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ORIGINAL ARTICLE – MELANOMA

Age and Lymphovascular Invasion Accurately Predict Sentinel Lymph Node Metastasis in T2 Melanoma Patients

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ABSTRACT

Background. The risk of sentinel lymph node (SLN) metastasis in melanoma is related directly to tumor thickness and inversely to age. The authors hypothesized that for T2 (thickness 1.1–2.0 mm) melanoma, age, and other factors may be able to identify a cohort of patients with a low risk of SLN metastases.

Methods. The authors developed logistic regression models to predict positive SLNs in patients undergoing SLN biopsy for T2 melanoma using the National Cancer Database. Classification and regression-tree analysis were used to identify groups of patients with high and low risk for SLN metastases. The prediction model then was applied to a separate data set from a multicenter randomized clinical trial.

Results. The study identified 12,918 patients with T2 melanoma undergoing SLN biopsy with clinically node-negative melanoma. In the multivariable analysis, increasing thickness, younger age, lymphovascular invasion (LVI), mitotic rate of 1/mm^2 or more, axial location, and Clark level of 4 or 5 were independent risk factors for SLN metastases. A cohort based on age (> 56 years) and no LVI was identified with a relatively low risk (7.8%; 95% confidence interval 7.2–8.4%) of SLN metastases. The independent data set of 1531 patients with T2 melanoma confirmed these findings. Among elderly patients (age > 75 years) with melanoma 1.2 mm or smaller and no LVI, the risk of a positive SLN was 4.9% (95% confidence interval 3.3–7.1%).

Conclusions. Younger age and LVI are powerful predictors of SLN metastases for patients with T2 melanoma. This prediction model can inform shared decision-making regarding whether to perform SLN biopsy for older patients with otherwise low-risk T2 melanoma.

Sentinel lymph node (SLN) biopsy is routinely used to determine the status of the regional lymph nodes in patients who have clinically node-negative cutaneous melanomas with a Breslow thickness of at least 1 mm. The current guidelines recommend SLN biopsy for all patients without clinically apparent lymph node disease who have T2 (> 1–2 mm) and T3 (> 2–4 mm) melanomas. Most institutions use SLN biopsy for T4 melanomas as well.[1] Our practice is to perform SLN biopsy for T4 melanomas when the patient has no clinical evidence of metastatic or regional nodal disease because the status of the SLN provides valuable prognostic information in this high-risk group, although this practice is not without controversy.[2,3]

The use of SLN biopsy in the intermediate-thickness group allows for accurate prognosis stratification.[4–6] Although many centers no longer perform routine completion lymph node dissection (CLND) for patients with tumor-positive SLN based on the results of two prospective randomized trials,[7,8] some controversy still exists regarding

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the role of CLND. A SLN biopsy allows identification of node-positive patients, enabling appropriate discussion of the risks and benefits of CLND. In the current era of effective adjuvant immunotherapy and targeted therapy, SLN biopsy also offers an effective, minimally invasive approach to identifying patients with stage 3 disease who may potentially benefit from adjuvant immunotherapy.

SLN biopsy is more invasive than a simple wide local excision (WLE) of the primary melanoma, which usually can be performed with the patient under local anesthesia. In most centers, general anesthesia is used for patients undergoing SLN biopsy. These risks may not be very significant for younger, otherwise healthy patients, but may become significant for older patients with multiple comorbidities. Melanoma is primarily a disease of older patients. A current analysis of the Surveillance, Epidemiology, and End Results (SEER) database found that more than 40% of patients with newly diagnosed melanoma are 65 years old or older. More than 20% of these patients are 75 years old or older (authors' own analysis).

Multiple studies have shown that the risk of SLN metastases substantially decreases with increasing age.[9–11] Weighing the risks and benefits of performing SLN biopsy for patients with T2 melanoma is a very common clinical problem, especially for elderly patients. When the risk of nodal metastasis is lower (T1 melanoma), the decision to forego SLN biopsy is relatively straightforward. For elderly patients with T3 or T4 melanoma, the risk of nodal metastasis often outweighs the risk of general anesthesia and SLN biopsy.

We hypothesized that for patients with T2 (1.1–2.0-mm-thick melanoma, 8th edition of the American Joint Committee on Cancer [AJCC] staging system),[12] we could use standard clinicopathologic factors to identify a cohort of patients with a low risk of SLN metastases for whom SLN biopsy may be optional. To test this hypothesis, we used the National Cancer Database (NCDB) and confirmed the findings using the results of the multicenter Sunbelt Melanoma Trial.

METHODS

The first data source used was the NCDB 2015 Melanoma Public Use File. Records from 2010 to 2015 were queried. Invasive melanoma histologies were identified using codes 8720–8723, 8730, 8740, 8742–8745, 8761, and 8770–8772. Only records of patients undergoing SLN biopsy were analyzed. We selected T2 melanoma records using a thickness of 1.05–2.04 mm. Patients with clinical or pathologic M1 disease and those with clinically apparent nodal metastases were eliminated from the data set. As an additional quality control measure, all records with pathologic variables not internally consistent or congruent with clinically node-negative T2 melanoma were eliminated. The NCDB has no specific "SLN status" field. We inferred that these patients underwent an SLN biopsy rather than a therapeutic lymph node dissection based on the quality control measures used to eliminate any clinically apparent lymph node disease, as discussed earlier. Regional nodal status in this selected cohort was thus inferred to represent the results of a SLN biopsy. Any records that did not have all the pathologic variables of interest were eliminated. These variables were ulceration, mitotic rate (MR, recorded as per mm^2), lymphovascular invasion (LVI), anatomic site, and Clark level.

The second data source was the Sunbelt Melanoma Trial, a multicenter randomized trial described previously.[13] To create the independent comparison data set, patients from the Sunbelt Melanoma Trial with a melanoma thickness of 1.05–2.04 mm who were clinically node-negative and had undergone a SLN biopsy were selected.

Univariable logistic regression models were used to estimate the effect of clinical and pathologic variables on the risk of a positive SLN biopsy. A backward selection process (criterion, $p < 0.05$) was used to build a multivariable logistic regression model to predict the odds of a positive SLN biopsy. All variables of interest were initially placed in the model for backward selection. Interaction effects between age and thickness, age and LVI, age and Clark level, age and MR, and age and gender were evaluated. None were identified. Classification and regression tree (CART) analysis was used to select variables that would stratify patients into cohorts with significantly different risks of a positive SLN biopsy.

All risk factors were initially entered into the CART modeling, and recursive partitioning was used to select the best risk factors for predicting a positive SLN biopsy using a cost-complexity pruning algorithm.[14] The classification criteria then were applied to the Sunbelt validation set to verify the risk of a positive SLN biopsy in an independent data set. The 95% confidence intervals (CIs) for these estimates were constructed using exact binomial proportions. The Hosmer–Lemeshow goodness-of-fit test was used to evaluate model-fitting of the logistic regression model derived from the NCDB that was applied to the Sunbelt dataset.

Statistical analysis was performed with SAS 9.4 (SAS, Cary, NC, USA). Use of the Sunbelt Melanoma Trial data for research purposes was approved by the University of Louisville Institutional Review Board, and use of the public use files from the NCDB was exempt from review board approval.

RESULTS

For the analysis, 12,918 records were selected from the analytic data set developed from the NCDB public use file. The overall rate of a tumor-positive SLN biopsy in this cohort was 11%. The clinicopathologic factors of the cohort are summarized in Table 1. The findings of the univariable logistic regression models are summarized in Table 2. The multivariable model is presented in Table 3.

Thickness (direct relationship), age (inverse relationship), LVI, MR, axial location, and Clark level all were independent risk factors for a positive SLN in this T2 cohort. Gender and ulceration were removed during the backward selection process and not included in the final model as independent predictors of a positive SLN.

The CART analysis allows an investigator to use recursive partition to create segments of data that best model a categorical response (classification tree) or a continuous response (regression tree). All variables presented in Table 1 were included in the analysis for consideration. Cut points for the continuous variables (age, thickness) were computationally chosen by CART analysis using recursive partitioning (Fig. S1).

The CART analyses were performed with three, four, five, and six final categories requested. We present the findings of the three category model because the four, five, and six category models did not identify additional low-risk categories for a positive SLN.

In the CART analysis, three groups were identified using age and LVI, with distinctly different risks of a positive SLN biopsy (Fig. 1). Using an age cutoff of 56 years, this model was able to identify low-, intermediate-, and high-risk groups for a positive SLN biopsy in T2 melanoma. Older patients (age > 56 years) without LVI had the lowest risk of a positive SLN biopsy (7.8%; 95% CI 7.2–8.4%). This low-risk group comprised the majority of patients with T2 melanoma in the data set (60%). The median melanoma thickness in this low-risk cohort was 1.4 mm, and 25% of this cohort had a thickness of 1.2 mm or less. Younger patients (age ≤ 56 years) had an intermediate risk for a positive SLN biopsy (14.5%; 95% CI

TABLE 2 Risk factors for a positive SLN biopsy in T2 melanoma shown by unadjusted analysis

Risk factor	OR (95% CI)	*p* value
Age (continuous)	0.98 (0.97–0.98)	< 0.0001
Age (years) (categorical)		
< 40 (*n* = 1362)	Reference	
40–65 (*n* = 6614)	0.60 (0.51–0.70)	< 0.0001
> 65 (*n* = 4942)	0.39 (0.33–0.47)	< 0.0001
Thickness (continuous)	1.01 (1.008–1.011)	< 0.0001
Ulceration (*n* = 2343)	1.28 (1.12–1.47)	0.0004
Female gender (*n* = 5396)	1.06 (0.94–1.18)	0.35
MR (continuous)	1.082 (1.062–1.103)	< 0.0001
MR ≥ 1/mm^2 (*n* = 10,540)	2.02 (1.69–2.41)	< 0.0001
LVI (*n* = 391)	3.70 (2.96–4.64)	< 0.0001
Site		0.0023
Axial (*n* = 6543)	Reference	
Extremity (*n* = 6375)	0.84 (0.75–0.94)	
Clark level ≥ 4 (*n* = 10,430)	1.42 (1.22–1.66)	< 0.0001

SLN sentinel lymph node, *OR* odds ratio, *CI* confidence interval, *MR* mitotic rate, *LVI* lymphovascular invasion

TABLE 1 Clinical and pathologic factors in SLN-positive and -negative T2 melanoma

	SLN-negative (*n* = 11,535) *n* (%)	SLN-positive (*n* = 1383) *n* (%)	*p* value
Median age: years (IQR)	62 (51–71)	56 (45–67)	< 0.0001
Age categories			< 0.0001
< 40 (*n* = 1362)	1120 (9.7)	242 (17.5)	
40–65 (*n* = 6614)	5859 (50.8)	755 (54.6)	
> 65 (*n* = 4942)	4556 (39.5)	386 (27.9)	
Median thickness: mm (IQR)	1.37 (1.20–1.63)	1.50 (1.25–1.75)	< 0.0001
Ulceration present (*n* = 2343)	2044 (17.7)	299 (21.6)	0.0004
Females (*n* = 5396)	4802 (41.6)	594 (42.9)	0.35
MR ≥ 1/mm^2 (*n* = 10,540)	9304 (80.7)	1236 (89.4)	< 0.0001
LVI (*n* = 391)	276 (2.4)	115 (8.3)	< 0.0001
Site			0.0023
Axial (*n* = 6543)	5789 (50.2)	754 (54.5)	
Extremity (*n* = 6375)	5476 (49.8)	629 (45.5)	
Clark level ≥ 4 (*n* = 10,430)	9251 (80.2)	1179 (85.3)	< 0.0001

SLN sentinel lymph node, *IQR* interquartile range, *MR* mitotic rate, *LVI* lymphovascular invasion

TABLE 3 Multivariable model that predicts the risk of a positive SLN biopsy in patients with T2 melanoma

Risk ractor	OR (95% CI)	*p* value
Thickness	1.009 (1.007–1.011)	< 0.0001
Age	0.977 (0.973–0.980)	< 0.0001
LVI	3.31 (2.63–4.18)	< 0.0001
MR $\geq$ 1/mm^2	1.77 (1.48–2.12)	< 0.0001
Extremity (vs. axial)	0.83 (0.74–0.93)	0.0010
Clark level $\geq$ 4	1.26 (1.07–1.48)	0.0046

SLN sentinel lymph node, *OR* odds ratio, *CI* confidence interval, *LVI* lymphovascular invasion, *MR* mitotic rate

13.6–15.6%). Finally, older patients with LVI had the greatest risk of a positive SLN biopsy (26.0%; 95% CI 20.4–32.2%). The rates for a positive SLN biopsy as defined by these two factors were similar in the Sunbelt Melanoma Trial data set (Fig. 2). A logistic regression model using age of 56 years or older and LVI applied to the Sunbelt data exhibited good model fitting, with the Hosmer–Lemeshow goodness-of-fit test showing no evidence for rejecting the null hypothesis that the model fits (p = 0.90).

In an exploratory analysis, a lower-risk cohort was identified. The risk of a positive SLN biopsy was 4.9% (range 3.3–7.1%) for patients older than 75 years with a melanoma thickness 1.2 mm or less and no LVI. This exact risk cohort could not be confirmed in the Sunbelt data set because patients older than 70 were not enrolled in the trial. We did find that the SLN-positive rate in the Sunbelt cohort for patients older than 56 years with no LVI, and a melanoma thickness of 1.2 mm or less was 4.9%, which matched the rate observed in the cohort older than 75 years with no LVI and a melanoma thickness 1.2 mm or less from the NCDB cohort. The median melanoma thickness in the low-risk Sunbelt group (age > 56 years, no LVI) was 1.3 mm, and 40% of the Sunbelt patients in the low-risk group had a melanoma thickness of 1.2 mm or less.

DISCUSSION

The most important finding in this study was that two simple factors, age and LVI, can predict the risk of micrometastatic lymph node disease for patients with T2 melanoma undergoing SLN biopsy. A low-risk group (older patients with no LVI and a melanoma thickness of $\leq$ 1.2 mm) has a risk of SLN metastases that approaches that of patients with T1 melanomas, for whom omission of SLN biopsy can be considered. These findings from a large hospital-based data set were confirmed in a separate multicenter clinical trial data set. This simple parsimonious risk model can help clinicians with shared decision-making for older comorbid patients for whom consideration of omitting an SLN biopsy might be reasonable.

The inverse relationship between age and risk of SLN biopsy was again demonstrated in this study. The increased risk of a positive SLN biopsy for younger patients with T1 melanoma has been reported by our group and others.[15–17] This relationship has prompted our group to be more liberal in considering SLN biopsy for young healthy patients with thin melanomas near the 1 mm threshold or with other adverse features such as a mitotic rate of one or more mitoses per mm^2. The inverse is also true: we are less likely to offer SLN biopsy to older patients with thin melanomas, even as they approach the 1-mm threshold, unless they have other high-risk features including age less than or equal to 56 years or at least one mitosis per mm^2.

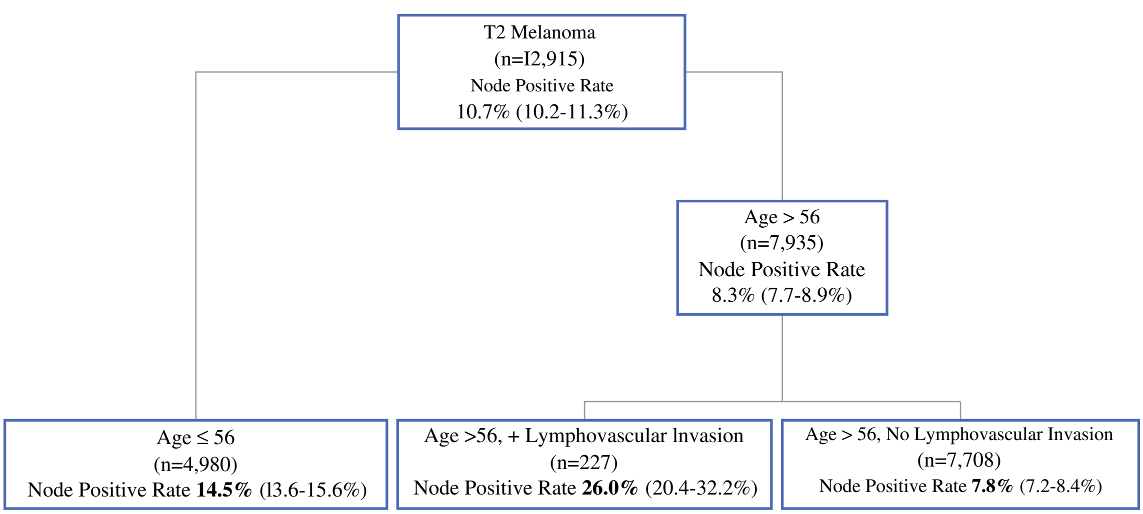

FIG. 1 Classification and regression-tree (CART) analysis identified three cohorts with distinctly different risks for a positive sentinel lymph node (SLN) biopsy in T2 melanoma

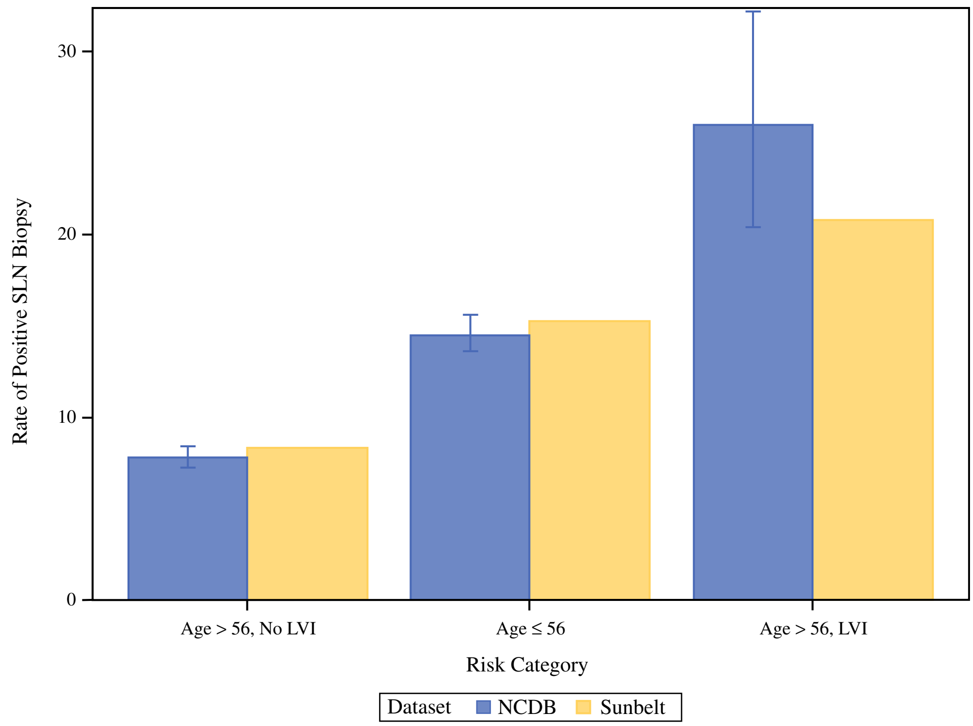

FIG. 2 Comparison of the predicted risk for a positive sentinel lymph node (SLN) biopsy from the National Cancer Database (NCDB) cohort and the actual rate of positive SLN biopsy in the Sunbelt data set

This study aimed to evaluate whether a similar approach, in which age and other clinical and pathologic factors can inform decision-making for selective application of SLN biopsy, should be considered for patients with T2 melanoma.

The generally accepted threshold for risk of micrometastatic lymph node disease that should prompt consideration of SLN biopsy is 5% according to the National Comprehensive Cancer Network (NCCN) guidelines.[18] In this study, a cohort of T2 melanoma patients with an estimated risk for SLN metastases statistically below the 5% threshold could not be defined. Thus, on the surface, the findings in this study might suggest that clinicians should continue offering SLN biopsy to all patients with T2 melanoma. However, this study was able to define groups with a low risk of SLN metastases, on the order of 5–8%. In fact, the majority of T2 patients (60%), could be categorized as having a relatively low risk of SLN metastases (7–8%). Among older patients with comorbidities that might increase the risk for a more invasive procedure with the patient under general anesthesia, the expected perioperative complication rate might exceed the expected positive SLN rate. Thus, the findings in this study provide some specific numbers that can be discussed with patients during the shared decision-making process.

Lymphovascular invasion, although relatively uncommon in this cohort of T2 patients (3%), is a powerful predictor of SLN metastases. This relationship in intermediate-thickness melanoma has been reported by others.[19–22] In general, LVI has been overshadowed by other pathologic risk factors in models that predict the risk of SLN metastases, with the most common pathologic risk factors being thickness, age, mitotic rate, and ulceration.[20–22] In the CART analysis in this study, these more traditional risk factors, including thickness, mitotic rate, and ulceration, did not significantly increase the ability to parse the data set into additional unique risk categories. When more final categories were requested in the CART modeling, thickness and mitotic rate further separated the high-risk groups (younger or older age with LVI). No additional lower-risk groups were identified in the modeling.

The CART analysis allows a parsimonious prediction model to be built that has real-world clinical utility. It turns the results of a logistic regression model into a clinical prediction tool. Ulceration was not an independent predictor of SLN metastases in the multivariate model. This finding is not wholly new, although it may seem somewhat surprising. Ulceration certainly is a risk factor for poor survival and risk of recurrence. However, an analysis from the Sunbelt Melanoma Trial showed previously that ulceration did not predict the risk of a positive SLN in T2 patients.[22] Thickness and mitotic rate do influence the risk of SLN metastases, but they are not the best risk factors for identifying a low-risk T2 cohort. In this study, age and LVI were the best risk factors for identifying a low-risk T2 cohort.

Hanna et al.[23] recently performed a similar analysis using T2–T3 melanoma patients in the NCDB data set. The findings in their study are similar to those in the current study, namely, that age and LVI inform the risk stratification of SLN metastases in intermediate-thickness melanoma. In their study, an age cutoff of 55 years was used together with a thickness cutoff of 1.7 mm, LVI, and ulceration to build prediction models. The take-home message from both studies is that although age is a powerful predictor of SLN risk for T2 patients, the presence of LVI cannot be ignored. Older patients with LVI should be considered as high risk for micrometastatic lymph node disease, and SLN biopsy should be considered. It must be recognized that LVI is a very uncommon pathologic finding in T2 melanoma. In the current study, only 3% of the patients had LVI. Nevertheless, when present, LVI is a powerful predictor of SLN metastases, particularly in older patients.

This study was limited by the usual constraints of using large national registries. Elimination of records with missing pathologic information may have resulted in findings that were biased. The NCDB represents a selection of Commission on Cancer (COC)-accredited facilities and thus may not represent the practice of melanoma surgery in general across the country. The NCDB registry does not clearly designate whether a regional lymph node basin procedure was an SLN biopsy or a therapeutic/diagnostic lymph node dissection. Every effort was made to eliminate records that indicated the presence of clinically evident nodal disease. Thus we infer that the patients in this study with a regional nodal basin procedure were undergoing a SLN biopsy.

The presence of mitoses in this T2 cohort was relatively high, approximately 80%. Hanna et al.[23] reported a similar rate of 70% in their NCDB study of T2 melanoma patients. In that report, they did not exclude missing or unknown values for mitoses, which explains why our estimated rates of mitoses might seem relatively high for a low-risk T2 cohort. This may represent a slight bias in our findings toward higher-risk T2 melanoma patients.

An important strength of this study, often lacking in large registry-based studies, was that the findings had been confirmed in an independent data set, in this case, data from a multicenter clinical trial. However, the fact that the Sunbelt Melanoma Trial did not include patients older than 70 years old limits application of the analysis for elderly patients.

In conclusion, most patients with T2 melanoma should continue to undergo routine SLN biopsy as part of their complete staging workup. However, for elderly patients for whom omission of a SLN biopsy is being considered, absence of LVI and relative thickness within the T2 category may help to identify a relatively low-risk group for which nodal observation rather than SLN biopsy may be reasonable.

DISCLOSURE Kelly M. McMasters serves on the Scientific Advisory Board for Elucida Oncology. The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC NCDB are the source of the de-identified data used in this study. They have not verified the statistical validity of the data analysis or the conclusions derived by the authors and are not responsible for these.

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