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

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Background: There is large variability in the risk of sentinel lymph node (SLN) positivity among patients with intermediate thickness melanoma (ITM), with a subgroup of patients exhibiting a low risk of nodal disease.

Objective: To identify a group of patients with ITM for whom the risk of nodal disease is low.

Methods: A retrospective cohort of patients with ITM who underwent wide excision and nodal evaluation from 2010 to 2013 was identified by using the National Cancer Database and analyzed for the presence of nodal disease. Classification and regression tree analysis identified the most important factors used in a model to identify groups at low risk of SLN positivity.

Results: Of 23,440 patients, 14.7% were found to have nodal metastasis. On classification and regression tree analysis, patients older than 55 years without lymphovascular invasion and with a lesion thickness less than 1.7 mm had an SLN positivity rate of 4.9%. A model using age and thickness in nonulcerated patients identified a low-risk subgroup with a corresponding SLN positivity rate of 4.7%.

Limitations: This was a retrospective study, and the model developed requires prospective validation.

Conclusions: Patient age is an important factor in estimating risk of SLN in patients with ITM and may help identify patients without ulceration who may be safely spared an SLN biopsy. (J Am Acad Dermatol 2019;80:433-40.)

Key words: age; intermediate thickness; melanoma; risk; sentinel lymph node.

For patients with clinically localized melanoma, assessment of metastasis to regional lymph nodes by using sentinel lymph node (SLN) biopsy is an important factor for staging, prognosis, and subsequent treatment.[1-5] Published guidelines from the National Comprehensive Cancer Network, as well as from the Society of Surgical Oncology and American Society of Clinical Oncology, recommend

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Funding sources: None.

Disclosure: Dr Elder is a consultant for SciBase and Myriad Genetics. Dr Hanna, Dr Sinnamon, Dr Roses, Dr Kelz, Dr Xu, Dr Pockaj, Dr Zager, Dr Fraker, and Dr Karakousis have no conflicts of interest to disclose.

Presented as a plenary presentation at the 13th Annual Academic Surgical Congress, Jacksonville, FL, January 30 to February 1, 2017.

Accepted for publication August 19, 2018.

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Published online August 27, 2018.

0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.08.022

routine SLN biopsy for all intermediate thickness (T2 and T3) melanomas.[6] Deeper T4 lesions, which are deemed at higher risk to yield nodal metastasis, also generally justify consideration of the procedure for staging and regional control of disease.[7] Numerous studies have reported clinical and pathologic factors associated with SLN positivity.[8-13] Among these factors, tumor thickness has consistently been among those most strongly associated with SLN positivity, with lesions more than 1 mm in thickness carrying an appreciable risk of regional disease.[4,5]

Although there is no defined threshold rate of SLN positivity to justify recommendation of the procedure, a commonly accepted implicit rate of 5% is used in clinical practice. This rate accounts for what is believed to be a clinically significant rate, the morbidity of the procedure, and its false-negative rate, which is estimated to be approximately 5%.[14-17] Although the overall rate of SLN positivity in melanoma less than 1 mm in thickness is less than 5%, SLN biopsy is considered in those patients with higher-risk pathologic features such as a thickness of at least 0.8 mm or the presence of ulceration, in which case the risk of nodal metastasis increases.[6,16]

Among patients with intermediate thickness melanoma (ITM), who as a group demonstrate an SLN positivity rate of 15% to 20%, there are currently no risk modifiers that influence the recommendation for SLN biopsy as there are for T1 lesions.[18-20] We have previously shown by using institutional data, however, that there exists significant heterogeneity in risk of SLN metastasis in this group of patients. Specifically, there may be subgroups of patients with ITM (based on age and thickness) with an SLN positivity rate less than 5%, for which consistent application of SLN would not be justified.[21] In this study, we have used a large national database to identify a subgroup of patients with a low risk of SLN positivity (< 5% risk), which is similar to that in patients with thin melanomas, for whom SLN biopsy is not routinely recommended. These data could help clinicians and patients to make a more informed collective decision about the utility of SLN biopsy on an individual basis.

CAPSULE SUMMARY

- Risk of nodal disease among intermediate thickness melanoma is variable, with this study supporting the important role of age in the risk of nodal metastasis.
- Select older patients may be safely spared a sentinel lymph node biopsy.

METHODS

The patient data originated from the melanoma National Cancer Database (NCDB). The NCDB is a program supported by both the American College of Surgeon's Commission on Cancer and the American Cancer Society that gathers hospital registry data for specific types of cancer from hospitals accredited by the Commission on Cancer. This database represents approximately 70% of all cancers diagnosed in the United States but accounts for only one-third of all hospitals.[22,23] This study, which was conducted by using de-identified data, was submitted for review to the University of Pennsylvania Institutional Review Board and deemed exempt from further ongoing oversight.

Patients selected for inclusion in the study were at least 18 years old and underwent wide local excision of clinically localized cutaneous melanoma with lymph node evaluation. The Breslow thickness of lesions was greater than 1.0 mm and up to and including 4.0 mm. Only patients whose melanoma was diagnosed from 2010 to 2013 were included after the updates for the seventh edition of the American Join Commission on Cancer staging system. Patients with distant metastatic disease, death within 90 days, clinically evident nodes, or internal inconsistency in recorded data regarding pathologic variables and/or staging were excluded.

The patient characteristics used in the analysis included age, sex, and Charlson/Deyo score, a comorbidity index dichotomized to 0 or 1. The tumor variables analyzed included melanoma thickness, Clark level, presence or absence of mitoses, ulceration, lymphovascular invasion (LVI), and the anatomic site of melanoma (which was categorized as head and/or neck, upper extremity and/or shoulder, trunk, and lower extremity and/or hip). The primary outcome was the presence or absence of lymph node metastasis. Because only patients with local disease and nodal evaluation were included in the cohort, SLN status was considered positive if there was at least 1 positive lymph node regardless of the number of lymph nodes evaluated.

Descriptive statistics comparing node-positive and node-negative patients were performed by using frequencies for categoric variables and medians for continuous variables. Univariate and multivariable logistic regression analyses were used to identify factors significantly associated with SLN metastasis. Classification and regression tree analysis (CART) was then used to identify the most significant

Abbreviations used:

CART: classification and regression tree
CI: confidence interval
ITM: intermediate thickness melanoma
LVI: lymphovascular invasion
NCDB: National Cancer Database
OR: odds ratio
RR: relative risk
SLN: sentinel lymph node

factors for risk stratification of the study cohort. The Gini rule was used for cross validation with prior probabilities proportional to the observed data frequencies and 0 or 1 loss functions utilized. Terminal nodes were set to have a sample size of at least 1000 subjects.

To develop a clinically relevant and useful model, a reduced regression using the important factors identified in CART analysis was performed specifically for patients without ulceration. Relative risk ratios (RRs) were estimated from the resulting odds ratios (ORs) by using the relation

$$RR = \frac{OR}{(1 - P_0) + (P_0 \times OR)},$$

where P_0 is the incidence of the outcome (SLN positivity) among the reference group, which was calculated from the intercept of the reduced regression.[24] Keeping SLN positivity risk constant at 5% allowed for the construction of a simple linear function using the variables included in the CART analysis, which was then approximated to a simple model. All statistical analyses were performed with R software (R Foundation for Statistical Computing, Vienna, Austria), and because of the large cohort size, only logistical regression *P* values less than .0001 were considered statistically significant.[25,26]

Table I. Patient characteristics

	Cohort, n (%)		
Variable	**Overall (N = 23,440)**	**Node-negative (n = 19,999)**	**Node-positive (n = 3441)**
Median age, y (IQR)	62 (51-72)	63 (51-73)	57 (46-68)
Sex			
Male	14,050 (59.9)	11,964 (59.8)	2086 (60.6)
Female	9390 (40.1)	8035 (40.2)	1355 (39.4)
Site			
Head and neck	4388 (18.7)	3908 (19.5)	480 (13.9)
Lower extremity or hip	4797 (20.5)	3922 (19.6)	875 (25.4)
Trunk	7545 (32.2)	6157 (30.8)	1388 (40.3)
Upper extremity or shoulder	6710 (28.6)	6012 (30.1)	698 (20.4)
Charlson/Deyo score			
0	20,028 (85.4)	17,096 (85.5)	2932 (85.2)
≥1	3412 (14.6)	2903 (14.5)	509 (14.8)
Median thickness, mm (IQR)	1.66 (1.25-2.40)	1.60 (1.22-2.30)	2.05 (1.50-2.80)
Clark level			
II	579 (2.4)	527 (2.6)	52 (1.5)
III	2766 (11.8)	2426 (12.2)	340 (9.9)
IV/V	16,093 (68.7)	13,580 (67.9)	2513 (73.0)
Unknown	4002 (17.1)	3466 (17.3)	536 (15.6)
Mitoses			
Absent	3226 (13.8)	2942 (14.7)	284 (8.3)
Present	16,551 (70.6)	13,810 (69.1)	2741 (79.7)
Unknown	3663 (15.6)	3247 (16.2)	416 (12.0)
Ulceration			
Absent	16,811 (71.7)	14,681 (73.4)	2130 (61.9)
Present	6140 (26.2)	4875 (24.4)	1265 (36.8)
Unknown	489 (2.1)	433 (2.2)	46 (1.3)
Lymphovascular invasion			
Absent	17,580 (75.0)	15,211 (76.1)	2369 (68.8)
Present	1029 (4.4)	625 (3.1)	404 (11.7)
Unknown	4831 (20.6)	4163 (20.8)	668 (19.5)

IQR, Interquartile range.

Table II. Univariate and multivariable predictors of SLN positivity

	Univariate model		Multivariable model	
Variable	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
Age, 10 y*	0.83 (0.81-0.84)	<.0001	0.80 (0.78-0.83)	<.0001
Sex				
Male	1 (reference)		1 (reference)	
Female	0.97 (0.90-1.04)	.38	0.857 (0.79-0.93)	.0002
Site				
Head and neck	1 (reference)		1 (reference)	
Lower extremity or hip	1.82 (1.61-2.05)	<.0001	1.81 (1.59-2.06)	<.0001
Trunk	1.84 (1.64-2.05)	<.0001	1.74 (1.55-1.95)	<.0001
Upper extremity or shoulder	0.95 (0.83-1.07)	.37	0.98 (0.86-1.11)	.71
Charlson/Deyo score				
0	1 (reference)		1 (reference)	
≥1	1.02 (0.92-1.13)	.67	1.14 (1.02-1.27)	.02
Thickness, mm	1.65 (1.58-1.72)	<.0001	1.56 (1.48-1.63)	<.0001
Clark level				
II	1 (reference)		1 (reference)	
III	1.42 (1.05-1.93)	.03	1.41 (1.02-1.87)	.03
IV/V	1.88 (1.16-2.34)	.0002	1.49 (1.03-1.94)	.009
Unknown	1.57 (1.16-2.11)	.003	1.35 (0.99-1.84)	.06
Mitoses				
Absent	1 (reference)		1 (reference)	
Present	2.06 (1.81-2.34)	<.0001	1.63 (1.42-1.86)	<.0001
Unknown	1.33 (1.13-1.56)	.0004	1.19 (1.01-1.42)	.04
Ulceration				
Absent	1 (reference)		1 (reference)	
Present	1.79 (1.66-1.93)	<.0001	1.35 (1.24-1.47)	<.0001
Unknown	0.72 (0.53-0.97)	.03	0.82 (0.60-1.14)	.25
Lymphovascular invasion				
Absent	1 (reference)		1 (reference)	
Present	4.15 (3.64-4.74)	<.0001	3.18 (2.77-3.66)	<.0001
Unknown	1.03 (0.94-1.13)	.53	1.08 (0.98-1.20)	.12

CI, Confidence interval; *OR*, odds ratio; *SLN*, sentinel lymph node.
*OR corresponds to every increment of 10 years.

RESULTS

Baseline characteristics

A total of 28,924 patients with ITM underwent wide local excision with nodal evaluation between 2010 and 2013. About 10% of these patients were excluded from our cohort because of clinically evident nodes or metastatic disease. Another 991 patients were excluded because they were younger than 18 or older than 90 years. Finally, 1570 patients were excluded because of internally inconsistent pathologic data. Therefore, a total of 23,440 patients met inclusion criteria for the study. Patient and pathologic characteristics for the entire cohort, as well as only those with and without lymph node positivity, are displayed in Table I. LVI, mitoses, and ulceration status were unknown in 20.6%, 15.6%, and 2.1% of the cohort, respectively. Among those with known pathologic variables, 82.8% of tumors were Clark level IV or V, with mitoses present in 16,551 patients (83.7%), ulceration present in 6140 patients (26.8%), and LVI present in 1029 patients (5.5%).

Predictors of regional lymph node metastasis

A total of 3441 patients were found to have lymph node metastasis, corresponding to a rate of 14.7% (95% confidence interval [CI], 14.2%-15.1%). Patient and pathologic factors associated with lymph node positivity are displayed in Table II. On multivariable regression performed only in the subgroup of patients with complete pathologic information, the same factors were found to be statistically significant in their association with similar effect sizes (data not shown).

CART analysis

A classification and regression tree algorithm was developed to identify important subgroups of

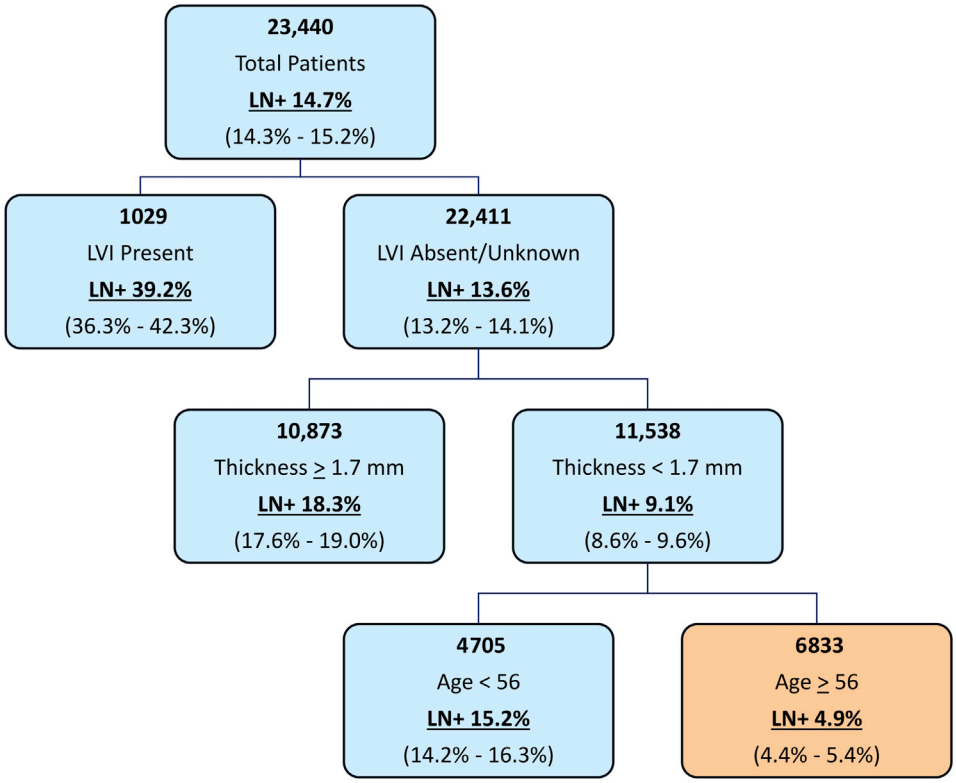

Fig 1. Classification and regression tree analysis for risk of lymph node (LN) positivity. A recursive partitioning algorithm identified patient age and tumor thickness as important determinants of nodal positivity in patients without lymphovascular invasion (LVI). Numbers in parentheses are 95% confidence intervals. *LN+*, Positive lymph node.

patients associated with lymph node positivity (Fig 1). Patients who were older than 55 years, with absent LVI, and with a tumor thickness less than 1.7 mm, which represented more than 25% of the entire cohort (n = 6833), were noted to have an SLN positivity rate of 4.9% (95% CI, 4.4%-5.4%). This cohort corresponded to 53% of all patients older than 55 years and 75% of all patients with a tumor thickness less than 1.7 mm. When the CART analysis was performed in those patients with complete pathologic information, the same splits were generated, with a resulting SLN positivity rate of 5.1% (95% CI, 4.5%-5.8%) in 4901 patients older than 55 years and with a tumor thickness less than 1.7 mm.

Lymph node metastasis risk model formulation and application

On the basis of the results of the CART analysis, the variables age and thickness were used for development of a predictive model for selecting patients with a low risk of SLN positivity, defined as those with lower than a 5% rate of nodal metastasis. CART analysis performed in only ulcerated patients failed to demonstrate any clinically significant subgroups with rates of lymph node metastasis lower than 10%. Therefore, only patients with nonulcerated lesions were included in the model.

The reduced regression from which the model was derived is shown in Table III. Relative risk was estimated from these ORs by using the formula previously described, with use of the intercept of the reduced regression as P_o. The calculated RRs derived from the ORs are also displayed in Table III. With use of the equation

$$risk > P_0 \times \left(1.5^{thickness}\right) \times \left(0.81^{age/10}\right),$$

and substitution of the desired target risk of 0.05 (or 5%), an equation relating the various age and thickness combinations that would be expected to yield a rate of SLN positivity of 5% or lower can be derived. This equation is

$$thickness < (age \times 0.052) - 1.63,$$

which can be approximated to the equation

$$thickness < (age \times 0.05) - 1.5$$

The clinical interpretation of this equation for patients with ITM without ulceration is as follows:

Table III. Reduced regression of nonulcerated patients with use of age and thickness

Variable	OR (95% CI)	*P* value	Risk ratio*
Intercept	0.09 (0.07-0.11)	<.0001	0.10
Age, 10 y†	0.79 (0.78-0.81)	<.0001	0.81
Thickness, mm	1.58 (1.51-1.66)	<.0001	1.50

CI, Confidence interval; *OR*, odds ratio.
*Please see manuscript text for calculation of risk ratio.
†OR corresponds to every increment of 10 years.

starting at age 50, each additional 10 years of age permits an additional 0.5 mm of tumor thickness greater than 1.0 mm while still maintaining a lymph node metastasis rate of 5% or lower. As shown in Fig 2, out of 16,811 patients with absent ulceration, 7540 patients would be classified into the low-risk category group, with 355 having a lymph node metastasis, resulting in a rate of lymph node positivity of 4.7% (95% CI 4.2%-5.2%). Notably, this low-risk subgroup comprised 47% of all patients older than 55 years in the study cohort. There was no significant difference in the distribution of melanomas based on anatomic site within the low-risk subgroup and the remaining cohort. In all, 46% of the low-risk subgroup had melanomas in a location in the upper extremities, shoulder, head, or neck, whereas 47% of the remaining cohort had melanomas in these locations.

DISCUSSION

Concordant with data from the ITM population in the Multicenter Selective Lymphadenectomy Trial-1 trial, as well as with data from previously published retrospective series, the overall rate of SLN positivity in our cohort with ITM was approximately 15%. Additionally, factors associated with SLN positivity in our study, such as younger age, increased thickness, Clark level, mitoses, LVI, and ulceration, have been previously reported.[8-13]

Using CART and multivariable logistic analysis, we demonstrated that the risk of regional lymph node positivity is heterogeneous among various subgroups of the cohort with ITM, ranging from 40% SLN positivity to less than 5% SLN positivity. Notably, ulceration was not identified in the initial splits on the CART analysis, likely because there is less heterogeneity in the risk of SLN metastasis among patients with ulcerated lesions.

In a similar analysis performed on the subgroup of patients with melanomas between 1 and 2 mm in thickness who participated in the Sunbelt Melanoma Trial, Mays et al[27] found the rate of SLN positivity to be 8.7% in patients with melanomas less than 1.6 mm thick versus 19.3% in those with melanomas between 1.6 and 2.0 mm thick. Although the authors concluded that SLN biopsy should be recommend for all melanomas between 1 and 2 mm thick, they did identify a subgroup in which SLN biopsy may be selectively considered. Patients who were older than 59 years and had absent LVI with a tumor thickness less than 1.6 mm had a rate of SLN positivity of 4.9%.

In a previously published work using our own institutional database, an SLN positivity risk less than 5% was identified in select patients with intermediate thickness melanoma who were either age 60 years or older or had lesions with a thickness less than 1.5 mm.[21] These results are congruent with those of the current study, in which a lesion thickness less than 1.7 mm and patient age older than 55 years in lesions with absent LVI yielded a rate of SLN positivity of 4.9%. One in every 2 patients who were older than 55 years was part of this low-risk cohort, as were 3 out of every 4 patients with a tumor thickness less than 1.7 mm.

Different studies will generate different cutoff points in identifying low-risk populations based on variable methodology and patient cohorts. We sought to create a model assessing risk for SLN positivity that would provide additional granularity by considering patient age and thickness as continuous variables. The model focused on patients with lesions that were nonulcerated because the presence of ulceration was found to confer a significant risk of nodal metastasis, even among older patients and intermediate thickness lesions with lower depth. These results suggest that the presence of ulceration in itself is an appropriately concerning finding in the pathologic evaluation of ITM and should remain a strong indication to pursue SLN biopsy irrespective of age or thickness.

The model developed to identify nonulcerated patients that could potentially be spared an SLN biopsy indicates that starting at age 50, for each additional decade of life, an additional 0.5 mm of lesion thickness greater than 1 mm would be permissible while still maintaining a risk of lymph node metastasis lower than 5%. If the model is applied to our cohort, nearly a third of all patients (32%) would have an estimated rate of SLN positivity lower than 5%. More importantly, 47% of all patients older than 55 years would have an expected risk of SLN positivity of 5% or lower.

Although this model requires rigorous and prospective validation before being used clinically, the results of this study in combination with the findings of prior published studies nonetheless argue for consideration of *selective*, rather than *routine*, application of SLN biopsy in patients with ITM, and

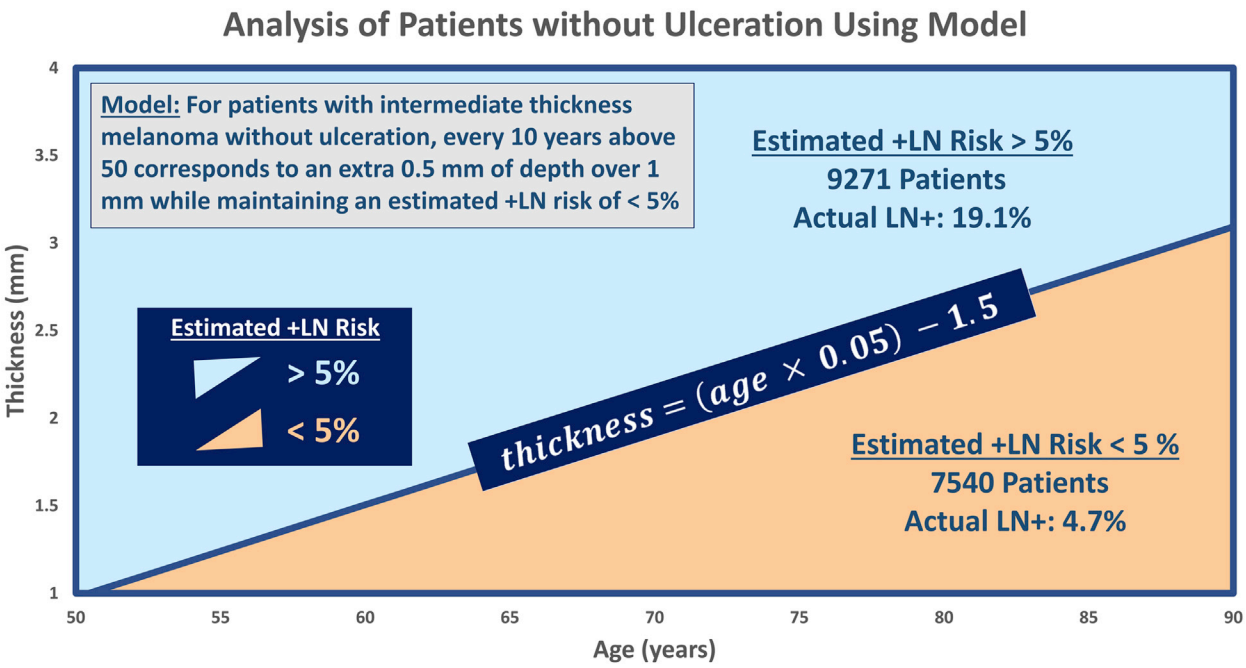

Fig 2. Application of model and corresponding lymph node (LN) positivity rates. A graphic representation of the model, with corresponding LN positivity rates for those patients without ulceration who had an estimated risk of LN positivity less than 5% and greater than 5%. *LN+*, Positive lymph node.

specifically, for consideration of patient age in addition to thickness during the decision-making process. If clinical guidelines are developed on the basis of the anticipated risk of lymph node metastasis (which is why early thin lesions are not considered for SLN biopsy), these same risk assessments should be consistently applied across the spectrum of melanoma thickness, accounting for other important risk modifiers. The present study adds to the existing evidence that patient age appears to be 1 such important risk modifier that may be used in conjunction with lesion thickness in selection of patients for SLN biopsy.

Although the NCDB offers the advantage of a large sample size and its associated increase in statistical power, the current study has several limitations that are worth noting. The first is its retrospective nature and the questionable utility of a model created with a retrospective data set, further emphasizing the need for vigorous prospective validation. Second, the NCDB is created from a hospital-based sample and not a population-based sample such as the Surveillance, Epidemiology, and End Results registry, as a result of which it may not be as generalizable to the entire population, as the NCDB represents only about one-third of hospitals nationally.[23] The NCDB does, however, provide more granular data with regard to melanoma, including the presence of mitoses and LVI, which the Surveillance, Epidemiology, and End Results registry does not. To mitigate the impact of coding errors inherent in large registry databases, the current study excluded any patients with internally inconsistent data. Although a minority of patients had missing pathologic data, this is unlikely to have had a significant effect, as information on the 2 main factors considered in this study, age and thickness, was available for all patients and data on ulceration was available for 98% of patients. The final limitation worth noting is that SLN status is not an explicit data field in the NCDB and may lead to inaccurate rates of SLN positivity. The inclusion of patients with only clinically localized disease allows data fields describing the presence of any positive nodes to act as a surrogate for nodal metastasis status. This method of describing SLN status seems accurate, however, as the rate of nodal positivity noted in this cohort is comparable to that in prior published reports of SLN positivity in patients with ITM.

CONCLUSION

Using a large national data set, we identified a low-risk subgroup for SLN positivity among patients with ITM based on readily reported clinical and pathologic factors. Although the overall rate of lymph node positivity in our study was 15%, we found significant heterogeneity in the risk for regional lymph node metastasis based on thickness and patient age in this

group for whom SLN biopsy is otherwise routinely recommended. A subgroup of patients accounting for one-third of the intermediate thickness cohort demonstrated a rate of lymph node positivity lower than 5%; an even higher proportion of patients older than 55 years, approximately one-half, were part of this low-risk category. These are patients with absent ulceration who, after careful discussion and consideration, may be safely spared the SLN procedure on the basis of their low risk of identification of nodal metastasis. This model, which requires further external validation by other institutional data sets, may provide a more personalized approach to SLN biopsy in patients with ITM and may have important implications in reducing morbidity and costs, particularly among older patients.

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