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Dermal Melanoma: A Report on Prognosis, Outcomes, and the Utility of Sentinel Lymph Node Biopsy

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Abstract

Introduction—Historically dermal melanoma (DM) has been labeled as either stage IIIB (in-transit) or stage IV (M1a) disease. We sought to investigate the natural history of DM and the utility and prognostic significance of sentinel lymph node biopsy (SLNB).

Methods—Patients with DM undergoing SLNB at a single center from 1998 to 2009 were identified.

Results—Eighty-three patients met criteria, 10 (12%) patients had a positive SLNB. Of those, 5 (50%) recurred (all with distant disease). Twenty-one (29%) of the 73 SLNB negative patients recurred and of those, 15 (71%) developed distant metastases, whereas 6 (29%) developed local or regional recurrence, including two false-negative regional nodal recurrences. No in-transit recurrences were recorded. Five-year recurrence-free and disease-specific survival was significantly better for patients with a negative SLNB versus positive SLNB (56.8% vs. 22.2% $P=0.02$, 81.1% vs. 61.0%, $P=0.05$, respectively).

Conclusion—SLNB has prognostic significance for RFS and DSS, and should be utilized in the management of DM based on a >10% yield and low false-negative rate. Our data demonstrate patients with DM do not recur in an in-transit fashion, which along with the survival outcomes suggest the behavior of DM is consistent with primary cutaneous melanoma of similar thickness rather than an isolated in-transit or distant dermal metastasis from a regressed cutaneous primary.

Keywords

dermatopathologist; in-transit disease; regression; metastases

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INTRODUCTION

The incidence of melanoma is rising faster than any other cancer, with an estimated lifetime risk of 1 in 53. In the United States in 2014, over 76,100 cases of invasive melanoma were diagnosed, with an estimated 9,480 deaths [1]. The incidence of histologically-proven metastatic melanoma from unknown primary tumors ranges from 2% to 6% [2]. These metastatic lesions can present in skin, soft tissue, lymph nodes, or solid organs. An entity that has been increasingly identified in the literature is a solitary melanoma of unknown origin situated in the dermis, without evidence or history of a primary cutaneous melanoma. The uncharacteristically high 5-year survival rates of these patients compared to patients with dermal metastasis from a known primary cutaneous melanoma [3,4] has led some authors to conclude primary dermal melanoma (DM) is a distinct clinical entity. Though most reported studies demonstrate a high survival associated with DM, others report a poor prognosis similar to a stage IIIB (in-transit) or stage IV (M1a) melanoma (Table I) [5,6]. The incidence of primary dermal melanoma is low, ranging from 0.4% to 1.0% of all melanoma cases [7]. Since these lesions are rare, there is a lack of understanding regarding their natural course and prognosis. Defining the prognostic significance and categorizing these lesions will allow for more accurate evaluation and treatment.

DM is defined as a solitary focus of melanoma lacking an epidermal (junctional/in situ) component, confined to the dermis or the subcutaneous tissue without evidence of trauma, regression, or systemic disease (Fig. 1) [8–13]. Currently, DM is not specifically addressed in the American Joint Committee on Cancer (AJCC) Staging Manual 7th edition, though it is mentioned as a potential variant of primary melanoma [14]. Sentinel lymph node biopsy (SLNB) has not been routinely employed for staging of DM (Table I). A study by Lee et al. demonstrated the rate of nodal metastases to be as high as 23% when DM is staged with SLNB [7]. This study illustrated the potential prognostic value of SLNB. The purpose of our study was to evaluate the natural history of DM and the utility and further characterize the prognostic value of SLNB.

PATIENTS AND METHODS

After obtaining Institutional Review Board approval, a retrospective series of consecutive patients with DM were identified from a single-institution database of patients with localized melanoma treated with SLNB. A total of 83 patients with DM underwent wide excision (WE) and SLNB at the same institution from 1998 to 2009. The criteria for SLNB were the same as those applied to a primary intermediate thickness melanoma. SLNB was performed in patients with a melanoma ≥ 1.0 mm and without palpable lymphadenopathy or evidence of distant metastatic disease.

All patients seen at our institution with a potential diagnosis of DM, which was defined as melanoma present in the dermis and lacking an epidermal (junctional/in situ) component, had their slides reviewed and confirmed by one of two board-certified dermatopathologists as part of the multidisciplinary review of the case. Pathology data analyzed included Breslow thickness, mitotic rate (MR), vertical growth phase and lymphovascular invasion (Table II), although these features were not uniformly recorded for all patients, as well as

SLNB status. Breslow thickness was determined in standard fashion, measuring from the granular layer of the overlying epidermis to the deepest areas of invasion.

Inclusion criteria included all patients diagnosed with a solitary focus of DM. All patients included in the study underwent a SLNB and mapped to a nodal basin on lymphoscintigraphy. Exclusion criteria included a preexisting melanocytic nevus or in situ component and clinical evidence of regression or trauma. All patients had cross-sectional imaging and those with documented clinical or radiographic evidence of distant metastatic disease were excluded. No patient with a history of melanoma or previous surgical removal of melanoma were included in the study.

Tumors were removed with either a 1 or 2 cm margin based on thickness consistent with primary cutaneous melanoma WHO and NCCN guidelines and institutional practices. Pathologic SLNB evaluation consisted of serial sectioning and examination of hematoxylin and eosin-stained (H&E) sections, as well as immunohistochemical staining for S-100. MART-1 was also performed in select cases if S-100 staining was equivocal. All patients with positive SLN's were offered completion lymph node dissection (CLND) as standard of care. Pathologic evaluation of CLND specimens consisted of evaluation of an H&E-stained representative section through the largest diameter area of the larger lymph nodes, while nodes <3 mm were evaluated in their entirety.

Statistical Analysis

Demographic data and clinical variables were collected and analyzed. Chi-square tests were performed on categorical variables. Wilcoxon rank sum tests or analysis of variance tests were used for continuous variables to test for differences between SLN positive and negative groups. Five year overall survival (OS), disease-specific survival (DSS) and recurrence-free survival (RFS) rates were calculated using the Kaplan-Meier method of estimation and survival curves were compared with the log-rank test. Statistical significance was determined by a *P*-value of 0.05. Hazard ratios were estimated by Cox proportional hazards model. All analysis was done in R (A language and environment for statistical computing, version 3.1.0).

RESULTS

Patient Characteristics

A total of 83 patients met the study criteria and were included for review and analysis. Patient demographics and tumor characteristics are shown in Table II. The median age of the cohort was 63 years and the majority of patients were male (63%). The median Breslow thickness for the entire cohort was 2.80 mm with a range of 0.7–17.2 mm. Three patients (4%) did not have a Breslow thickness reported. The majority of the tumors were distributed in the extremities (43.4%) or head and neck (37.3%) areas. The remainder were located in the trunk (19.3%). Ulceration and regression were not present in any of the tumors analyzed in the study.

Sentinel Lymph Node Status

All 83 patients underwent SLNB; a positive SLN was seen in 10 (12.0%). In patients with a positive SLNB, the median Breslow thickness was 3.2 mm (range, 1.2–14.4), compared to a median Breslow thickness of 2.8 mm (range, 0.7–17.2 mm) in patients with a negative SLNB ($P=0.29$). Lymphovascular invasion (LVI) was the only tumor characteristic significantly associated with a positive SLN ($P=0.03$). LVI was seen in 20% of patients with a positive SLN and 2.7% with a negative SLN. CLND was performed in 9 of the 10 patients with a positive SLN. The remaining patient refused CLND and opted to be followed by serial ultrasound examination of the nodal basin. Of the 9 patients who received CLND, 3 (33.3%) were found to have additional metastatic disease in their lymphadenectomy specimens (non-sentinel node positivity).

Recurrence

The median follow-up was 27.1 months (range 0.43–140 months). Twenty-six patients had recurrence, and of these, 5 had a positive SLN (5 of 10 SLNB positive patients, 50%). All 5 of these patients with a positive SLN underwent a CLND and recurred with distant metastasis. Of the 73 patients with a negative SLN, 21 (28.8%) developed recurrences. Of those 21, 15 (71.5%) developed distant metastases. Four (19%) developed local recurrences, while 2 (9.5%) had regional nodal recurrences. Both represented false-negative nodal recurrences in the same mapped nodal basin despite a previously negative SLN, for a false-negative rate of 16.7% (2/12 [10 SLN positive +2 false negative cases]) and a predictive value of a negative SLNB of 97.3% (71 true-negative/73 total negative SLNB). No in-transit recurrences were recorded.

Patients with a positive SLNB were more likely to recur than those with a negative SLNB, though this was not statistically significant (50% vs. 28.8%; $P=0.32$). The 5-year RFS for the entire cohort was 53%. The 5-year RFS was 56.8% in SLNB negative patients and 22.2% in SLNB positive patients (log rank $P=0.02$). Likewise, the median RFS was significantly better for SLNB negative patients at 92.3 months compared to those with a positive SLNB at 15.9 months ($P=0.02$; Fig. 2).

Overall Survival and Disease-specific Survival

At the time of last follow-up, 61 (73.5%) patients were alive (50 were alive without evidence of melanoma and 11 with evidence of recurrent melanoma). Twenty-two (26.5%) patients had died. Of those, 11 (50%) died of disease and 11 died from other causes. The median OS for the entire cohort was 108.7 months. The 5-year OS for the entire cohort was 68%. Five year OS for SLNB positive and SLNB negative patients was 53.3% and 69.8%, respectively (HR =2.74, 95%CI 0.96, 7.14, $P=0.05$; Fig. 3). The 5-year DSS for the entire cohort was 78.5% (95%CI 68.7, 93.1). The 5-year DSS for SLNB positive and SLNB negative patients was 61.0% and 81.1%, respectively (log rank $P=0.02$). Median survival time of the entire cohort was not reached for DSS as depicted in Figure 3.

DISCUSSION

No consensus exists in the literature on how to classify melanoma confined to the dermis or subcutaneous tissue without evidence of metastatic disease or synchronous primary. Studies have labeled these cases as solitary dermal melanoma, metastatic melanoma to the skin of unknown primary, or assigned a distinct subtype, known as primary dermal melanoma [4,10,13,15]. Current literature has reported this entity as being less aggressive compared to dermal metastases of primary cutaneous melanoma or cutaneous metastatic melanoma from an unknown primary as evidenced by 5-year survival rates as high as 80–100% [16]. Historically DM was presumed to be stage IIIB (in-transit) or IV (M1a) disease, with a predicted 5-year survival ranging from 19% to 40% [5,17]. DM is not specifically addressed in the AJCC Cancer Staging Manual 7th edition, though a melanoma localized to the skin or subcutaneous tissue without a known primary site is defined as stage III [14]. The goal of our study was to determine the natural history of DM and the overall utility of SLNB.

The natural history and behavior of DM has been subject to controversy in the literature, which may be due to the rarity of the disease itself. This is evidenced by the incidence of 0.39–0.92% of melanoma cases seen across the literature, with multiple cohorts having as few as 3–15 patients with a wide range of recurrence and survival rates [10]. We report a 5-year RFS of 53% for our entire DM cohort. Sosman et al. performed a prospective multicenter trial in which patients with stage IV disease (M1a, M1b, M1c) had complete resection of their disease to assess for relapse-free survival. Sixty-four patients were completely resected of all gross disease, and all but six experienced a disease recurrence. Of the 64, the majority had M1a disease. They reported a 4-year relapse-free survival of 13% [18]. Our reported higher RFS compared to published data on resected stage IV disease suggest the behavior is more consistent with a primary cutaneous melanoma of similar thickness rather than an isolated dermal metastatic lesion. Survival outcomes have also been reported herein to help clarify the behavior with the potential to help further classify and correlate them with the current staging system.

In our series of 83 patients treated with WE and SLNB, which is one of the larger series reported in the literature, we reported the OS and DSS of our entire cohort and compared this for patients with a negative and positive SLNB. The majority of previous studies have been reported as single-center series or case reports with documented OS rates from 80% to 100% at 5-years (Table I). We included DSS in our final analysis since this is the survival statistic that is represented in the AJCC staging database. Hence, it appears as if DM behaves similarly to known primary cutaneous melanoma of similar thickness and sentinel node status, rather than a solitary dermal metastasis (stage IV M1a) from a remote primary site or in-transit disease (stage IIIB).

Most of the data on the use of SLNB is derived from small, single institution studies, which make it difficult to draw any significant conclusions on its value and utility [19]. Hu et al. reviewed a prospectively collected database of patients who presented with melanoma at a single institution over a 16-year period. A total of 16 patients with solitary DM were identified, and of those 11 had a SLNB. They constructed a Markov model to compare management strategies of WE of DM with and without the use of SLNB. The authors

concluded patients in the SLNB arm were more likely to remain in the disease-free state compared to those who had a WE followed by observation alone [19]. In the final analysis of the MSLT-1 trial, patients with intermediate thick melanomas (1.2–3.5 mm) who were randomized to SLNB had a significant improvement in relapse-free survival compared to those in the observation arm ($P=0.01$) [20]. The authors concluded SLNB significantly reduces recurrence for both intermediate melanomas by essentially decreasing subsequent nodal relapse [20,21]. This is similar to our data, which show a significant improvement in RFS in those with a negative SLNB, though the procedure did not have any impact on melanoma-specific survival.

SLNB has prognostic significance for RFS, but it should also be considered and utilized based on the yield and false-negative rate. All the patients included in our study had a SLNB, with a calculated yield of 12%. Morton et al. reported a yield of 16% with 1.2–3.5 mm melanomas [22]. The lower incidence of positive sentinel lymph nodes and higher false-negative rates seen in our study could theoretically be due to the dermal melanoma representing an intralymphatic melanoma with disease that has not reached the nodal basin. However, this does not hold true when looking at the survival of the DM patients in this study, which is closer to stage IIA/B and IIIA melanoma, whereas a dermal metastatic lesion with positive nodes (false negative or on SLNB) would be staged as a IIIB melanoma and have a much lower survival rate. The yield of positive sentinel lymph nodes and acceptable false-negative rate reported in our study would support the use of SLNB as an effective staging tool for DM.

Some recognized limitations in our study are derived from the inherent flaws of the retrospective design and missing data for some patients. Another limitation seen in this study was only including patients who had a WE and SLNB of the DM. Patients deemed to have DM and not offered a SLNB were excluded from the final database, which introduces a selection bias. Even though all patients received SLNB, we note that the rate of nodal metastasis is consistent with that described in the literature for a given Breslow thickness [23,24]; hence, results should be broadly applicable to the overall patient population clinically eligible for SLNB staging. The rate of metastasis may be slightly lower than originally thought given the large range of Breslow thickness. One final limitation is the use of DSS and its inherent difficulty in accurately assessing it in a retrospective study. All the patients included in our study had close follow-up, which was reflected in the clinical notes.

CONCLUSION

In our experience, patients with a solitary DM without a history of a primary lesion have a low risk of in-transit recurrence and increased RFS compared to resected distant metastatic disease published in the literature. In this small series of patients with DM, the behavior and survival mimics those of a known primary cutaneous melanoma of similar thickness. The survival of a patient with DM and a negative SLNB is closer to a IIA/IIB cutaneous melanoma, while the survival of those with a positive SLNB is closer to a IIIA/IIIB melanoma. SLNB should be utilized in the management of DM based on a SLNB yield of 12% and the low false-negative rate. SLNB provides prognostic value by identifying patients with regional nodal disease who may benefit from CLND followed by potential adjuvant

treatment or enrollment in a clinical trial. This should only be done after the appropriate work up including a comprehensive physical examination and imaging studies have excluded metastatic disease.

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Fig. 1.

(A) High-power field showing the relationship of the tumor pushing on the undersurface of the epidermis without a distinct connection and lack of intraepidermal melanocytes (arrows).

(B) Low-power field showing a well-circumscribed tumor within the dermis.

Fig. 2. Recurrence-free survival (RFS). The entire cohort of 83 patients is compared with the 10 sentinel lymph node (SLN) positive patients and the 73 SLN negative patients.

Fig. 3. Overall survival (OS) (top) and disease-specific survival (DSS) (bottom). The entire cohort is compared with the 10 sentinel lymph node (SLN) positive and 73 SLN negative patients on their respective disease curves.

TABLE I

Summary of Retrospective Studies Reporting Dermal Melanoma Survival

Study	Year	Dermal melanoma (# of pts)	Median follow-up (months)	SLNB	5-year OS (%)	5-year DSS (%)	Median DSS survival (months)
Schlagenhauff et al.	1997	30	22	No	100	NR	NR
Anbari et al.	1997	3	— [*]	No	100 ^a	NR	NR
Bowen et al.	2000	11	46	No	83	NR	NR
Swetter et al.	2004	7	34	Yes	100	NR	NR
Katz et al.	2005	12	16	No	25	NR	NR
Cassarino et al. ^b	2008	13	36	Yes	NR	92 ^c	NR
Lee et al.	2009	71	68	Yes ^d	73	NR	158.4
(Current Study) Doepker et al.	2014	83	27	Yes	67.7	78.5	Not reached

OS, overall survival; DSS, disease-specific survival; NR, not reported.

^{*} Median follow-up was not reported.

^a Overall survival for this cohort was not reported beyond 4 years.

^b This is an extension of the results reported by Swetter et al., with an additional 6 patients and increase in median duration of follow-up to 36 months (range, 6–94 months).

^c Survival reported at 44 months.

^d SLNB was performed in only 20 patients.

TABLE II

Patient Demographics and Tumor Characteristics Stratified by SLN Status

Characteristics	Entire cohort DM N =83	SLN Positive n =10 (12%)	SLN Negative n =73 (88%)	P value ^a
Age at diagnosis (years)				
Median (range)	63 (22–91)	62 (32–91)	63 (22–87)	0.66
Gender (%)				
Male	52 (62.7)	7 (70.0)	45 (61.6)	0.75
Female	31 (37.3)	3 (30.0)	28 (38.4)	
Breslow Depth (mm)				
Median (range)	2.8 (1.0–17.2)	3.2 (1.2–14.4)	2.8 (0.7–17.2)	0.29
T stage (%)				
T1	2 (2.4)	0	2 (2.7)	0.95
T2	29 (34.9)	3 (30.0)	26 (35.6)	
T3	17 (20.5)	2 (20.0)	15 (20.6)	
T4	32 (38.6)	5 (50.0)	27 (37.0)	
Unknown	3 (3.6)	0	3 (4.1)	
Mitotic rate (%) ^b				
<1	4 (4.9)	0	4 (5.5)	NA ^c
1–2	3 (3.6)	0	3 (4.1)	
>2	8 (9.6)	0	8 (11.0)	
LVI (%) ^b				
Present	4 (4.8)	2 (20.0)	2 (2.7)	0.03
Absent	16 (19.3)	0	16 (21.9)	
VGP (%) ^b				
Present	16 (19.3)	1 (10.0)	15 (20.5)	0.99
Absent	1 (1.2)	0	1 (1.4)	
Location of DM (%)				
Head and neck	31 (37.3)	2 (20.0)	29 (39.7)	0.44
Trunk	16 (19.3)	2 (20.0)	14 (19.2)	
Extremities	36 (43.4)	6 (60.0)	30 (41.1)	
SLN Basin (%)				
Axilla	41 (49.4)	6 (60.0)	35 (47.9)	0.56
Neck	30 (36.1)	2 (20.0)	28 (38.4)	
Groin	12 (14.5)	2 (20.0)	10 (13.7)	

NA, not applicable; DM, dermal melanoma; SLN, sentinel lymph node; LVI, lymphovascular invasion; VGP, vertical growth phase.

^aThe normal scores test was used for continuous variables and Pearson's χ^2 test with Monte Carlo simulation for *P*-value calculations used for categorical variable.

^bData unavailable or missing for mitotic rate in 68 cases, for LVI in 63 cases, and for VGP in 66 cases; unavailable or missing data has been removed prior to testing.

^c*P*-value is unable to be calculated due to all 10 mitotic rates missing for the SLN positive group.