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Transected thin melanoma: implications for sentinel lymph node staging

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Abstract

Background and Objectives—Indications for sentinel lymph node (SLN) biopsy in patients with thin melanoma (≤ 1 mm thick) are controversial. We asked whether deep margin (DM) positivity at initial biopsy of thin melanoma associates with SLN positivity.

Methods—Cases were identified using prospectively maintained databases at two melanoma centers. Patients who had undergone SLN biopsy for melanoma ≤ 1 mm were included. DM status was assessed for association with SLN metastasis in univariate and multivariate analyses.

Results—1413 cases were identified, but only 1129 with known DM status were included. 39% of patients had a positive DM on original biopsy. DM-positive and DM-negative patients did not differ significantly in primary thickness, ulceration, or mitotic activity. DM-positive and DM-negative patients had similar incidence of SLN metastasis (5.7% vs 3.5%; $p=0.07$). Positive DM was not associated with SLN metastasis on univariate analysis (OR 1.69, 95% CI: 0.95–3.00, $p=0.07$) or on multivariate analysis adjusted for Breslow depth, Clark level, mitotic rate, and ulceration (OR=1.59, 95% CI: 0.89–2.85; $p=0.12$).

Conclusions—For patients with thin melanoma, a positive DM on initial biopsy is not associated with risk of SLN metastasis, so DM positivity should not be considered an indication for SLN staging in an otherwise low-risk patient.

Keywords

Melanoma; sentinel lymph node; transected; thin

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Introduction

The incidence of cutaneous melanoma continues to rise, affecting approximately 76,380 people in the United States in 2016 and accounting for 10,130 deaths [1]. Up to 70% of melanomas are “thin”, defined as less than or equal to 1 mm in Breslow thickness. While patients with thin melanoma have a lower risk of death from melanoma than those with intermediate and thick lesions, data from the Surveillance, Epidemiology and End Results (SEER) registry indicate that thin melanomas remain the cause of 30% of melanoma-associated mortality [2].

The risk of sentinel lymph node (SLN) metastasis is directly related to the Breslow thickness of the primary lesion. Among patients with thin melanoma, the risk of SLN metastasis is <5% [3]. Various investigators have attempted to identify characteristics of thin melanomas that are associated with a significant risk of SLN metastasis. In an analysis of 1,250 patients with thin melanoma who had a SLN biopsy, Han et al. found that Breslow depth >0.75 mm, Clark’s Level IV, and ulceration (but not mitotic rate) were independent predictors of SLN metastasis [4]. Two studies have demonstrated an association between SLN positivity and an elevated mitotic rate [5,6], although increased mitotic activity is more commonly associated with poorer survival [7–9]. Based on these reports, the presence of ulceration and/or mitotic activity (in conjunction with thickness) are considered indications for SLN staging in patients with thin melanoma. The National Comprehensive Cancer Network (NCCN) guidelines recommend SLN biopsy for patients with melanoma between 0.76 and 1 mm when there is ulceration and/or mitotic activity. The guidelines suggest *consideration* of the procedure for patients at lower risk (no ulceration or mitosis) with tumors between 0.76 and 1 mm thick (<https://www.nccn.org>). The impact of unknown primary depth due to transection of a primary or extension of the lesion to the base of the biopsy is not addressed by the current guidelines. Patients with a transected melanoma < 1 mm in Breslow thickness with no other adverse features may undergo SLN biopsy due to the assumption that they are at higher risk of SLN metastasis. Because of the ubiquity of shave biopsy, these patients represent a significant proportion of newly diagnosed melanoma patients. Indeed, the presence of a positive deep margin at biopsy occurs in more than half of patients with clinically localized melanoma [10]. Because the vast majority of melanoma patients have early disease, and because a significant proportion of these will have a positive deep margin, the medical and economic implications of using DM positivity as an indication for SLN staging are potentially enormous. For this reason, we asked whether patients with thin melanoma with a (+)DM on initial biopsy are at higher risk of SLN metastasis than DM (–) patients. If so, SLN may be justified in a significant percentage of patients with thin but transected melanoma.

Materials and Methods

For this retrospective study, Institutional Review Board approval and a waiver of patient informed consent requirements were obtained prior to study initiation at Memorial Sloan Kettering Cancer Center (MSKCC) and the University of Pennsylvania (UPenn). Patients with thin melanoma who had a SLN biopsy at presentation to MSKCC or UPenn were included. Prospectively maintained databases were queried to identify patients with thin

melanoma (1.0 mm) who underwent SLN biopsy between January 1995 and June 2014. We eliminated patients who had SLN biopsy performed elsewhere. Patients initially diagnosed with thin melanoma who were found to have a deeper lesion at wide excision were not included in the study. Demographic data, initial biopsy technique, margin status at initial biopsy, tumor characteristics, and pathologic results were collected and analyzed.

Pathology reports were reviewed from the referring institutions and the treating institution to determine the DM status of the initial biopsy. DM status was recorded as positive when the pathology report specified that the deep margin was positive or the Breslow depth was listed as “at least” 0.X mm. The biopsy method was also determined from the pathology reports, although no distinction could be made between superficial and deep-shave or scalloping techniques. The mitotic rate was determined using the “hot spot” technique, and dichotomized as either 0 or 1/mm². Information regarding lymphovascular invasion, vertical growth phase, and regression were not routinely detailed in each pathology report, and thus were not examined. SLN status was recorded, with a positive SLN determined by either hematoxylin and eosin or immunohistochemical staining. Follow-up data reflected the last time the patient was seen at the treating institution.

Descriptive statistics were used for patient demographic characteristics, tumor characteristics (Breslow depth, tumor ulceration, mitotic rate), and SLN status. Patients were separated into two groups, those with a positive vs. negative DM on initial biopsy. Chi-square analysis was used to determine whether the incidence of SLN positivity was different between the two groups. P values less than 0.05 were considered statistically significant. Univariate analysis was performed to determine which characteristics were associated with SLN involvement. Variables with a p value <0.10 were included in the multivariate analysis of factors associated with SLN positivity.

Results

A total of 1413 patients with thin melanoma who had a SLN biopsy were identified. Of these, 1129 had complete margin data to permit comparison of those with positive vs. negative DMs (see Figure 1 for specific exclusion criteria). The mean age of the patients was 52.2 +/- 15.1 years, and about half were male (606/1129 [53.6%]). In the 586 patients for whom information regarding the initial biopsy technique was available, 325 patients (55%) were diagnosed using a shave biopsy (Table 1). Among all patients, the initial biopsy resulted in a (+) DM in 39%. Of patients who had a shave biopsy a (+) DM occurred in 199/311 cases (64.0%).

Among all patients in the study, the mean Breslow thickness of the tumors was 0.76 +/- 0.2 mm. The Breslow thickness was slightly higher in patients who had a (+) DM compared with those with a (-)DM (0.77 mm vs. 0.75 mm; p=0.08), but this difference was not statistically significant. Nearly 60% of the melanomas were Clark’s Level IV. There were no Clark’s Level V lesions. Only 58 (5.5%) of 1048 patients with known ulceration status had ulcerated melanoma. There was no significant difference between the incidence of ulceration between patients with a (+) DM (25/409 [6.1%]) compared to those with a (-) DM (33/639, 5.2%; p=0.51). Pathology reports included comments on mitotic rate in 994/1129 (88.0%).

Of these, 655/994 (65.9%) had ≥ 1 mitosis/mm². There was no difference in mitotic rate between patients with a positive vs. negative DM on original biopsy (255/380 [67.1%] vs. 400/614 [65.1%], $p=0.53$). Of the entire group of 1129 patients, only 49 had a positive SLN biopsy (4.3%).

The incidence of SLN metastasis was higher in the group of patients with a (+) DM, 25/437 (5.7%) vs. 24/692 (3.5%), but this was not statistically significant ($p=0.07$). Of the 498 patients with primary tumors ≤ 0.75 mm in depth, there were only 6 patients with SLN metastases (1.2%). The incidence was higher for patients with a (+)DM (2.7% vs. 0.32%, $p=0.02$). For patients with primary tumors >0.75 mm in depth, the incidence of SLN metastasis was 23/382 (6.0%) and 20/249 (8.0%) for patients with negative vs. positive DMs on initial biopsy ($p=0.33$). Of note, of patients with primary tumors >0.75 mm in depth, only 130 had no ulceration and a mitotic rate of 0. In this small subgroup, 2/41 (4.9%) with (+) DM had a positive sentinel lymph node, while 5/82 with (–) DM (6.1%) had a positive sentinel lymph node.

On univariate analysis, Breslow thickness >0.75 mm (compared to ≤ 0.75) was most strongly associated with SLN metastasis risk (OR 6.0, 95% CI 2.53–14.2, $p<0.001$). Clark's Level IV (vs. Clark's Level II or III) and mitotic rate ≥ 1 /mm² were also statistically significantly associated with SLN involvement. None of the other factors including age, sex, and ulceration were associated with SLN metastasis (Table 2). On multivariate analysis, only Breslow thickness >0.75 mm and Clark's Level IV were independent predictive factors for SLN metastasis (Table 3).

Discussion

There is a general consensus that, in the management of primary melanoma, Breslow thickness ≤ 1 mm and either ulceration or mitotic activity in patients with melanoma < 1 mm are features of primary melanoma that may warrant a SLN biopsy. However, other factors such as histologic evidence of primary regression, the presence of lymphovascular invasion, and the presence of a (+) DM on initial biopsy may influence the surgeon to recommend a SLN biopsy. To our knowledge, there are only two other studies that specifically address the implications of a (+) DM with regard to SLN metastasis. Koshenkov and colleagues found that patients ($n=72$) with a melanoma ≤ 0.75 mm and a (+) DM had a similar incidence of SLN metastasis as 188 patients with thicker tumors (0.76–2.0 mm in depth) [11]. Theirs was a small study ($n=260$), however, and the conclusions were based on a lack of statistical difference in the frequency of SLN involvement between the two groups. There was also a very high incidence of SLN metastasis in patients with melanoma ≤ 0.75 mm in depth (6/72 patients [8.3%]). Lowe et al evaluated the impact of shave biopsy on patients with thin melanoma. Similar to our study, there was no difference in the incidence of SLN metastasis in 260 patients stratified by deep margin status [12]. Involvement of the DM on initial biopsy was *not* associated with an increased risk for SLN metastasis. This finding alone should *not* prompt regional nodal staging in an otherwise low-risk patient.

Shave biopsies are more likely to result in a (+) DM when compared to punch or excision biopsies [10]. Shave biopsies remain the most frequently performed type of biopsy in

patients with pigmented lesions, however, despite an increased risk of transecting the tumor. Nevertheless, very few tumors are upstaged when wide excision is performed following a shave biopsy with a (+) DM [13,14].

In recent updates to the NCCN guidelines and American Joint Commission on Cancer (AJCC) staging criteria, elevated mitotic rate has supplanted Clark's Level in the T-staging of thin melanoma. Several studies have demonstrated a correlation between elevated mitotic rate and a lower survival probability in patients with early melanoma [7,9,15]. The association between mitotic rate and SLN metastasis is less well established, however, with some studies demonstrating a significant association [5,6], and others showing none [4,16]. In our study, an elevated mitotic rate was common in this group of patients with thin melanoma undergoing SLN biopsy (655/994 [65.9%]), including a significant proportion of patients with melanoma ≤ 0.75 mm thick. While elevated mitotic rate was significantly associated with SLN metastasis on univariate analysis, significance was lost on multivariate analysis. Conversely, Clark's Level IV, present in a similar proportion of study patients (60%), retained a significant association with SLN metastasis on both univariate and multivariate analysis.

Current NCCN guidelines do not recommend SLN staging for melanomas ≤ 0.75 mm in Breslow depth. The reason that SLN biopsy was performed in the patients in our study with melanoma ≤ 0.75 mm in Breslow could not be accurately ascertained in this retrospective study. However, most of these patients had other high-risk features, including ulceration and/or mitotic activity, and those with a (+) DM on initial biopsy. Regardless, the incidence of SLN metastasis was still quite low at 6/498 (1.2%). These results suggest that SLN staging is not appropriate in these patients, even in the presence of a (+) DM on initial biopsy.

The markedly low incidence of SLN metastasis in patients with tumors ≤ 0.75 mm in thickness in our study approximates the incidence of 1.4% in a study examining the cost-effectiveness of SLN biopsy for patients with thin melanoma [17]. The addition of a SLN biopsy often changes a simple clinic procedure under local anesthetic into outpatient ambulatory surgery involving the operating room and anesthesia. The Multicenter Selective Lymphadenectomy Trial (MSLT) demonstrated no benefit in melanoma-specific survival for patients with intermediate-thickness melanoma undergoing SLN biopsy, compared to wide excision, further supporting the prudence of wide excision alone in even lower risk patients [18].

This is the largest study to examine the relationship between a (+) DM on initial biopsy and the risk of SLN metastasis in patients with thin melanoma. The overall incidence of SLN involvement was quite low (4.3%), and statistical analysis did not demonstrate any association between a (+) DM and SLN metastasis. Furthermore, though SLNB was performed on a number of patients with melanoma ≤ 0.75 mm, the incidence of nodal involvement was far too low, in our experience, to justify the procedure.

Limitations of our study include its retrospective nature, which precluded the ability to accurately determine the reason for SLNB in patients with thin melanoma. In addition, our

data do not reflect the population of patients with thin melanoma overall, only those that were selected for SLN staging at two tertiary referral centers. While some patients did have residual disease on definitive wide excision, we were not able to identify cases where the provider's clinical suspicion of residual melanoma affected management. In addition, it is possible that the size of the patient population was insufficient to demonstrate a small difference in the risk of SLN metastasis in patients with tumors with negative as compared to positive DM on initial biopsy.

Conclusions

Our data suggest that in patients with thin melanoma and no residual lesion suspicious for more advanced disease, DM involvement alone should not be used as a criterion to perform SLN staging.

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Synopsis

Indications for sentinel lymph node biopsy (SLNB) in thin melanoma are controversial. We determined that melanoma patients with a thin primary were not at increased risk of SLN metastasis compared to those with negative deep margin.

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Figure 1.

The study population was derived from 1413 patients identified from two institutional databases who underwent SLN staging for thin melanoma and had a known deep margin status. The reasons for exclusion of cases are illustrated.

Table 1

Demographics and tumor characteristics of patients who underwent sentinel lymph node biopsy for melanoma 1 mm in Breslow depth.

Characteristic	Overall	Deep margin positive	Deep margin negative	P value
Total Patients	1129	437(39%)	692(61%)	
Age (mean)	52.2 +/- 15.1	54.4 +/- 15.1	50.9 +/- 15	<0.001
Sex (male)	606/1129 (53.6%)	226/437 (51.7%)	380/692 (54.9%)	0.29
Breslow Depth	0.76 mm	0.77 mm	0.75 mm	0.10
Clark Level				
II	74/1093 (6.8%)	22/423 (5.2%)	52/670 (7.8%)	0.10
III	368/1093 (33.7%)	130/423 (30.7%)	238/670 (35.5%)	0.10
IV	651/1093 (59.6%)	271/423 (64.1%)	380/670 (56.7%)	0.016
Ulceration	58/1048 (5.5%)	25/409 (6.1%)	33/639 (5.2%)	0.51
Mitotic Rate 1/mm ²	655/994 (65.9%)	255/380 (67.1%)	400/614 (65.1%)	0.53
Sentinel Lymph Node Metastasis	49/1129 (4.3%)	25/437 (5.7%)	24/692 (3.5%)	0.07

NOTE: Denominators are provided when complete information was not available for all study patients.

Table 2

Univariate analysis of primary tumor characteristics associated with sentinel lymph node metastasis in patients with thin melanoma.*

Characteristic	Odds ratio (95% CI)	p Value
Breslow Depth > 0.75mm	6.00 (2.53 – 14.21)	<0.001
Clark Level IV (vs. III)	4.18 (1.86 – 9.40)	0.001
Mitotic Rate 1/mm ²	2.55 (1.18 – 5.53)	0.018
Deep Margin positive	1.69 (0.95 – 3.00)	0.073
Ulceration	1.20 (0.36 – 4.00)	0.765

* Univariate analysis included tumor characteristics demonstrated in the literature to be associated with positive sentinel lymph nodes, as well as a positive deep margin. CI, confidence interval.

Table 3

Multivariate analysis of tumor characteristics associated with sentinel lymph node metastasis in patients with thin melanoma.*

Characteristic	Odds ratio (95% CI)	p Value	(+) SLN
Breslow Depth >0.75mm	4.38 (1.81 – 10.58)	0.001	6.8%
Clark Level IV (vs. lower)	2.86 (1.25 – 6.52)	0.013	6.4%
Mitotic Rate 1/mm ²	1.66 (0.75 – 3.67)	0.211	6.8%
Positive Deep Margin	1.59 (0.89 – 2.85)	0.119	6.9%

* Multivariate analysis included factors from the univariate analysis with a p<0.10. (+) SLN=positive sentinel lymph node; CI, confidence interval