RESIDENT COMPETITION RESEARCH ARTICLES

Sentinel Lymph Node Predictors in Melanoma of Breslow Thickness 0.8-1.0 mm

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ABSTRACT

Introduction: Current melanoma staging guidelines consider all patients staged T1b to have the same metastatic risk and recommends that sentinel lymph node biopsy (SLNB) be considered in this disparate group. The goals of this study were to specifically determine predictors of sentinel lymph node positivity and those predictive for obtaining a SLNB in melanomas of Breslow thickness 0.8 mm to 1.0 mm, which has not been previously studied.

Methods: Retrospective review between January 1997 and July 2019 of patients with melanomas between 0.8 mm-1.0 mm in thickness. Patient demographics and primary tumor characteristics were correlated with SLN status.

Results: Of the 458 patients found to meet Breslow thickness criteria, 223 (61.8%) underwent SLNB. Multivariate analyses demonstrated that < 60 years of age (OR 2.42), increasing Breslow thickness (OR 1.27), mitotic rate >1 (OR 2.32) and presence of tumor infiltrating lymphocytes (OR 3.33), were associated with performing a SLNB. Positive SLNB was found in 20 (8.1 %). Univariate analyses revealed females (p=0.016) to have an increased risk for positive SLNB.

Limitations: Limited number of positive SLN and survival data available.

Conclusions: Younger age, Breslow thickness ≥0.9 mm, mitotic rate >1, and presence of tumor infiltrative lymphocytes were found to be factors predictive of performing SLNB. Female gender significantly increased the odds of a positive SLN.

INTRODUCTION

The prognosis, management, and surveillance of patients with cutaneous melanoma (CM) is primarily based on staging adopted by the American Joint Committee on Cancer (AJCC).[1] The AJCC identifies patients with thin melanomas (≤ 1.0 mm in Breslow thickness) as having an overall

favorable prognosis with low probability of metastatic spread.[2] However, a small percentage of these patients may go on to develop advanced disease. Based on the shared 5%-10% metastatic risk in patients with primary melanoma of Breslow thickness < 0.8 mm with ulceration and 0.8 mm – 1.0 mm with or without ulceration, these two different patient cohorts are staged as T1b and the National Comprehensive Cancer Network (NCCN) melanoma guidelines recommend considering SLNB in these two populations.[3]

The potential metastatic risk in patients with thin melanomas has led to an extensive attempt to determine predictors of sentinel lymph node (SLN) positivity in thin melanomas, of which primary tumor thickness and ulceration have been shown to be the most important factors associated with a positive sentinel lymph node.[4] Additional clinicopathologic factors, for which a prognostic value is less clear due to variability among studies, include Clark level, mitotic rate, lymphovascular invasion, anatomic site, tumor infiltrating lymphocytes, regression, and patient characteristics such as gender and age.[5-12]

Interestingly, melanomas of Breslow thickness between 0.8 mm to 1.0 mm are considered to have the same risk for positive SLN regardless of any other associated risk factors, and the NCCN recommends considering SLNB in this population, along with thinner melanomas (< 0.8 mm) with ulceration[3]. However, if ulceration and other patient and tumor characteristics are independent predictive factors of progression and survival, we would expect that patients whose melanomas are associated with other risk factors would have a higher likelihood for regional metastasis. To our knowledge, no studies have been conducted regarding SLN predictors in this specific population.

Therefore, we sought to determine predictive factors for performing SLNB and those predictive of positive SLN in this particular cohort.

METHODS

After approval by the University Hospitals Cleveland Medical Center Institutional Review Board (IRB). Electronic records of patients with biopsy-proven melanoma were reviewed at our institution from January 1, 1997 through July 31, 2019. Patients who met criteria for Breslow thickness between 0.8 mm and 1.0 mm were initially identified through our electronic pathology record system, Copath. Medical records were then reviewed to identify patients who did and did not have a SLNB at the time of primary tumor excision. Patients were excluded if they had a previous history of other thicker melanomas or if no data on SLN outcomes were available. Patient demographics, primary tumor characteristics, and nodal status data were collected.

Statistical methods
Study covariates included in the analyses were age at diagnosis, gender, anatomic site, Breslow thickness, histologic type, dermal mitotic rate (MR), ulceration, regression, Clark level, lymphovascular invasion (LVI) and tumor infiltrating lymphocytes (TIL). Age at diagnosis was categorized into groups (< 60 years, ≥ 60 years). MR was grouped as < 1 or ≥ 1. Tumor site was designated as head and neck, trunk, upper extremities, lower extremities, or genitalia. Ulceration, regression, and LVI, and TIL were classified as being present or absent.

The primary aim of this study was to identify predictors for performing a SLNB. Multiple logistic regression was used to investigate associations between study covariates and

whether a SLNB was performed. Estimates of odds ratios (OR) and 95% confidence intervals (CI) were provided to evaluate the effects of these associations. Using this analytical framework, we further investigated predictors for SLNB positivity (within SLNB-performed patient group). A p-value ≤ 0.05 was considered statistically significant. All statistical analyses were performed by using R version 3.6.2 (2019).
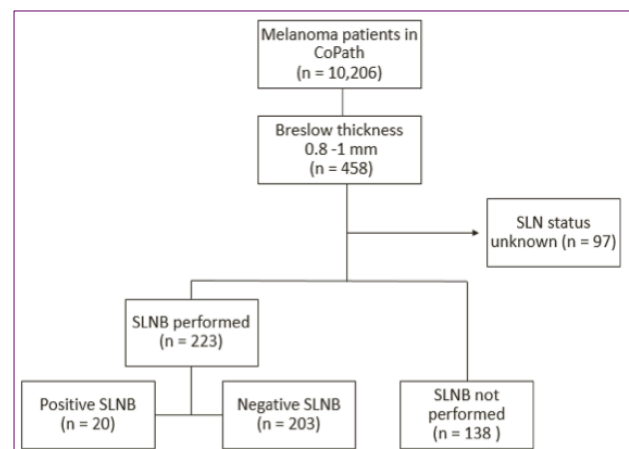
RESULTS

A total of 10,206 patients diagnosed with primary cutaneous melanoma were identified, of which 458 met criteria for Breslow thickness between 0.8 mm and 1.0 mm. A total of 87 patients were excluded, leaving a cohort of 361 patients available for analysis (**Figure 1**). Of these, 223 (62.8%) underwent SLNB and 138 (51.3%) did not (**Table 1**). Univariate analyses demonstrated that age, Breslow thickness, Clark level, histologic type, MR, and TILs were significantly different between patients in which SLNB was performed and not performed. No difference was found among gender, anatomic location, ulceration, regression, and LVI. Multivariate analyses using these six significant variables demonstrated in univariate analysis revealed that patients 60 years or younger (OR = 2.42, 95% CI = 1.48-4.01), increasing Breslow thickness (0.9 mm: OR=1.27, 95% CI=0.73-2.21; 1 mm: OR=2.44, 95% CI=1.26-4.88), MR > 1 (OR=2.32, 95% CI=1.19-4.8), and presence of TILs (OR=3.33, 95% CI=1.72-6.61), significantly predicted whether patients underwent SLNB (**Table 2**). Clark level and histologic type were not significant in predicting whether patients underwent SLNB.

Within the subset of patients that underwent SLNB, 20 (8.9%) were found to be positive and 203 (91.1%) negative (**Table 3**). The majority of patients were male (53.8%), however the positive SLNB group was predominately composed of female patients (70.0%). Univariate analyses found significant differences in patient gender, with females having an increased risk for positive SLNB (OR=3.66, 95% CI=1.34-11.67, p= 0.016) as compared to males. No other variables were significant.

Figure 1 Breakdown of patient selection. SLNB, sentinel lymph node biopsy.

DISCUSSION

To our knowledge, this is the first study reporting predictors for performing SLNB in patients with thin melanomas, specifically those measuring 0.8-1.0 mm. Our results showed that younger age (<60 years), Breslow thickness (≥0.9 mm), mitoses (>1), and presence of TIL were all predictive factors for performing SLNB at our institution. The strong evidence in support of Breslow tumor thickness and mitoses as factors independently predictive of melanoma outcomes led to their incorporation into AJCC staging.[1] At our institution, we follow AJCC/NCCN guidelines to stage melanomas and provide recommendations. Although mitoses are no longer used in staging of thin melanomas, this was a risk factor used in previous AJCC staging editions and explains

Table 1. Patient demographics and primary tumor characteristics for patients in which SLNB was and was not performed.

Characteristic	SLNB performed (n = 223) No. (%)	SLNB not performed (n = 138) No. (%)	P value
Age, years			< 0.001
< 60	130 (59.4)	47 (34.1)	
≥ 60	89 (40.6)	91 (65.9)	
Gender			0.728
Female	99 (45.2)	66 (47.8)	
Male	120 (54.8)	72 (52.2)	
Location			0.234
Head and neck	31 (14.2)	23 (16.6)	
Trunk	78 (35.6)	51 (37)	
Upper extremities	52 (23.7)	40 (29)	
Lower extremities	57 (26)	24 (17.4)	
Genitalia	1 (0.5)	0	
Breslow thickness (mm)			<0.001
0.8	90 (41.1)	79 (57.3)	
0.9	64 (29.2)	40 (28.9)	
1.0	65 (29.7)	19 (13.8)	
Histologic type			0.022
Superficial spreading	175 (79.9)	89 (64.5)	
Lentigo maligna	23 (10.5)	30 (21.7)	
Nodular	2 (0.9)	2 (1.5)	
Acral lentiginous	7 (3.2)	6 (4.4)	
Other	9 (4.1)	10 (7.2)	
Unknown	3 (1.4)	1 (0.7)	
Clark level			0.019
≤ III	42 (19.2)	41 (29.7)	
≥ IV	175 (79.9)	95 (68.8)	
Unknown	2 (0.9)	2 (1.5)	
Ulceration			0.327
Present	11 (5)	4 (3)	
Absent	208 (95)	134 (97)	
Mitotic rate per mm²			< 0.001
<1	88 (40.1)	112 (81.2)	
> 1	130 (59.4)	26 (18.8)	
Unknown	1 (0.5)	0	
Regression			0.276
Present	28 (12.8)	23 (16.7)	
Absent	185 (84.5)	115 (83.3)	
Unknown	6 (2.7)	0	
LVI			0.086
Present	24 (10.9)	0	
Absent	192 (87.7)	138 (100)	
Unknown	3 (1.4)	0	
TILs			< 0.001
Present	197 (88.3)	103 (74.6)	
Absent	16 (7.3)	35 (25.4)	
Unknown	6 (2.7)	0	

Abbreviations: SLNB, sentinel lymph node biopsy; LVI, lymphovascular invasion; TILs, tumor-infiltrating lymphocytes.

Table 2. Multivariable logistic regression analysis for predictors of undergoing SLNB (performed on significant variables demonstrated in univariable analysis)

Variable	OR	95% CI	P value
Age			< 0.001
≥ 60		Reference	
<60	2.42	1.48 to 4.01	
Gender			0.197
Male		Reference	
Female	0.72	0.43 to 1.18	
Breslow thickness (mm)			0.032
0.8		Reference	
0.9	1.27	0.73 to 2.21	
1	2.39	1.26 to 4.88	
Clark level			0.246
I – III		Reference	
IV – V	1.40	0.79 to 2.46	
Mitotic rate per mm²			0.014
≤ 1		Reference	
> 1	2.32	1.19 to 4.8	
TILs			< 0.001
Absent		Reference	
Present	3.33	1.72 to 6.61	
Histologic type			0.235
Superficial spreading		Reference	
Acral lentiginous	0.92	0.26 to 3.35	
Lentigo maligna	0.46	0.23 to 0.92	
Nodular	0.54	0.04 to 3.83	
Other	0.65	0.21 to 2.01	
Ulceration			0.489
Absent		Reference	
Present	1.55	0.46 to 6.21	

Abbreviations: SLNB, sentinel lymph node biopsy; OR, odds ratio; CI, confidence interval; TILs, tumor-infiltrating lymphocytes.

why mitotic rate may have been considered when recommending SLNB in this specific group.

When management recommendations are not clearly stated in NCCN guidelines, we follow an evidence-based approach to provide appropriate recommendations. Although younger age (<60 years) is not used as part of melanoma staging per AJCC, this patient-specific factor has been shown to be an important independent predictor of melanoma outcomes[13] and its association with a positive SLNB in thin melanomas has

Table 3. Patient demographics and primary tumor characteristics for positive and negative SLNB.

Characteristic	Positive SLNB (n = 20) No. (%)	Negative SLNB (n = 203) No. (%)	P value
Age, years			0.738
< 60	11 (55)	121 (59.6)	
≥ 60	9 (45)	82 (40.4)	
Gender			0.010
Female	14 (70)	88 (43.3)	
Male	6 (30)	115 (56.7)	
Location			0.314
Head and neck	2 (10)	30 (14.8)	
Trunk	4 (20)	75 (36.9)	
Upper extremities	6 (30)	47 (23.2)	
Lower extremities	8 (40)	50 (24.6)	
Genitalia	0	1 (0.5)	
Breslow thickness (mm)			0.378
0.8	9 (45)	83 (40.9)	
0.9	4 (20)	61 (30)	
1.0	7 (35)	59 (29.1)	
Histologic type			0.859
Superficial spreading	17 (85)	160 (78.8)	
Lentigo maligna	1 (5)	22 (10.8)	
Nodular	0	2 (1)	
Acral lentiginous	1 (5)	6 (3)	
Other	1 (5)	9 (4.4)	
Unknown	0	4 (2)	
Clark level			0.298
≤ III	2 (10)	40 (19.7)	
≥ IV	18 (90)	161 (79.3)	
Unknown	0	2 (1)	
Ulceration			0.154
Present	0	11 (5.4)	
Absent	20 (100)	192 (94.6)	
Mitotic rate per mm²			0.657
< 1	9 (45)	82 (40.4)	
≥ 1	11 (55)	120 (59.1)	
Unknown	0	1 (0.5)	
Regression			0.271
Present	5 (25)	23 (11.3)	
Absent	15 (75)	174 (85.7)	
Unknown	0	6 (3)	
LVI			0.459
Present	1 (5)	23 (11.3)	
Absent	19 (95)	177 (87.2)	
Unknown	0	3 (1.5)	
TILs			0.885
Present	18 (90)	180 (88.6)	
Absent	2 (10)	17 (8.4)	
Unknown	0	6 (3)	

Abbreviations: SLNB, sentinel lymph node biopsy; LVI, lymphovascular invasion; TILs, tumor-infiltrating lymphocytes.

been demonstrated in several studies.[9-12] Our results show that younger age (<60 years) is a predictive factor for performing SLNB and thus aligns with currently published data demonstrating an increased risk for positive SLNB in this population.

Why the presence of TIL is a predictive factor for performing SLNB is less clear. There is conflicting evidence regarding the association between TIL and regional nodal metastasis in melanoma. Although some studies have reported a lower risk for positive SLNB in melanomas with TIL,[14-18] others have not shown such a relationship.[8-9,19-21] Absence of TIL has been demonstrated to be an independent predictor of SLN positivity.[14,22] It is unlikely that patients in our cohort underwent SLNB based on TIL alone given the available evidence. The results are possibly due to the relatively small number of cases. Further studies are needed to specifically determine the significance of TIL in thin melanomas, if any.

Although several studies have attempted to evaluate clinicopathologic predictors of SLN positivity in thin melanomas, no study has specifically looked at melanomas measuring 0.8 to 1.0 mm in thickness. Thus, we reviewed our cohort to determine which characteristics were predictive of SLN positivity in this specific population. Our results revealed that female gender significantly increases the odds of having a positive SLN. This correlates with the findings from Wright *et al.*[10] but contrasts with other studies in which male gender was found to increase regional metastatic risk.[9,23] Given the inconsistency among reports, no consensus currently exists regarding the association between gender and risk for metastasis in thin melanomas.

Ulceration has been reported to be an important risk factor in patients with thin melanomas.[7,9,24-31] As a result, AJCC designates a more advanced stage for

melanomas with Breslow thickness <0.8 mm with ulceration as compared to melanomas <0.8 mm without ulceration. Interestingly, melanomas of Breslow thickness 0.8-1 mm are given the same stage regardless of ulceration status. This grouped staging is likely the result of variability in data and lack of a strong correlation between ulceration and metastatic risk as thin melanomas become thicker. Our study, which focuses on this very specific group, revealed zero patients with ulcerated melanomas in the positive SLNB group. All patients with ulcerated melanomas (n=11) had a negative SLNB. Thus, no increased risk for SLN metastasis was found based on ulceration alone. Other patient and tumor characteristics variably reported in the literature to increase the risk for positive SLN, including age, Breslow thickness, mitotic rate, Clark level, TIL, and regression, were not found to significantly increase the risk for positive SLNB in this group.

Limitations to our study include its retrospective and single institution nature, likely introducing selection bias, and a limited number of cases available for review, making it difficult to statistically assess for significant differences. Several other studies have encountered a similar limitation given that certain tumor traits, such as ulceration and SLN metastasis, in thin melanomas are uncommon. Moreover, we attempted to study survival outcomes in this group, but there were not enough cases with a positive SLN or survival data available for a significant statistical analysis.

CONCLUSION

In summary, our study represents the first analysis of predictors of performing SLNB and of increased risk for positive SLN in patients with melanomas of Breslow thickness between 0.8 and 1.0 mm. Our results revealed that younger age (<60 years), increased Breslow thickness (≥0.9 mm), mitotic rate >1, and presence of TIL were predictive factors of performing SLNB. Female gender was found to be the only statistically significant factor to increase the risk for positive SLN. We believe these findings can potentially improve management recommendations and enhance patient care.

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