy.

Table I. Demographic and tumor characteristics of patients based on sentinel lymph node status

	Sentinel lymph node status		
	Negative (n = 8729)	Positive (n = 457)	*P* value
Age, y, n (%)			.022
<30	562 (92.9)	43 (7.1)	
30-39	1129 (93.9)	73 (6.1)	
40-49	1183 (94.9)	63 (5.1)	
50-59	2004 (95.0)	105 (5.0)	
60-69	2116 (95.9)	91 (4.1)	
≥70	1735 (95.5)	82 (4.5)	
Male sex, n (%)	4572 (94.8)	250 (5.2)	.356
Charlson/Deyo comorbidity (%)			.234
0	7712 (95.0)	410 (5.0)	
1	881 (96.0)	37 (4.0)	
2	136 (93.2)	10 (6.8)	
Primary site, n (%)			.006
Head and neck	1397 (95.9)	60 (4.1)	
Upper extremities	2510 (95.9)	107 (4.1)	
Trunk	2955 (94.6)	168 (5.4)	
Lower extremities	1829 (93.9)	118 (6.1)	
Not specified	38 (90.5)	4 (9.5)	
Laterality, n (%)			.545
Left	3978 (94.7)	221 (5.3)	
Midline	1025 (95.5)	48 (4.5)	
Right	3623 (95.2)	181 (4.8)	
Unknown	103 (93.6)	7 (6.4)	
Histologic type, n (%)			.005
Acral lentiginous	91 (93.8)	6 (6.2)	
Lentigo maligna	361 (98.4)	6 (1.6)	
Nodular melanoma	271 (91.6)	25 (8.4)	
Other	203 (95.8)	9 (4.2)	
Superficial spreading	4022 (95.0)	210 (5.0)	
Unspecified	3781 (95.0)	201 (5.0)	
Breslow thickness 0.8-1.0 mm, n (%)	3807 (94.2)	235 (5.8)	.001
Clark level, n (%)			<.001
I-III	3774 (96.2)	149 (3.8)	
IV-V	3362 (93.9)	217 (6.1)	
Unknown	1593 (94.6)	91 (5.4)	
Ulceration, n (%)			.001
Absent	7820 (95.3)	387 (4.7)	
Present	671 (92.0)	58 (8.0)	
Unknown	238 (95.2)	12 (4.8)	
Dermal mitoses, n (%)			<.001
Absent	2986 (97.0)	92 (3.0)	
Present	4946 (93.8)	325 (6.2)	
Unknown	797 (95.2)	40 (4.8)	
Regression, n (%)			.518
Absent	5700 (95.1)	294 (4.9)	
Present	1241 (95.4)	60 (4.6)	
Unknown	1788 (94.6)	103 (5.4)	

Interestingly, the presence of dermal mitoses increased the odds of positive SLN by 95%, ulceration increased odds by 63%, and Clark level IV to V increased the odds by 47% when accounting for age and sex. In addition, patients without ulceration but with dermal mitoses had 92% increased odds for SLN positivity in multivariate analysis.

Our finding that patients <60 years of age with thin melanomas are more likely to have positive SLN are in accordance with a recent study evaluating regional lymph nodes in patients from the NCDB.[13] Several other studies have also found an inverse correlation between patient age and SLN positivity.[14-18]

Male sex was associated with a higher risk of SLN positivity among the NCDB cohort and some previous studies. Contrasting findings were found in several smaller studies.[18,19] Interestingly, the negative prognostic effects of male sex were not present in the subgroup of patients with ulceration. This finding could be related to the lower number of male patients without ulceration; having a larger cohort of males without ulceration could change these findings.

Clark level is historically considered an important prognostic factor in melanoma.[20] While the effects of Clark level are generally smaller than both ulceration and dermal mitoses, it may still have value for the decision-making process. A meta-analysis found that patients with Clark levels IV to V were at 84% increased odds of positive SLN (unadjusted OR 1.84 [95% CI 1.3-2.59]).[6] In addition, Bartlett et al[5] found an 8.2% rate of SLN positivity in thin melanomas among those with Clark level IV to V and a dermal mitotic rate ≥1.0 per mm^2. In contrast, Wong et al[19] and Mozzillo et al[21] found no association between Clark level and SLN positivity.

It is well known that dermal mitoses increase the risk of positive SLNB in thicker melanomas, but because of the prognostic value of Breslow thickness, management of these patients is not changed.[22] However, the importance of the dermal mitotic rate for the staging and prognosis of thin melanomas has been a point of contention, particularly because of the risks and costs involved with obtaining an SLNB specimen.[5,23]

In the NCDB cohort, dermal mitotic rate was an important predictive factor for SLNB positivity in thin melanomas. Several studies are in agreement with ours.[5,6,21,24-30] Across 5 unadjusted studies containing 1764 participants (OR 3.04 [95% CI 1.37-6.75])

Table II. Predictors of sentinel lymph node positivity*

Variable	OR (95%CI)
Age, y, n (%)	
<30	Reference
30-39	0.82 (0.56-1.22)
40-49	0.64 (0.43-0.96)
50-59	0.63 (0.43-0.92)
60-69	0.52 (0.35-0.77)
≥70	0.56 (0.38-0.84)
Sex	
Female	Reference
Male	1.32 (1.07-1.63)
Charlson/Deyo comorbidity	
0	Reference
1	0.85 (0.59-1.2)
2	1.66 (0.8-3.07)
Primary site	
Head and neck	Reference
Lower extremities	1.36 (0.94-1.98)
Not specified	2.79 (0.8-7.58)
Trunk	1.19 (0.86-1.67)
Upper extremities	0.89 (0.62-1.28)
Laterality	
Left	Reference
Midline	0.84 (0.57-1.2)
Right	0.89 (0.73-1.09)
Unknown	1.06 (0.44-2.2)
Histologic type	
Superficial spreading	Reference
Lentigo maligna	0.39 (0.15-0.82)
Acral lentiginous	1.41 (0.54-3.05)
Nodular melanoma	1.49 (0.94-2.28)
Other	0.83 (0.39-1.55)
Unspecified	1.03 (0.84-1.27)
Breslow thickness, mm	
<0.8	Reference
0.8-1.0	1.24 (1.02-1.51)
Clark level	
I-III	Reference
IV-V	1.48 (1.19-1.85)
Unknown	1.38 (1.04-1.81)
Ulceration	
Absent	Reference
Present	1.64 (1.21-2.18)
Unknown	0.94 (0.47-1.72)
Dermal mitoses	
Absent	Reference
Present	1.95 (1.54-2.49)
Unknown	1.47 (0.96-2.2)
Regression	
Absent	Reference
Present	1.01 (0.75-1.34)
Unknown	1.15 (0.9-1.46)

CI, Confidence interval; *OR*, odds ratio.
*Model is adjusted for age, sex, Charlson/Deyo comorbidity, primary site, laterality, histologic type, Breslow thickness, Clark level, ulceration, dermal mitoses, and regression.

and 2 adjusted studies consisting of 1190 participants (OR 6.64 [95% CI 2.77-15.9]), dermal mitotic rate ≥1/mm^2 was associated with a higher rate of SLN positivity.[6] Most recently, a study using multivariate analysis to examine the relationship between dermal mitotic rate and nodal positivity with NCDB data also confirmed our findings; however, this study did not focus on SLN.[31] In addition, an analysis of dermal mitotic rate ≤2/mm^2, 3-5/mm^2, and ≥6/mm^2 demonstrated that those with thin melanomas and a higher dermal mitotic rate are at increased risk for positive SLN; however, we were unable to confirm these findings because of the limited availability of continuous dermal mitotic rate data in the NCDB.[25]

However, some studies conflict with ours.[6,16-19,32-36] Among the largest studies is Han et al,[33] which concluded that mitotic rate was not predictive of SLN positivity in a cohort of 1250 patients with thin melanomas after adjusting for Breslow thickness, ulceration, Clark level, and regression. Similarly, Speijers et al[18] reported that in a cohort of 453 patients, dermal mitotic rate was not an independent prognostic factor for SLN positivity in melanoma after adjusting for age, Breslow thickness, and ulceration. More recently, in a cohort of 512 patients, Durham et al[17] found that presence of mitoses was not associated with higher rates of SLN positivity after adjusting for age, Breslow thickness, and ulceration. Furthermore, Wat et al[32] concluded that dermal mitotic rate was not associated with positive SLN in thin melanomas, and that as Breslow thickness decreases so does the effect of dermal mitotic rate on SLN positivity. However, it is important to note that the majority of studies both confirming and conflicting with our findings had a smaller sample size, and were retrospective, single-institution studies, with many reporting only univariate analysis.

This study is not without limitations. First, because it is a cancer registry, there are potential problems with underreporting and the miscoding of variables that could affect the accuracy of these findings. Indeed, SLNB was underreported before 2012, leading to exclusion of these data from the dataset.[11] Next, NCDB is hospital-based rather than population-based, potentially biasing the data toward people who are more likely to receive care at larger clinical centers, which may impact the decision to proceed with SLNB. In addition, it is possible that patients whose melanomas lack high-risk features (ie, dermal mitoses and ulceration) were not seen at Commission on Cancer reporting facilities. Lastly, the database contains only 3 years of overall survival data, limiting our ability to examine the impact of positive SLNB on survival among this cohort.

From a dermatopathology standpoint, interobserver variability for histopathologic predictors is important. Firstly, Spatz et al[37] demonstrated that interobserver reproducibility for ulceration was poor; however, later studies demonstrated excellent concordance and interobserver reliability.[38,39] These findings are potentially related to a learning curve to distinguish traumatic from tumoral ulceration as ulceration became part of the AJCC staging system only 3 years before the publication of Spatz et al.[37] Next, Clark level demonstrates good concordance and moderate reproducibility, with levels IV to V having better reproducibility.[38,39] Finally, there is an excellent interobserver reliability and concordance for tumor mitotic rate, with discordance more likely in ulcerated melanomas.[39]

Most newly diagnosed melanomas are thin, making it critical to understand which clinical and histopathologic factors predispose to a positive SLN. Various studies have explored predictors of positive SLN in thin melanoma; however, because of the relative rarity of positive SLNs in this group and small sample sizes, these studies have yielded inconsistent results. While the new AJCC guidelines have removed dermal mitoses from the staging of thin melanoma, our data indicate that the presence of dermal mitoses increases the chance for a positive SLNB. In addition, a recent article by Mandala et al[40] shows that dermal mitotic rate is not only important for SLN positivity in thin melanomas, but for any melanoma with a Breslow thickness >1.0 mm.

In conclusion, we found that male sex, age <60 years, ulceration, Clark level IV to V, the presence of dermal mitoses, and Breslow thickness between 0.8 to 1.00 mm are significant predictors for SLN positivity in thin melanomas. Because the NCDB began releasing SLNB data in 2012, there are only about 3 years of follow-up data available, making it difficult to form conclusions about the effects of mitoses and Clark level on survival data when adjusting for SLN positivity in this cohort. We routinely perform SLNB for thin and thick melanomas according to the criteria set by the NCCN. While the new AJCC guidelines no longer include dermal mitoses in staging, we recommend taking it into consideration when deciding whether to proceed with SLNB. In addition, Clark level IV to V should also be taken into consideration when deciding to pursue SLNB. We recommend that dermatopathologists continue to evaluate and report dermal mitotic rate and Clark level because they may be critical to establishing clear recommendations for SLNB in thin melanoma. Finally, guidelines for performance of SLNB in more unusual sites such as eyelids are lacking, and future multi-institutional and population studies are necessary.[41]

We thank Katherine Glass for assistance with accessing data.

REFERENCES

1. Weinstock MA. Epidemiology, etiology, and control of melanoma. *Med Health R I*. 2001;84:234-236.
2. American Cancer Society website. Cancer facts and figures 2017. Available at: https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html. Accessed October 2, 2018.
3. National Cancer Institute website. SEER cancer statistics review, 1975-2013. Available at: https://seer.cancer.gov/archive/csr/1975_2013/. Accessed October 2, 2018.
4. Gimotty PA, Guerry D, Ming ME, et al. Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. *J Clin Oncol*. 2004;22:3668-3676.
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*. 2013;21:643-649.
6. Cordeiro E, Gervais MK, Shah PS, Look Hong NJ, Wright FC. Sentinel lymph node biopsy in thin cutaneous melanoma: a systematic review and meta-analysis. *Ann Surg Oncol*. 2016;23:4178-4188.
7. Warycha MA, Zakrzewski J, Ni Q, et al. Meta-analysis of sentinel lymph node positivity in thin melanoma (<or=1 mm). *Cancer*. 2009;115:869-879.
8. National Comprehensive Cancer Network website. NCCN guidelines for patients. Melanoma. Available at: https://www.nccn.org/patients/guidelines/melanoma/files/assets/common/downloads/files/melanoma.pdf. Accessed October 2, 2018.
9. American Joint Committee on Cancer. *AJCC Cancer Staging Manual*. 8th ed. Springer International Publishing; 2017.
10. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Ann Surg Oncol*. 2008;15:683-690.
11. National Cancer Institute website. National Cancer Database. Scope of regional lymph node surgery. Available at: https://seer.cancer.gov/seerstat/variables/seer/regional_ln/. Accessed October 2, 2018.
12. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173:676-682.
13. Sinnamon AJ, Neuwirth MG, Yalamanchi P, et al. Association between patient age and lymph node positivity in thin melanoma. *JAMA Dermatol*. 2017;153:866-873.
14. 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;21:1075-1081.
15. Cavanaugh-Hussey MW, Mu EW, Kang S, Balch CM, Wang T. Older age is associated with a higher incidence of melanoma death but a lower incidence of sentinel lymph node metastasis in the SEER databases (2003-2011). *Ann Surg Oncol*. 2015;22:2120-2126.
16. Venna SS, Thummala S, Nosrati M, et al. Analysis of sentinel lymph node positivity in patients with thin primary melanoma. *J Am Acad Dermatol*. 2013;68:560-567.

17. 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;116:1185-1192.
18. Speijers MJ, Bastiaannet E, Sloot S, Suurmeijer AJ, Hoekstra HJ. Tumor mitotic rate added to the equation: melanoma prognostic factors changed? A single-institution database study on the prognostic value of tumor mitotic rate for sentinel lymph node status and survival of cutaneous melanoma patients. *Ann Surg Oncol*. 2015;22:2978-2987.
19. Wong SL, Brady MS, Busam KJ, Coit DG. Results of sentinel lymph node biopsy in patients with thin melanoma. *Ann Surg Oncol*. 2006;13:302-309.
20. Sekula-Gibbs SA, Shearer MA. Sentinel node biopsy should be offered in thin melanoma with mitotic rate greater than one. *Dermatol Surg*. 2011;37:1080-1088.
21. Mozzillo N, Pennacchioli E, Gandini S, et al. Sentinel node biopsy in thin and thick melanoma. *Ann Surg Oncol*. 2013;20:2780-2786.
22. Mahiques Santos L, Oliver Martinez V, Alegre de Miquel V. Sentinel lymph node status in melanoma: prognostic value in a tertiary hospital and correlation with mitotic activity. *Actas Dermosifiliogr*. 2014;105:60-68.
23. Kirkland EB, Zitelli JA. Mitotic rate for thin melanomas: should a single mitotic figure warrant a sentinel lymph node biopsy? *Dermatol Surg*. 2014;40:937-945.
24. Kesmodel SB, Karakousis GC, Botbyl JD, et al. Mitotic rate as a predictor of sentinel lymph node positivity in patients with thin melanomas. *Ann Surg Oncol*. 2005;12:449-458.
25. Ranieri JM, Wagner JD, Wenck S, Johnson CS, Coleman JJ 3rd. The prognostic importance of sentinel lymph node biopsy in thin melanoma. *Ann Surg Oncol*. 2006;13:927-932.
26. Donizy P, Kaczorowski M, Leskiewicz M, et al. Mitotic rate is a more reliable unfavorable prognosticator than ulceration for early cutaneous melanoma: a 5-year survival analysis. *Oncol Rep*. 2014;32:2735-2743.
27. Tejera-Vaquerizo A, Perez-Cabello G, Marinez-Leborans L, et al. Is mitotic rate still useful in the management of patients with thin melanoma? *J Eur Acad Dermatol Venereol*. 2017;31:2025-2029.
28. Mori M, Sugiura M, Kono M, et al. Clinicopathologic analysis of 66 Japanese thin melanomas with metastasis of sentinel or regional lymph node. *J Cutan Pathol*. 2013;40:1027-1034.
29. Oliveira Filho RS, Ferreira LM, Biasi LJ, Enokihara MM, Paiva GR, Wagner J. Vertical growth phase and positive sentinel node in thin melanoma. *Braz J Med Biol Res*. 2003;36:347-350.
30. 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;11:247-258.
31. Wheless L, Isom CA, Hooks MA, Kauffmann RM. Mitotic rate is associated with positive lymph nodes in thin melanomas. *J Am Acad Dermatol*. 2018;78:935-941.
32. Wat H, Senthilselvan A, Salopek TG. A retrospective, multicenter analysis of the predictive value of mitotic rate for sentinel lymph node (SLN) positivity in thin melanomas. *J Am Acad Dermatol*. 2016;74:94-101.
33. Han D, Zager JS, Shyr Y, et al. Clinicopathologic predictors of sentinel lymph node metastasis in thin melanoma. *J Clin Oncol*. 2013;31:4387-4393.
34. Cooper C, Wayne JD, Damstetter EM, et al. A 10-year, single-institution analysis of clinicopathologic features and sentinel lymph node biopsy in thin melanomas. *J Am Acad Dermatol*. 2013;69:693-699.
35. Mitteldorf C, Bertsch HP, Jung K, et al. Sentinel node biopsy improves prognostic stratification in patients with thin (pT1) melanomas and an additional risk factor. *Ann Surg Oncol*. 2014;21:2252-2258.
36. Murali R, Haydu LE, Quinn MJ, et al. Sentinel lymph node biopsy in patients with thin primary cutaneous melanoma. *Ann Surg*. 2012;255:128-133.
37. Spatz A, Cook MG, Elder DE, Piepkorn M, Ruiter DJ, Barnhill RL. Interobserver reproducibility of ulceration assessment in primary cutaneous melanomas. *Eur J Cancer*. 2003;39:1861-1865.
38. Murali R, Hughes MT, Fitzgerald P, Thompson JF, Scolyer RA. Interobserver variation in the histopathologic reporting of key prognostic parameters, particularly Clark level, affects pathologic staging of primary cutaneous melanoma. *Ann Surg*. 2009;249:641-647.
39. Niebling MG, Haydu LE, Karim RZ, Thompson JF, Scolyer RA. Reproducibility of AJCC staging parameters in primary cutaneous melanoma: an analysis of 4,924 cases. *Ann Surg Oncol*. 2013;20:3969-3975.
40. Mandala M, Galli F, Cattaneo L, et al. Mitotic rate correlates with sentinel lymph node status and outcome in cutaneous melanoma greater than 1 millimeter in thickness: a multi-institutional study of 1524 cases. *J Am Acad Dermatol*. 2017;76:264-273.e2.
41. Pfeiffer ML, Savar A, Esmaeli B. Sentinel lymph node biopsy for eyelid and conjunctival tumors: what have we learned in the past decade? *Ophthalmic Plast Reconstr Surg*. 2013;29:57-62.