Should Sentinel Lymph Node Biopsy Be Performed for All T1b Melanomas in the New 8th Edition American Joint Committee on Cancer Staging System?

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BACKGROUND: In the 8th edition of the American Joint Committee on Cancer melanoma staging system, the T1b category has been redefined based solely on thickness and ulceration. National Comprehensive Cancer Network guidelines recommend consideration of sentinel lymph node biopsy (SLNB) for all patients with T1b melanomas (0.8 to 1.0 mm thick). We hypothesized that the new staging system would lead to excessive use of SLNB in patients with non-ulcerated T1b melanomas with a low risk of positive sentinel lymph nodes.

STUDY DESIGN: The National Cancer Database 2015 Melanoma Public Use File was used to select patients undergoing SLNB for thin T1 cutaneous melanoma from 2010 to 2015. Clinicopathologic risk factors for having a positive SLNB were evaluated. Univariable and multivariable logistic regression models and classification and regression tree analysis were performed to identify groups with high and low risk of positive SLNB.

RESULTS: We selected patients undergoing SLNB without ulceration with thickness 0.75 to 1.04 mm, staged T1b in the new 8th edition American Joint Committee on Cancer by thickness criteria alone (6,894 patients). Independent risk factors for a positive sentinel lymph node were age 56 years or younger (odds ratio [OR] 1.74; 95% CI 1.38 to 2.17), thickness 1.0 vs 0.8 to 0.9 mm (OR 1.36; 95% CI 1.09 to 1.70), female sex (OR 1.36; 95% CI 1.09 to 1.69), and mitotic rate $\geq 1/mm^2$ (OR 2.01; 95% CI 1.54 to 2.64). Classification and regression tree analysis identified 2 groups based on age, mitotic rate, and thickness with a risk of positive SLNB <5%. These 2 groups made up 55% of T1b, nonulcerated melanoma patients who underwent SLNB.

CONCLUSIONS: The new 8th edition American Joint Committee on Cancer melanoma staging system T1b category should not be used to determine use of SLNB in thin melanoma, as more than one half of T1b lesions without ulceration have a low risk of positive sentinel lymph nodes. (J Am Coll Surg 2019;228:466–473. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

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Current National Comprehensive Cancer Network guidelines for cutaneous melanoma recommend offering sentinel lymph node biopsy (SLNB) for all T2a or greater, clinically node-negative patients, and consideration of SLNB for stage IB (T1b) melanomas. The general principle for considering SLNB suggested by the National Comprehensive Cancer Network in T1b melanoma patients is a >5% risk of sentinel lymph node (SLN) metastasis.[1] Several pathologic risk factors, including ulceration, mitotic rate (MR), and lymphovascular invasion, can inform this decision making in T1b melanoma patients.

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Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
CART = classification and regression tree
MR = mitotic rate
NCDB = National Cancer Database
SLN = sentinel lymph node

The new 8th edition of the American Joint Committee on Cancer (AJCC) staging system redefined the definition of T1b melanoma.[2] Previously, a T1 melanoma (thickness $\leq$1.00 mm) was classified as T1b in the presence of ulceration or mitotic rate $\geq$1/mm^2, defining a T1b cohort with decreased survival compared with T1a.[3] These factors (ulceration and MR) also identified T1 melanomas at higher risk of SLN metastases and were the most common criteria used for selective application of SLNB in T1 melanoma.[4-6] The new 8th edition AJCC specified that thickness should be rounded to the nearest one-tenth of a millimeter (eg 0.75-mm-thick is now 0.8-mm-thick). The new staging system also eliminated MR from the classification of T1 melanomas, instead relying solely on ulceration and thickness 0.8 to 1.0 mm to define T1b melanomas.[2] This was done because these factors alone could define a T1b cohort with worse survival, without using MR.[7] Even though this cohort defines a high-risk thin melanoma cohort with decreased overall survival, it does not necessarily define a thin melanoma group at high risk of SLN metastases. There is widespread consensus that the presence of ulceration, regardless of tumor thickness, is an indication for SLNB.[8] Therefore, we focused our analysis on nonulcerated T1 melanomas in the new staging system. We hypothesized that the new T1b definition would result in overuse of SLNB in patients with nonulcerated thin melanomas that are T1b by thickness criteria alone (0.8 to 1.0 mm), a group that overall has a low risk of SLN metastasis.

METHODS

The National Cancer Database (NCDB) 2015 Melanoma Public Use File was used as the data source. The file was queried for all patients diagnosed with a cutaneous invasive melanoma histology (8720 to 8723, 8730, 8740, 8742 to 8745, 8761, 8770 to 8772) from 2010 to 2015. The year 2010 was chosen to capture a time period of uniform staging (AJCC 7th edition[9]). Thin melanoma was defined as thickness of 0.75 to 1.04 mm to conform with the AJCC 8th edition recommendation to round thickness to the nearest 0.1 mm. The data set was narrowed by eliminating all M1 patients (clinical or pathologic stage) and those with clinically apparent nodal disease. We selected only patients with pathologic stage N0 to 2A, as those are the only patients who would fit our nonulcerated, clinically node-negative cohort. The data set was further cleaned by eliminating any records with inconsistencies in the pathologic variables that raised doubt as to whether the record represented a clinically node-negative, T1 melanoma. As a final quality-control measure, we eliminated any record that did not have a full complement of our pathologic variables of interest: ulceration, MR (denoted per mm^2), lymphovascular invasion, anatomic site, and Clark level. Records were designated as T1b by 8th edition thickness criteria alone if ulceration was not present.

Clinical and pathologic factors were compared between groups of interest using chi-square or nonparametric Wilcoxon rank sum testing, as appropriate. Univariable logistic regression models were constructed to estimate the effect of factors of interest on risk of positive SLN. Multivariable logistic regression models were developed using a backward selection process after including all variables of interest. Interaction effects were checked for age-sex, age-MR, age-Clark level, age-lymphovascular invasion, and age-thickness. Classification and regression tree (CART) analysis was used to identify a parsimonious classification of patients according to clinicopathologic factors that best stratified risk of SLN metastases. The 95% CIs were constructed for the estimated SLN risk using exact binomial proportions. Analysis was performed using SAS, version 9.4 (SAS Institute). This study was considered exempt from IRB approval based on the use of public use data.

RESULTS

Based on the initial selection criteria, 8,497 records were identified from the NCDB Melanoma Public Use File. Of these, 7,501 (88%) underwent SLNB. We then eliminated the records of 607 patients with ulceration, for a final cohort of 6,894 records that would be considered T1b according to the AJCC 8th edition staging system based solely on thickness (0.8 to 1.0 mm). The differences in the relevant clinicopathologic factors between those that were SLN-negative and positive are summarized in Table 1. The overall rate of a positive regional node (positive SLN) was 5.1% in this cohort; selected subgroup analysis of risk of positive SLN are presented in Table 2. Younger age, greater thickness, female sex, presence of mitotic figures, and Clark level IV/V were associated with increased risk of a positive SLN (Table 3 and Figs. 1 and 2). No statistically significant interaction effects were identified between the factors evaluated.

Using the CART analysis, a parsimonious model was made based on 3 factors (age, thickness, and MR) to

Table 1. Clinicopathologic Factors Associated with a Positive Regional Node in T1b Melanoma

Variable	Regional node negative (n = 6,546)	Regional node positive (n = 348)	p Value
Thickness, mm, median (IQR)	0.90 (0.80–0.96)	0.90 (0.83–1.00)	0.0016
Thickness category, n (%)			0.0259
0.8 mm (n = 2,306)	2,208 (33.7)	98 (28.2)	—
0.9 mm (n = 2,224)	2,115 (32.3)	109 (31.3)	—
1.0 mm (n = 2,364)	2,223 (34.0)	141 (40.5)	—
Age, y, median (IQR)	58 (47–68)	53 (40–63.5)	<0.0001
Age category, n (%)			<0.0001
<40 y (n = 978)	895 (13.7)	83 (23.9)	—
40–65 y (n = 3,778)	3,592 (54.9)	186 (53.5)	—
>65 y (n = 2,138)	2,059 (31.5)	79 (22.7)	—
Male sex (n = 3,724), n (%)	3,572 (54.6)	153 (44.0)	0.0001
Lymphovascular invasion (n = 107), n (%)	99 (1.5)	8 (2.3)	0.25
Site, n (%)			0.85
Axial (n = 3,462)	3,289 (50.2)	173 (49.7)	—
Extremity (n = 3,432)	3,257 (49.8)	175 (50.3)	—
Clark level IV/V (n = 4,181)	3,950 (60.3)	231 (66.4)	0.0247

IQR, interquartile range.

Table 2. Risk of Positive Sentinel Lymph Node in T1b Nonulcerated Melanoma in Select Clinicopathologic Categories

Variable	Risk of positive regional node (sentinel lymph node), %
Overall	5.1
Age	
<40 y	8.5
40–65 y	4.9
>65 y	3.7
Thickness	
0.8 mm	4.2
0.9 mm	4.9
1.0 mm	6.0
Sex	
Male	4.1
Female	6.2
Mitotic rate	
$<1/mm^2$	3.0
$\geq 1/mm^2$	6.1
Lymphovascular invasion	
Absent	5.0
Present	7.5
Primary site	
Axial	5.0
Extremity	5.1
Clark level	
II/III	4.3
IV/V	5.5

identify 4 cohorts with distinct risks of SLN metastases (Fig. 3). Patients with <1 mitoses/mm^2 had a low risk of SLN metastases, regardless of age or thickness (3.0%; 95% CI 2.3% to 3.8%). Another group, those with MR $\geq 1/mm^2$, age older than 56 years, and thickness 0.8 to 0.9 mm, also had a low risk of SLN metastases (3.7%; 95% CI 2.8% to 4.8%). These 2 groups had a <5% risk of SLN metastases. These groups did not meet the National Comprehensive Cancer Network guideline threshold for consideration of SLNB (5%). These 2 groups represented 55% of the nonulcerated T1b records in the data set.

Using the age and thickness cutoffs derived from the CART analysis, a multivariable logistic regression model was constructed. Age, thickness, sex, and MR were all independent risk factors for a positive SLN in non-ulcerated T1b melanoma patients undergoing SLNB (Table 4).

DISCUSSION

The most important finding in this work is that the new T1b classification in the 8th edition of the AJCC staging system for melanoma should not be used as the sole criteria for selecting patients for SLNB. Patients who are classified as T1b based exclusively on thickness (non-ulcerated, 0.8 to 1.0 mm) overall have a 5% risk of a positive SLN. However, based on age, thickness, and presence of mitotic figures, approximately half of these patients can be spared SLNB, as they have a <5% risk of a positive SLN.

Table 3. Predictors of Sentinel Lymph Node Metastases in T1b Nonulcerated Melanoma, Univariable Analysis

Variable	Odds ratio (95% CI)	p Value
Age, continuous	0.98 (0.97–0.99)	<0.0001
Age, category		
<40 y	ref	—
40–65 y	0.56 (0.43–0.73)	<0.0001
>65 y	0.41 (0.30–0.57)	<0.0001
Thickness, continuous	1.02 (1.01–1.03)	0.0015
Thickness, category		
0.8 mm	ref	—
0.9 mm	1.16 (0.88–1.54)	0.29
1.0 mm	1.43 (1.10–1.86)	0.0081
Female	1.53 (1.23–1.90)	0.0001
Mitotic rate $\geq 1/mm^2$	2.10 (1.61–2.75)	<0.0001
Lymphovascular invasion	1.53 (0.74–3.18)	0.25
Site		
Axial	ref	—
Extremity	1.02 (0.82–1.27)	0.85
Clark level		
II/III	ref	—
IV/V	1.30 (1.03–1.63)	0.0251

The new T1 classification, which eliminates MR in favor of thickness and ulceration to classify T1b melanomas, was performed because of a recognized separation in survival based on these factors.[7] This is a reasonable change, because the purpose of a staging system is to stratify patients into distinct risk groups based on risk of dying from the disease. Staging systems are not necessarily meant to inform treatment decisions, but they are often used for this purpose.[10] The potential unintended consequence, however, will be that pathologists might no longer report MR routinely for T1 melanomas because

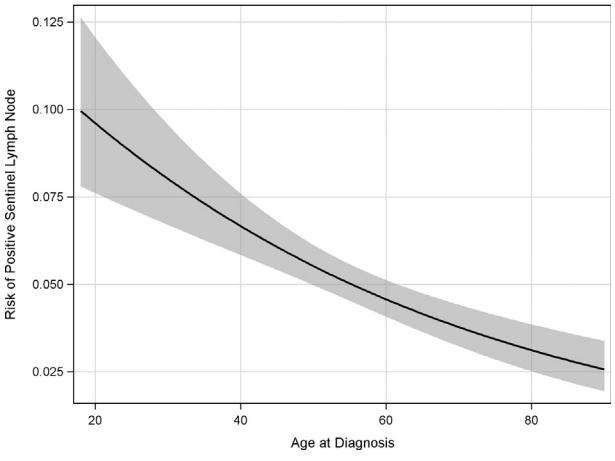

Figure 1. Age is inversely related to the risk of sentinel lymph node metastasis in T1b nonulcerated melanoma.

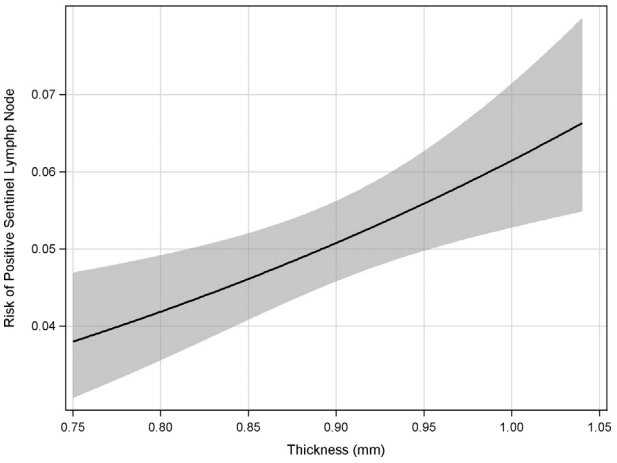

Figure 2. Thickness is directly related to the risk of sentinel lymph node metastasis in T1b nonulcerated melanoma.

it is only recommended, not required, for staging. The 7th edition AJCC staging system for T1 melanomas, based on ulceration and MR, could be used as a complementary tool for identifying thin melanomas with a >5% risk of a positive SLN, for which it was reasonable to discuss the potential benefit of SLNB.[9] Changes in the classification of T1 melanoma in the AJCC staging system are associated with changes in the use of SLNB in thin melanoma.[11,12] We consider that changes in the classification of thin melanoma in the 8th edition of the AJCC staging system, which are perfectly reasonable in light of demonstrable survival differences, might be misinterpreted as a change in the indication for SLNB in thin melanoma. Therefore, we performed this study to evaluate whether classic risk factors for a positive SLN (MR) along with newer risk factors (age) can be used to clarify how the new T1b definition should be used to select thin melanomas for SLNB.

Mitotic rate has been a well-described risk factor for both poor prognosis and risk of SLN metastases. The AJCC staging committee recognized the impact that MR had on survival in thin melanoma and included it in the 7th edition for T1 classification.[3] Mitotic rate is a risk factor for positive SLNB in thin melanomas.[4,6,13] Mitotic rate also informs overall prognosis in melanoma across all thickness categories and is an important pathologic element for risk stratification.[14,15] The AJCC staging committee recommends that MR continue to be collected and considered in the risk stratification of patients with melanoma, even though it is not a formal element of stage classification.[2]

The impact of age on the risk of SLN metastasis and prognosis has been well recognized in research conducted during the last decade. Multiple reports have

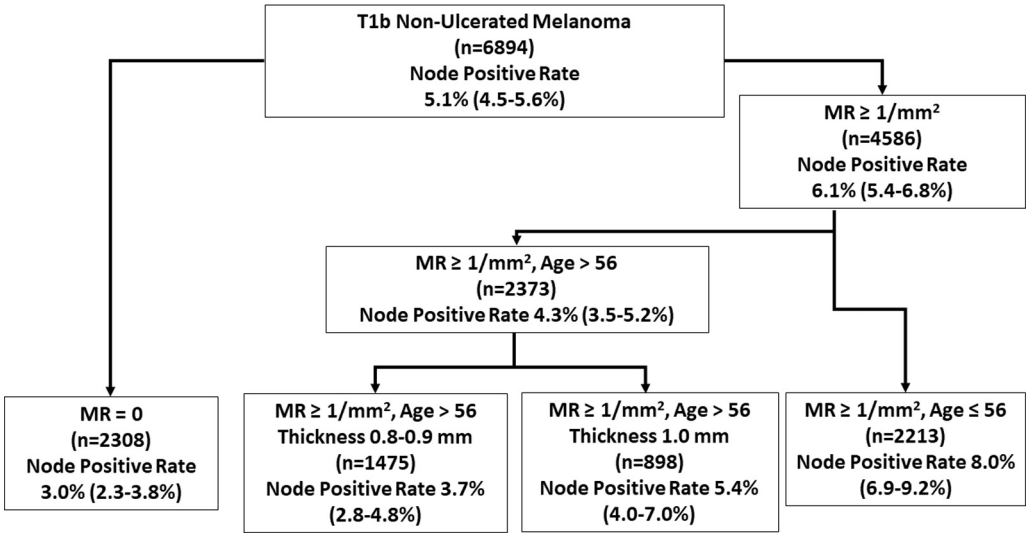

Figure 3. Age, presence of mitotic figures, and thickness can identify 4 subgroups of nonulcerated T1b melanoma with distinctly different risks of sentinel lymph node metastases. MR, mitotic rate.

demonstrated that younger patients are at an increased risk of a positive SLN.[13,16] The curious discrepancy in this finding that has been repeated in multiple studies is that, despite this increased risk of SLN metastasis, younger patients will often have a more favorable prognosis compared with otherwise matched older patients.[17-19] These findings might influence surgeons to be more liberal in the recommendation of SLNB in younger patients, particularly those with thin melanomas that are otherwise at low risk of SLN metastases. Alternatively, surgeons might be less likely to recommend SLNB in older patients, particularly those with medical comorbidities in whom the difference in medical risk between wide local excision alone under local anesthesia and SLNB under general anesthesia might be particularly relevant.

Table 4. Adjusted Risk of a Positive Sentinel Lymph Node in Nonulcerated T1b Melanoma Undergoing Sentinel Lymph Node Biopsy

Variable	Adjusted odds ratio	p Value
Age, category		
>56 y	ref	—
≤56 y	1.74 (1.38−2.17)	<0.0001
Thickness, category		
0.8−0.9 mm	ref	—
1.0 mm	1.36 (1.09−1.70)	0.0064
Sex		
Male	ref	—
Female	1.36 (1.09−1.69)	0.0073
Mitotic rate		
<1/mm^2	ref	—
≥1/mm^2	2.01 (1.54−2.34)	<0.0001

This study suggests that not all patients with nonulcerated T1b melanomas should undergo SLNB. Age and MR, though not considered in the formal AJCC staging criteria, can identify patients with a <5% risk of a positive SLN, in whom a SLNB can be reasonably avoided. Other groups have explored the interaction of age, MR, and other factors in the prediction of SLN metastases in thin melanoma. Sinnamon and colleagues[20] used a similar cohort of patients from the NCDB to conclude that age is an important criterion for selecting patients with thin melanomas for SLNB, along with MR and thickness. Conic and colleagues[21] using NCDB data, and Tejera-Vaquerizo and colleagues,[22] using multi-institutional data, both make the argument that MR continues to inform the risk of a positive SLN in thin melanoma patients. This study is a unique addition to the literature in that it focuses on the nonulcerated T1b population who would otherwise potentially undergo SLNB based on thickness alone (0.8 to 1.0 mm). The CART analysis allows one to develop a novel, simple, risk-stratification model based on thickness, age, and MR to identify T1b patients with <5% risk of a positive SLN. This is an important finding from a healthcare delivery standpoint. Clinical stage IA and IB melanomas are the most common stages of melanoma seen; approximately 75% of newly diagnosed melanoma are T1.[23] Approximately 16% of T1 melanomas are 0.75 to 1.0 mm in thickness.[24] With an expected incidence of melanoma in the US in 2018 of 91,000, if SLNB was adopted uniformly for patients with T1b melanoma, then approximately 10,000 new melanoma patients with thickness 0.75 to 1.00 mm would undergo SLNB in the US in 2018.[25] Perhaps

as many as half of these patients are low risk and should not undergo SLNB. In some patients who are understandably anxious about their prognosis with thin melanoma, a negative SLNB might ease their concerns. However, one must also consider that SLN is not without complications (approximately 5%).[26]

This study needs to be interpreted with its limitations in mind. We selected a cohort of patients from NCDB data with complete pathologic records. Because NCDB is a hospital-based registry of Commission on Cancer-accredited facilities, these findings might not represent the general practice of melanoma surgery across the country, especially in this limited data set in which we selected only records with complete pathologic data. This data set likely represents a sample from high-quality and potentially high-volume cancer centers. The NCDB does not clearly designate whether the regional nodal basin was sampled as a SLN procedure. We are inferring that these patients all underwent SLNB rather than a formal lymphadenectomy, based on our inclusion criteria and the elimination of any records that were suggestive of clinically positive nodes or with inconsistent staging data. Ideally, the classification model needs to be validated in a separate data set to estimate the variability of the predictions of SLN positivity made in this study.

CONCLUSIONS

The new 8th edition AJCC melanoma staging system T1b category should not be used to determine use of SLNB in patients with nonulcerated thin melanomas, as more than one-half of T1b lesions without ulceration have a low risk of positive SLN. Specifically, SLNB should be reserved in nonulcerated patients for T1b melanomas aged 56 years and younger with MR $\geq$1, and for patients older than 56 years with MR $\geq$1 only in the 1.0-mm thickness category.

Author Contributions

Study conception and design: Egger, Stevenson, Bhutiani, Jordan, Scoggins, Philips, Martin, McMasters
Acquisition of data: Egger, Stevenson, Bhutiani
Analysis and interpretation of data: Egger, Stevenson, Bhutiani, Jordan, Scoggins, Philips, Martin, McMasters
Drafting of manuscript: Egger, Stevenson, McMasters
Critical revision: Egger, Stevenson, Bhutiani, Jordan, Scoggins, Philips, Martin, McMasters

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Discussion

DR DOUGLAS TYLER (Galveston, TX): Recent advances in the fields of immunotherapy and targeted therapies have markedly changed the therapeutic landscape for melanoma patients, especially those with metastatic disease, where less than 10 years ago mean survivals of 6 months have given way to treatment options that now are associated with 50% long-term survival.

Given all the interest in the metastatic setting, the changes in the 8th edition American Joint Committee on Cancer (AJCC) staging manual for early-stage disease really almost went unnoticed. These changes tried to redefine a high-risk group of stage 1 patients who have a worse prognosis and end up going back to a subgroup analysis or a subgroup based on tumor thickness. Although the staging system does successfully identify that patients with tumors 0.8 to 1 millimeter thick have a worse prognosis, the real focus of this paper is determining at what level probability for metastasis to a sentinel lymph node a sentinel lymph node biopsy is indicated.

Is the 5% bar frequently used clinically and for the analysis in this paper appropriate, especially in the wake of new effective adjuvant therapies for stage 3 melanoma patients? At what probability of metastasis to a sentinel lymph node does it become cost-effective to perform this procedure? In absolute terms, each year, more melanoma patients die with tumor thickness <4 millimeters, but have an initial negative sentinel lymph node biopsy and not a positive one. Where do you see genomic predictors of risk of the primary tumor fitting into this type of process? And could they replace sentinel lymph node biopsy at some point in the future altogether?

What do you do for the patient who is below whatever bar you pick or set for metastasis in performing the sentinel lymph node biopsy procedure, but is tremendously anxious and all but demands the operation? When does the therapeutic value of a negative result in terms of ease of mind trump population health logic?

DR KEITH DELMAN (Atlanta, GA): It is important to recognize the limitations of the National Cancer Database (NCDB). While I agree with Dr McMasters that it is an ideal setting to study this question and it is certainly attractive to analyze big data, the selection of patients requires that they be sent to a cancer center. Many patients who have thin melanomas are treated by dermatologists, especially given an ongoing bias by many in that discipline against the use of sentinel node biopsy, and therefore are never collected in such an analysis. This is highlighted by the fact that the authors' query of the NCDB only captured approximately 1.8% of all melanomas diagnosed over the 5-year time period that was analyzed, which, even with the limited thickness selected and the criteria, seems to be a very small proportion of what we otherwise would expect. Cancer registrars collect only the first line of treatment for reporting of data in the NCDB, so any recurrence after a negative sentinel lymph node biopsy would not be reflected in this data set. I would like the authors to comment on this and how it might bias their results.

By definition, the analysis reflects data from before the adoption of the T1b stage in the 8th edition. Do the authors believe that the use of sentinel node biopsy, which, as they mentioned, is characterized as "offer" in the National Comprehensive Cancer Network (NCCN), but in the American Society of Clinical Oncology/Society of Surgical Oncology consensus guidelines, the recommendation is to counsel a patient "based on their individual risk," do the authors feel that such a recommendation, as the consensus guidelines suggest, is reasonable? If so, what do the authors, in their personal practice, consider when counseling a patient about undergoing sentinel node biopsy for T1b disease? I ask the authors to consider the fact that the pathologic reclassification of patients is prognostically to stage 1a, if they do undergo sentinel lymph node biopsy and are negative with a T1b lesion, but that they remain stage 1B if they go unstaged. That goes back to Dr Tyler's comment about the reassurances of sentinel node biopsy.

Furthermore, the authors state that the patients classified as T1b in this analysis have a 5% incidence of node positivity, but, in fact, that is not really true because they have excluded all ulcerated patients from this analysis. As a result, the true incidence of node positivity in this entire data set is actually higher when you consider all T1b patients. I recognize the analysis is designed to subset out specific patients, but I would like the authors to clarify this because it can be misleading the way the data were presented.

The authors mentioned an unintended consequence of dropping mitotic rate from the staging system. They note that mitotic rate was dropped, but it was dropped mostly because of statistical loss of power, which was a function of the subjective nature of the field and the variability of applying it, and, as such, it lost its statistical power in the analysis.