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Desmoplastic Melanoma: Is There a Role for Sentinel Lymph Node Biopsy?

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Abstract

Background—The utility of sentinel lymph node biopsy (SLNB) for desmoplastic melanoma (DM) is debated. We describe a large single-institution experience with SLNB for DM to determine clinicopathologic factors predictive of SLN metastasis.

Methods—Retrospective review identified 205 patients with DM who underwent SLNB from 1992 to 2010. Clinicopathologic characteristics were correlated with SLN status and outcome.

Results—Median age was 66 years, and 69 % of patients were male. Median Breslow thickness was 3.7 mm. In 128 cases (62 %), histologic subtype data was available; 61 cases (47.7 %) were mixed and 67 cases (52.3 %) were pure DM. A positive SLN was found in 28 cases (13.7 %); 24.6 % of mixed and 9 % of pure DM had SLN metastases. Multivariable analysis demonstrated that after controlling for age, histologic subtype correlated with SLN status [odds ratio (OR): 3.0 for mixed vs pure, 95 % confidence interval (95 % CI): 1.1–8.7; $p < .05$]. Completion lymph node dissection was performed in 24 of 28 positive SLN patients with 16.7 % of cases having additional nodal disease. After a median follow-up of 6.3 years, 38 patients developed recurrence and 61 patients died. Positive SLN patients had a significantly higher risk of melanoma-related death compared with negative SLN patients ($p = .01$).

Conclusions—The overall risk for SLN metastasis for DM is 13.7 % and is significantly higher for mixed (24.6 %) compared with pure (9.0 %) DM. We believe that these rates are sufficient to justify consideration of SLNB for both histologic variants, especially since detection of SLN disease appears to predict a higher risk for melanoma-related death.

Desmoplastic melanoma (DM) represents <4 % of all primary cutaneous melanomas and is characterized by a paucicellular proliferation of malignant spindled melanocytes within an abundant collagenous/myxoid (“desmoplastic”) stroma.^{1–4} DM is usually found on the head and neck of older males and often presents as a thicker tumor compared with nondesmoplastic melanoma (non-DM).^{1,4–7} Despite the greater thickness, some studies report lower rates of nodal metastases compared with non-DM, suggesting a potentially different biologic behavior.^{6,8} Interestingly, activating BRAF^{V600E} mutations, present in ~50 % of non-DM, are lacking in DM, providing further evidence for a different biology.⁹ However, studies on DM demonstrate inconsistent rates of nodal metastases, varying from 0 to 15 %.^{5,6,8,10–17}

In 2004, Busam et al.⁴ proposed subdividing DM into pure and combined variants based on extent of desmoplasia. In 2005, Hawkins et al.⁷ renamed the combined variant as the “mixed” subtype. Pure DM was defined by a predominance of stromal fibrosis with >90 % desmoplasia. Mixed DM was characterized by desmoplasia in <90 % but >10 % of the tumor, with the remainder consisting of a conventional melanoma pattern of epithelioid and/or spindle areas without a significant stromal component.

After the introduction of histologic subtyping, some studies suggested differing rates of nodal involvement for mixed and pure variants.^{8,17} Other studies demonstrated no significant difference in positive sentinel lymph node biopsy (SLNB) rates between mixed and pure DM.¹⁵ The inconsistent reports on nodal involvement make it difficult to determine which patients with DM would benefit from SLNB. Furthermore, the recently published SSO/ASCO guidelines, which recommend SLNB for DM, differ from the NCCN guidelines, which do not recommend SLNB for pure DM.^{18–20} We examined our experience with SLNB for DM to determine clinicopathologic factors predictive of SLN metastasis.

Methods

After obtaining Institutional Review Board approval, a retrospective review was conducted from 1992 to 2010 to identify patients who were diagnosed with DM and underwent SLNB at Moffitt Cancer Center. Demographic, clinical, pathology, and outcome data were reviewed. Primary tumors were resected with appropriate margins based on Breslow thickness. Patients were evaluated for radiation therapy, which was used selectively and extensively for thicker lesions (>4 mm) or lesions with neurotropism. SLNB was performed according to previously described techniques.^{21,22}

All cases were reviewed by the staff dermatopathologist. Primary tumor characteristics were assessed and re-reviewed in cases with available tissue by a single dermatopathologist (JLM). Histologic subtype was characterized as pure or mixed using the 2004 MSKCC classification system.^{4,7} Pure DM was defined as a spindle cell melanoma with >90 % desmoplasia while mixed DM was defined by desmoplasia involving <90 % but >10 % of the melanoma (see Fig. 1). Assessment of SLNs consisted of submission of the entire lymph node and evaluation of sections stained with hematoxylin and eosin (H&E) and immunohistochemistry with S-100 and MART-1/Melan-A. Completion lymph node

dissection (CLND) specimens were submitted as a single section of large nodes, or complete submission of smaller (<4 mm) lymph nodes, and evaluated with H&E staining.

The Wilcoxon Rank-Sum test was used to compare age and Breslow thickness between two groups of patients. Chi-square or Fisher exact tests were used to study the association of SLNB status with various categorical demographic and disease characteristic variables. Continuous variables were discretized using either their medians or clinically meaningful cutpoints. Percentage of positive SLNB and its 95 % confidence interval (95 % CI) were reported in the entire study sample and in different subgroups of patients defined by covariates of interest. Univariable logistic regression modeling was conducted to determine whether a demographic, disease, or clinical variable significantly predicted SLNB status. Multiple logistic regression with the stepwise variable selection technique was adopted to select the most significant risk factors from a set of predefined covariates with the level of entry set at 0.10 and level of stay at 0.05. Both raw and adjusted odds ratios (OR) and their 95 % CIs were calculated for the odds of having a positive node. The Kaplan–Meier product-limit method was used to analyze recurrence-free survival (RFS) and overall survival (OS). The log-rank test was used to test for differences in RFS and OS between any two subgroups of interest. Gray's competing risks methodology was used to calculate melanoma-specific mortality (MSM) in order to take into account competing risks (i.e., non-melanoma related or unknown causes of death). Gray's modified log-rank test was used to compare the cumulative MSM curves between any two subgroups of interest. A *p* value of .05 was considered statistically significant. All statistical analyses were performed using SAS 9.2 or higher.

Results

Patient Demographics and Primary Tumor Characteristics

In total, 205 patients with DM had a SLNB. Overall median age was 66.3 years (range, 15.8–88.5 years), and the majority of patients (68.8 %) were male. Median ages for patients with mixed and pure DM were 68 and 70 years, respectively. Patient demographics are summarized in Table 1. A total of 28 patients (13.7 %) had a positive SLNB, while 177 patients had a negative SLNB. Of the 28 positive SLN patients, 24 (85.7 %) had a CLND, three were lost to follow-up, and in one case the reason for not performing a CLND was not documented. For the 24 patients undergoing CLND, additional positive nodes were found in four cases (16.7 %).

As shown in Table 1, the majority of tumors were on the head and neck (51.2 %). Overall median Breslow thickness was 3.7 mm (range, 0.5–35 mm) with no significant difference between mixed (median, 4.4 mm) and pure (median, 4.8 mm) DM (*p* = .54). Ulceration was present in 32 cases (19.4 %) where ulceration status was known (80.5 %), while a mitotic rate (MR) 1/mm² was seen in 57 cases (41.9 %) where MR had been evaluated (66.3 %). Perineural invasion was found in 89 (57.1 %) of 156 evaluated cases (76.1 %). Histologic subtype data was available in 128 cases (62.4 %) with 61 (47.7 %) and 67 (52.3 %) cases classified as mixed and pure, respectively.

Predictors of Sentinel Lymph Node Metastases

Positive SLN patients appeared to be significantly younger (median, 57.8 years) compared with negative SLN patients (median, 67.5 years; $p < .05$). Median Breslow thickness was greater for positive (4.9 mm) versus negative (3.6 mm) SLN patients, but this only trended toward significance ($p = .09$). SLN disease was found in 25 % of ulcerated cases compared with 13.5 % of nonulcerated cases ($p = .11$). A positive SLN was seen in 21.1 % of tumors with a MR $\geq 1/\text{mm}^2$ but only in 11.4 % of tumors with a MR $< 1/\text{mm}^2$ ($p = .12$). SLN metastasis rates in cases with (13.5 %) and without (16.4 %) perineural invasion were not significantly different ($p = .61$).

For the 128 cases with histologic subtype data, 21 cases (16.4 %) had a positive SLN. By univariable analysis, SLN metastases were seen at a significantly higher rate in mixed (24.6 %) compared with pure cases (9.0 %; OR, 3.3; 95 % CI, 1.2–9.2; $p < .05$). After controlling for age, which was the only other significant variable at .05 by univariable analysis, multivariable analysis showed that a mixed subtype remained significantly associated with SLN disease (OR: 3.0, 95 % CI: 1.1–8.7; $p < .05$).

Recurrence and Recurrence-Free Survival

Recurrence developed in 38 patients (18.5 %) with first sites of recurrence shown in Table 2. Local recurrences were uncommon and seen in 3.4 % of all patients. There were five negative SLN patients (2.8 %) who developed nodal recurrences, giving a negative predictive value of 97.2 % and a false-negative rate of 15.2 % (5 positive nodes missed of 33 total). Of these five false-negative cases, 4 (80 %) had head and neck primaries, 2 (40 %) had pure, and 3 (60 %) had mixed DM. Nodal recurrences also occurred in 2 of 28 positive SLN patients (7.1 %) with both developing in the 24 patients who had a CLND, resulting in a regional control rate of 91.7 % (22 of 24 patients). Distant recurrences occurred in 7.3 % of negative and 21.4 % of positive SLN patients.

As shown in Fig. 2a, RFS was worse for positive versus negative SLN patients; however, this was not a significant difference ($p = .31$). The 5-year RFS was 62.4 % (95 % CI: 39.9–78.5 %) and 76.4 % (95 % CI: 68.6–82.5 %) for positive and negative SLN patients, respectively.

Overall Survival

After an overall median follow-up of 6.3 years (4.6 and 4.7 years for mixed and pure cases, respectively), 61 deaths were seen. As shown in Table 2, 10 positive (35.7 %) and 51 negative (28.8 %) SLN patients died. In the positive SLNB group, eight deaths (28.6 %) were melanoma-related, one death (3.6 %) was not melanoma-related, and one death (3.6 %) had an unknown cause. In the negative SLNB group, 19 deaths (10.7 %) were melanoma-related, 18 deaths (10.2 %) were not melanoma-related, and 14 deaths (7.9 %) had unknown causes.

As shown in Fig. 2b, there was no significant difference in OS between positive and negative SLN patients ($p = .51$). The 5-year OS was 83.3 % (95 % CI: 61.3–93.4 %) and 79.3 % (95 % CI: 71.6–85.1 %) for positive and negative SLN patients, respectively.

Melanoma-Specific Mortality

Cumulative MSM as stratified by SLN status is shown in Fig. 3. Positive SLN patients were noted to have a significantly higher risk for melanoma-related death compared with negative SLN patients ($p = .01$).

In the pure DM group, a higher percentage of melanoma-related deaths occurred in positive SLN patients (2 melanoma-related deaths in 6 patients, 33.3 %) compared with negative SLN patients (4 melanoma-related deaths in 61 patients, 6.6 %). In the mixed DM group, 3 of 15 patients with a positive SLNB (20 %) died from melanoma compared with 12 melanoma-related deaths in the 46 patients with a negative SLNB (26.1 %).

Discussion

Studies looking specifically at SLNB for DM report SLN metastasis rates of 0–15 %.^{5,6,8,10–17} Our study is consistent with these prior reports since the overall risk for SLN disease was 13.7 %. In larger series assessing >80 DM patients (including the current study), the median tumor thickness ranged from 2.5 to 3.7 mm.^{1,6,11,13,15,17} Nodal metastasis rates for non-DM of comparable thickness (>3 mm) are >25 %, which is far greater than the rates reported for DM.^{1,7,11,23–29} Furthermore, Livestro et al.⁶ case-matched DM and non-DM patients by age, gender, and tumor thickness and showed that SLN metastasis rates were significantly lower for DM (8 %) compared with non-DM (33.8 %, $p = .13$). These results suggest that DM may behave in a biologically unique manner with a lower propensity for metastasizing to regional nodes. Interestingly, several studies on DM report a zero rate of SLN metastases, but these series were small and assessed <25 patients who underwent SLNB.^{5,11,12,16}

Investigators have looked for predictors of SLN disease in DM. Wasif et al. showed on multivariable analysis that age <69 years, extremity location, and Breslow thickness were significant predictors of SLN metastases, while Su et al. found no significant predictors for SLN disease.^{10,13} However, histologic subtype was not evaluated in these two studies.¹⁰ Murali et al.^{15,30} showed that SLN metastases occurred more often in mixed (8.5 %) versus pure (4.9 %) DM, although this was not a significant difference ($p = .25$), and in a second study they found no significant predictors of SLN disease. Mohebbati et al.¹⁶ reported on head and neck DM and found no SLN metastases in 15 and 8 patients with pure and mixed DM, respectively. In contrast, Pawlik et al.⁸ reported that SLN disease occurred at a significantly higher rate in mixed (15.8 %) versus pure (2.2 %) DM ($p < .01$). George et al.¹⁷ found that 22 % of mixed and 0 % of pure DM had nodal disease. We found a significantly higher positive SLN rate in mixed (24.6 %) compared with pure (9 %) DM, and by multivariable analysis, histologic subtype was the only significant predictor of SLN disease after adjusting for age groups.

Few studies have assessed the survival impact of SLN metastases specifically for DM. Murali et al.¹⁵ showed that SLN disease significantly predicted worse disease-free survival (DFS) but not OS. In contrast, Pawlik et al.⁸ reported that SLN metastases did not significantly predict DFS on multivariable analysis. Wasif et al.¹³ demonstrated that 5-year OS did not differ between node-negative (65 %) and node-positive (64 %) DM patients (p

= .86). Although we found no significant difference in RFS or OS between positive and negative SLN patients, MSM was found to be significantly worse for positive SLN patients ($p = .01$). In addition, histologic subtype may influence MSM since the percentage of melanoma-related deaths appeared to differ between positive and negative SLN patients in pure cases but not in mixed cases, despite the fact that mixed DM patients had significantly higher rates of SLN disease. However, definitive conclusions on MSM based on either histologic subtype or SLN status cannot be made in this study due to the low number of melanoma-related deaths.

In this older population, a considerable proportion of negative SLN patients died from non-melanoma causes, which may help explain why prior studies and the current study did not find significant differences in RFS or OS. The survival impact of SLN status was only seen when melanoma-related deaths were considered. Of note, a higher number of deaths were censored in the negative SLNB group (62.7 %), due to either unknown (27.5 %) or non-melanoma (35.3 %) causes of death, compared with the positive SLNB group where only a combined 20 % of deaths were censored. An assumption was made that deaths due to unknown or other causes occurred independently of melanoma-related deaths. Although the uneven censoring has the potential for bias, our results suggest that SLN status appears to have an impact on melanoma-specific survival in DM patients.

Scoggins et al.³¹ reported that the false-negative rate of SLNB for melanomas ≤ 1 mm was 10.8 %. The majority of DM are on the head and neck, and most studies of SLNB performed in this location report false-negative rates of 15–30 %.^{32–35} The false-negative rate in our series was 15.2 %, which is consistent with these prior studies. Considering the low false-negative and complication rates of SLNB, many surgeons use a 5–10 % risk of nodal metastasis as a reasonable threshold for performing SLNB.^{36,37} Using a 5 % or even 10 % risk threshold for SLN metastases, our results suggest that SLNB should be considered in both histologic variants, since SLN metastases were detected in 24.6 % of mixed and 9 % of pure DM. This is consistent with the SSO/ASCO guidelines that recommend SLNB for DM, but differs from the NCCN guidelines that do not recommend SLNB for pure DM.^{18–20} Of note, the finding of additional nodal disease in 16.7 % of CLND specimens is similar to non-DM, and our rate of regional control was also similar to non-DM positive SLN patients at 91.7 %.^{36,38}

In summary, patients with DM have a considerable risk for SLN metastases (13.7 %), and the risk is significantly higher for mixed (24.6 %) compared with pure (9 %) DM. Using a 5–10 % risk threshold for SLN disease, SLNB should be considered for both histologic variants. Our study provides further evidence that pure DM may behave in a manner that is biologically different from other types of melanoma. Nodal metastasis rates appear lower for pure DM than for mixed DM or non-DMs of similar thickness, and the melanoma-specific survival impact of SLN status may differ based on histologic subtype. Additional larger studies on DM are needed, particularly to determine the true impact of histologic subtype and nodal status on survival.

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Fig. 1.

Histologic subtypes of desmoplastic melanoma and sentinel lymph node metastasis. **a** Primary pure desmoplastic melanoma demonstrating paucicellular dermal growth of spindle melanocytes surrounded by desmoplastic stromal change filling the dermis and extending to base of section. **b** Mixed desmoplastic melanoma demonstrating areas of hypercellularity interspersed with areas of lower cellularity with desmoplastic stromal change (*arrow*). **c** Positive sentinel lymph node from a patient with pure desmoplastic melanoma. S-100 immunostain demonstrates areas of multifocal positivity. **d** Positive sentinel lymph node from another patient with pure desmoplastic melanoma. *Arrow* points to rare subcapsular aggregates of atypical spindle cells

Fig. 2.

a Recurrence-free survival stratified by sentinel lymph node (SLN) status. The 177 patients who had a negative SLN biopsy are compared with the 28 positive SLN patients. **b** Overall survival stratified by sentinel lymph node (SLN) status. The 177 patients who had a negative SLN biopsy are compared with the 28 positive SLN patients

Fig. 3. Cumulative melanoma-specific mortality stratified by sentinel lymph node (SLN) status. Positive SLN patients had a significantly higher risk of melanoma-related death compared with negative SLN patients ($p = .01$)

Table 1
Patient demographics, primary tumor characteristics, and correlation with sentinel lymph node status

	All patients (N = 205)	Positive SLNB (N = 28)	Negative SLNB (N = 177)	p value ^a
Age (years)				<.05 ^b
Mean ± SD	63.5 ± 15.1	58.5 ± 13.8	64.3 ± 15.2	
Median	66.3	57.8	67.5	
Range	15.8–88.5	34.6–82.2	15.8–88.5	
Gender (n, %)				NS
Male	141 (68.8)	21 (14.9)	120 (85.1)	
Female	64 (31.2)	7 (10.9)	57 (89.1)	
Breslow thickness (mm) ^c				NS
Mean ± SD	4.9 ± 4.3	5.6 ± 3.7	4.8 ± 4.3	
Median	3.7	4.9	3.6	
Range	0.5–35	1.3–18	0.5–35	
Tumor location (n, %)				NS
Head and neck	105 (51.2)	12 (11.4)	93 (88.6)	
Extremity	50 (24.4)	6 (12)	44 (88)	
Trunk	50 (24.4)	10 (20)	40 (80)	
Histologic subtype (n, %)				<.05 ^d
Mixed	61 (29.8)	15 (24.6)	46 (75.4)	
Pure	67 (32.7)	6 (9)	61 (91)	
Unknown	77 (37.6)	7 (9.1)	70 (90.9)	
Ulceration (n, %)				NS
Yes	32 (15.6)	8 (25)	24 (75)	
No	133 (64.9)	18 (13.5)	115 (86.5)	
Unknown	40 (19.5)	2 (5)	38 (95)	
Mitotic rate (n, %)				NS
1/mm ²	57 (27.8)	12 (21.1)	45 (78.9)	
<1/mm ²	79 (38.5)	9 (11.4)	70 (88.6)	
Unknown	69 (33.7)	7 (10.1)	62 (89.9)	
Perineural invasion (n, %)				NS
Yes	89 (43.4)	12 (13.5)	77 (86.5)	
No	67 (32.7)	11 (16.4)	56 (83.6)	
Unknown	49 (23.9)	5 (10.2)	44 (89.8)	

SLNB sentinel lymph node biopsy, SD standard deviation, NS not significant

^aFor comparison between positive SLNB and negative SLNB based on Wilcoxon, chi-square, or Fisher exact test

^bSignificant on univariable and multivariable logistic regression analysis based on age groups (divided by median) 66 vs >66 years for predicting SLNB status

^cData unavailable or missing for Breslow thickness in three cases

^dSignificant on univariable and multivariable logistic regression analysis adjusting for age for predicting SLNB status

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Table 2
Summary of recurrences and deaths

	All patients (N = 205)	Positive SLNB (N = 28)	Negative SLNB (N = 177)
Recurrence (n, %)	38 (18.5)	9 (32.1)	29 (16.4)
First site of recurrence (n, %)			
Local	7 (3.4)	1 (3.6)	6 (3.4)
Regional	7 (3.4)	2 (7.1)	5 (2.8)
Distant	19 (9.3)	6 (21.4)	13 (7.3)
Unknown	5 (2.4)	0	5 (2.8)
Number of deaths (n, %)	61 (29.8)	10 (35.7)	51 (28.8)
Melanoma related	27 (13.2)	8 (28.6)	19 (10.7)
Other causes	19 (9.3)	1 (3.6)	18 (10.2)
Unknown	15 (7.3)	1 (3.6)	14 (7.9)

SLNB sentinel lymph node biopsy