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Sentinel Lymph Node Biopsy Is Indicated for Patients With Thick Clinically Lymph Node-Negative Melanoma

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Abstract

BACKGROUND—Sentinel lymph node biopsy (SLNB) is indicated for the staging of clinically lymph node-negative melanoma of intermediate thickness, but its use is controversial in patients with thick melanoma.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Messina has received fees from Myriad Corporation and Glaxo-SmithKline for work performed outside of the current study. Dr. Sondak has acted as a member of the Speakers Bureau and as a consultant/member of the Advisory Board for Merck and as a consultant/member of the Advisory Board for Provectus, Navidea, Amgen, OncoSec, MabVax, and Polynoma as well as a member of the Data Safety Monitoring Boards for Bristol-Myers Squibb, Glaxo-SmithKline, and Novartis (all relationships involve <\$25,000 in annual income from any single source) for work performed outside of the current study. Dr. Zager has received honorarium as a member of the Advisory Boards for Amgen, Provectus, and IGEA Inc and has acted as a paid member of the Scientific Advisory Board for and received grant funding from Delcath.

METHODS—From 2002 to 2012, patients with melanoma measuring 4 mm in thickness were evaluated at a single institution. Associations between survival and clinicopathologic characteristics were explored.

RESULTS—Of 571 patients with melanomas measuring 4 mm in thickness and no distant metastases, the median age was 66 years and 401 patients (70.2%) were male. The median Breslow thickness was 6.2 mm; the predominant subtype was nodular (45.4%). SLNB was performed in 412 patients (72%) whereas 46 patients (8.1%) presented with clinically lymph node-positive disease and 113 patients (20%) did not undergo SLNB. A positive SLN was found in 161 of 412 patients (39.1%). For SLNB performed at the study institution, 14 patients with a negative SLNB developed disease recurrence in the mapped lymph node basin (false-negative rate, 12.3%). The median disease-specific survival (DSS), overall survival (OS), and recurrence-free survival (RFS) for the entire cohort were 62.1 months, 42.5 months, and 21.2 months, respectively. The DSS and OS for patients with a negative SLNB were 82.4 months and 53.4 months, respectively; 41.2 months and 34.7 months, respectively, for patients with positive SLNB; and 26.8 months and 22 months, respectively, for patients with clinically lymph node-positive disease ($P<.0001$). The median RFS was 32.4 months for patients who were SLNB negative, 14.3 months for patients who were SLNB positive, and 6.8 months for patients with clinically lymph node-positive disease ($P<.0001$).

CONCLUSIONS—With an acceptably low false-negative rate, patients with thick melanoma and a negative SLNB appear to have significantly prolonged RFS, DSS, and OS compared with those with a positive SLNB. Therefore, SLNB should be considered as indicated for patients with thick, clinically lymph node-negative melanoma.

Keywords

melanoma; sentinel lymph node biopsy; thick melanoma; false-negative rate; Breslow depth

INTRODUCTION

There will be a projected 76,100 new cases of invasive cutaneous melanoma diagnosed in the United States in 2014.¹ Excluding basal and squamous cell carcinomas, melanoma represents the fifth and seventh most common malignancy in males and females, respectively. Unlike the declining rates in most other cancer types (such as prostate, colorectal, and lung cancers), the incidence of melanoma has been increasing, with an estimated annual percentage increase ranging from 1.7% to 3.9%.¹ Improved detection of earlier and thinner melanomas was attributed to this increasing national incidence. However, a recent study of trends of melanoma thickness within the United States notes a stable percentage of thick melanomas over the years.² As tumor thickness increases, there is an associated significant decline in survival rates. The 10-year survival rate for patients with thin melanomas (measuring 1 mm) is 92%, but decreases to 50% in patients with T4 disease (defined as melanoma measuring >4 mm in thickness).³

The Multicenter Selective Lymphadenectomy Trial-I (MSLT-I), a large, prospective randomized trial, evaluated patients with clinically lymph node-negative melanoma who were undergoing sentinel lymph node biopsy (SLNB) or observation of their lymph node

basins.^{4,5} The MSLT-I helped to form the basis for the recent recommendation in the American Society of Clinical Oncology-Society of Surgical Oncology joint guideline that SLNB is indicated for patients with intermediate-thickness melanoma (measuring 1-4 mm).⁶ However, controversy remains regarding the use of SLNB in both patients with thin (measuring <1 mm) and thick (measuring >4 mm) melanoma.

Critics of SLNB for patients with thick melanoma cite the increased risk of occult systemic metastases in this high-risk cohort and the lack of a survival advantage for the treatment of occult lymph node-positive disease in these patients demonstrated in the MSLT-I.^{5,7} Proponents of SLNB cite improved prognostic and staging information that can affect decisions regarding adjuvant therapy.^{8,9} The results of the MSLT-I demonstrated that patients with thick, lymph node-negative melanomas frequently harbor micrometastases (32.9% in patients with primary tumors measuring >3.50 mm in thickness); that patients with thick, lymph node-negative melanomas who do not undergo SLNB experience frequent and relatively rapid lymph node disease recurrence (37.6% of patients developed disease recurrence within the lymph node basin at a median of 9.2 months); and that patients undergoing lymph node dissection for occult disease in the SLN had less morbidity compared with those undergoing the same procedure for clinically recurrent lymph node disease.^{5,10} The primary goal of the current study was to evaluate SLNB in patients with thick, clinically lymph node-negative melanoma to provide additional insight into the indications for and relative value of SLNB in this setting.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, a retrospective review was conducted involving patients referred to the H. Lee Moffitt Cancer Center and Research Institute (Moffitt Cancer Center) from 2002 through 2012 with thick cutaneous melanomas, defined as having a primary tumor Breslow thickness of ≥ 4 mm. Patients with distant metastases that were clinically evident at the time of diagnosis of the primary melanoma were excluded from the study. Patient demographics, primary tumor pathology, lymph node status, and patient outcomes were reviewed. Surgical treatment of primary tumors with or without SLNB was performed either at Moffitt Cancer Center or at referring institutions. However, the reported false-negative rate (FNR) was calculated based solely on patients who received their SLNB at Moffitt Cancer Center. All patients evaluated at Moffitt Cancer Center routinely underwent pathologic review of biopsies and surgical specimens by our dermatopathologists before definitive treatment. The following clinicopathologic features were recorded for each patient: sex, age, ethnicity, location of the primary tumor, histologic subtype, Breslow thickness, Clark level, ulceration, satellitosis, mitotic rate, regression, vertical growth phase, SLNB (yes or no), SLNB status, and use of adjuvant therapy. SLN specimens were serially sectioned and evaluated using hematoxylin and eosin (H & E) staining as well as S-100 and MART-1 (melanoma-associated antigen recognized by T cells [Melan-A]) immunostaining. In the SLN, a diagnosis of metastatic melanoma was made if cells positive for both immunohistochemical markers were observed, or if atypical cells noted on H & E staining and positive for S-100 and/or Melan-A immunostaining were noted. Completion lymph node dissection (CLND) specimens were evaluated by submitting all lymph nodes, either completely or by a representative section, and staining by H & E.

S-100 and/or Melan-A immunostains were performed on CLND specimens if atypical cells suspicious for metastatic melanoma were noted on H & E staining. During follow-up, melanoma recurrences were classified as follows: local/in-transit, regional lymph node metastases, or distant metastases.

At Moffitt Cancer Center, SLNB is routinely offered to patients with melanomas measuring 4 mm in thickness who demonstrate no signs of metastatic disease and are appropriate candidates for general anesthesia. Primary tumors are routinely resected with 2-cm margins whenever feasible for an acceptable functional and esthetic result. SLNB is performed in keeping with techniques previously described.^{11,12} Patients who did not undergo SLNB, for reasons such as patient preference, comorbid conditions, failure to map to a lymph node on preoperative lymphoscintigraphy, or presentation after prior wide excision, were followed with clinical examination and, in recent years, serial ultrasonography of the regional lymph node basin(s) at risk. Patients with SLN metastases are routinely offered CLND or encouraged to enroll in clinical studies such as the MSLT-II, in which patients were randomized to either immediate CLND or ultrasound surveillance of the affected lymph node basin.

Statistical Analysis

Patient and pathologic characteristics were evaluated using descriptive statistics. Continuous variables were dichotomized using established cutpoints or median values as appropriate. Patient and pathologic variables were tested for an association with SLNB positivity using the chi-square or Fisher exact tests, as appropriate. Logistic regression modeling was used to explore predictors of lymph node status. Overall survival (OS), recurrence-free survival (RFS), and disease-specific survival (DSS) were measured from the date of surgery. For OS, patients known to be alive at the time of last follow-up were censored on the last date of contact. RFS was defined as the time from the date of surgery to the date of recurrent disease or death, censoring those patients who were alive without disease at the time of last follow-up. DSS was defined as the time from surgery to melanoma-related death, censoring those patients who were alive or had died of other causes at the time of last follow-up. Kaplan-Meier survival curves and log-rank *P* values comparing differences in survival among predefined groups were generated. As a sensitivity analysis in examining differences in the risk of disease recurrence among groups, a competing risks model was fit considering death before disease recurrence as a competing risk. Cox proportional hazard models were used to estimate the association between patient and tumor variables and survival endpoints. Significant variables from univariable models were incorporated into multivariable models. Significance in all statistical tests was defined as a *P* value <.05.

RESULTS

Patient Characteristics

The characteristics of the 571 patients included in the current study are listed in Table 1. The median age of the patients was 66 years (range, 12-98 years). The majority of patients were male (401 patients; 70.2%). The median and mean Breslow thicknesses were 6.2 mm and 7.4 mm, respectively (range, 4-25 mm). The primary tumor locations were relatively evenly

distributed between the trunk, extremities, and head and neck areas. The predominant histologic subtype was nodular (259 patients; 45.4%). Ulceration was present in greater than one-half of the study group (312 patients; 54.6%).

SLN Status

After the exclusion of patients presenting with distant metastases, 571 patients were included in the current study (Fig. 1). Forty-six patients (8.1%) presented with clinically lymph node-positive disease and proceeded directly to therapeutic lymph node dissection. A total of 113 patients with clinically lymph node-negative disease did not undergo SLNB, 98 of whom (17.2% of the total) did not undergo SLNB secondary to medical comorbidities, patient preference, or other considerations (eg, prior wide excision or prior lymph node dissection in the expected draining regional lymph node basin). In these patients, the at-risk lymph node basins were followed with serial physical examination and, in most cases, ultrasonography at regular intervals. Eight patients underwent elective lymph node dissections despite having clinically negative regional lymph node basins; none were found to have metastatic disease in their lymphadenectomy specimens. An additional 7 patients failed to map to a lymph node basin and no SLN was retrieved; they were followed postoperatively in a manner similar to the patients undergoing lymph node observation.

SLNB was performed in 412 patients. The SLN was positive in 161 patients (39.1%) overall, including those patients who underwent SLNB at an outside institution and were referred to the study institution for further treatment. Excluding those patients who were referred with recurrent disease or who underwent their SLNB at an outside institution, we performed SLNB in 297 patients, among whom the SLN was found to be positive in 100 patients (33.7%). Factors associated with a positive SLNB are listed in Table 2. On univariable analysis, ulceration, a primary tumor location in the trunk and extremity compared with the head and neck, and the presence of satellitosis were found to be predictive of SLN metastasis. Mitotic rate (using 5 mitoses/mm² as a cutoff) and tumor regression were not found to be predictive of SLNB status. We did not find an association between Breslow thickness (using 6 mm as a cutoff) and SLN involvement in these patients. On multivariable analysis, a primary tumor location in the trunk (odds ratio [OR], 4.60; $P = .0003$) and extremity (OR, 3.17; $P = .008$) compared with a head and neck location, as well as the presence of satellitosis (OR, 10.31; $P = .006$), were found to be significant predictors of a positive SLNB. Compared with superficial spreading, desmoplastic histology was associated with a decreased likelihood of a positive SLN on univariable and multivariable analysis (OR, 0.09; $P = .001$). A total of 14 patients whose SLNB was performed at Moffitt Cancer Center eventually developed lymph node disease recurrence in the mapped basin despite a negative SLNB. To avoid referral bias, only these cases were used to calculate the FNR, which was 12.3% (14 of 114 lymph node-positive cases); the posttest probability of disease from a negative result was 7.1% (14 of 197 SLNB-negative cases).

Adjuvant Therapy

The majority of patients (379 patients; 66.4%) did not receive any adjuvant therapy. When it was used, the most common modality for adjuvant therapy was interferon (IFN)- α -2b; 78 patients received this treatment alone postoperatively. Seventy-five patients received

adjuvant radiotherapy to the primary site and/or regional lymph nodes without systemic therapy. Twenty patients received both radiotherapy and IFN- α -2b postoperatively. Nineteen additional patients were enrolled in clinical trials evaluating other adjuvant therapy options.

Survival Analysis

The median RFS was 21.2 months for the entire study population. The RFS was significantly better for SLNB-negative patients, with a median RFS of 32.4 months versus 14.3 months for SLNB-positive patients and 6.8 months for those with clinically lymph node-positive disease ($P<.0001$). On univariable analysis, SLNB status, Breslow thickness (≥ 6.2 mm vs <6.2 mm, dichotomized by the median value), mitotic rate (≥ 5 mitoses/mm² vs <5 mitoses/mm², dichotomized by the median value), primary tumor location, and satellitosis were found to be statistically significant predictors of RFS. On multivariable analysis, only SLNB status and mitotic rate remained statistically significant (Table 3). Treating death from nonmelanoma causes as a competing risk, the differences in disease recurrence among groups remained statistically significant ($P<.001$). At 2 years after surgery (near the median time to disease recurrence of 21.1 months), the estimated incidence of disease recurrence for patients with clinically lymph node-positive disease was 73.3% (95% confidence interval [95% CI], 60.4%-86.2%) and was 54.7% (95% CI, 46.5%-62.9%) for SLNB-positive patients, whereas it was only 34.3% (95% CI, 27.6%-40.9%) for SLNB-negative patients.

The median OS and DSS for the entire cohort were 42.5 months and 62.1 months, respectively (Fig. 2). A total of 237 patients (41.5%) were alive without evidence of melanoma at time of last follow-up. At the time of last follow-up, a total of 174 patients (30.5%) had died of disease, 57 patients (10%) were alive with disease, and 103 patients (18%) had died of other causes.

The median OS for patients with a negative SLNB was 53.4 months, which was significantly better than that for patients with a positive SLNB (34.7 months) or clinically positive lymph node disease (22.0 months) ($P<.0001$). The median DSS for patients with a negative SLNB was 82.4 months versus 41.2 months for patients with a positive SLNB and 26.8 months for those presenting with clinically lymph node-positive disease ($P<.0001$) (Fig. 2).

DISCUSSION

The main goal of the current study was to evaluate the usefulness and prognostic value of SLNB in patients with thick melanoma. Despite consensus regarding the role of SLNB in patients with intermediate-thickness melanoma, controversy persists concerning those patients at the periphery of the primary tumor thickness spectrum.⁶ The current study, which appears to be the largest series reported in the literature, indicated that 39% of patients with clinically lymph node-negative, thick melanoma had microscopic disease in their SLNs, a finding that is in agreement with previously published studies.¹³⁻¹⁵ Excluding those patients whose SLN mapping and biopsies were performed at an outside institution, the SLN positivity rate in the current study remained 33.7%, which is comparable to other large

published series. The vast majority of the patients with thick cutaneous melanoma in the current study were male (70.2%). This sex-based disparity may support proponents for a targeted melanoma screening program, particularly among older males.¹⁶⁻¹⁸

Since 1992, SLNB has been widely adopted and is considered extremely safe and accurate.¹² Much attention has been focused on the FNR associated with SLNBs. Although definitions can vary, we defined the FNR as the ratio of false-negative biopsies to the total number of positive lymph nodes biopsies (false-negative plus true-positive results).^{19,20} Excluding those patients whose SLNB was performed at other institutions, we noted a high success rate for identifying the SLN(s) (99.0%), a low posttest probability of lymph node disease after a negative SLNB (7.1%), and a low FNR (12.3%), illustrating that SLNB is an accurate tool in staging the regional lymph node basin in patients with thick melanoma. In addition, these results are comparable to previously published results among patients with intermediate-thickness melanoma regarding the accuracy of SLNB,^{20,21} which have been used to support the routine use of SLNB in those patients.⁶

Given the observed survival differences between patients with SLN-negative and SLN-positive disease in the current study, we believe that there is valuable prognostic information obtained from this procedure. In addition, patients with SLN-positive disease were found to be 2.2 times more likely to receive adjuvant therapy, radiotherapy, and/or IFN- α -2b ($P = .0002$). Previous retrospective studies have been mixed in their results evaluating the survival impact of SLNB status on patients with thick melanoma (Table 4).^{5,8,9,13-15,22-24}

Comparison between studies, particularly with what to our knowledge is the only prospective randomized trial published to date (MSLT-I), becomes problematic because the cutoff value for Breslow depth of thick melanoma differs among them. Although the American Joint Committee on Cancer definition of T4 melanoma is a primary tumor with a Breslow thickness >4 mm, we opted to include the 6 patients in the current series with a Breslow thickness of exactly 4 mm. Excluding these 6 patients did not change the statistical significance for any of the current study results. A large recent study published by Scoggins et al¹³ evaluated 240 patients with melanoma measuring >4 mm in thickness. The authors also demonstrated a significant difference in OS and DSS between patients with a negative SLNB and those with a positive SLNB. The current study, with 412 patients who underwent SLNB, demonstrated a similar significant RFS, OS, and DSS benefit. In addition, in a separate analysis using a competing risks approach for death, we confirmed a difference in disease recurrence rates between patients with SLNB-negative, SLNB-positive, and clinically lymph node-positive disease.

Although the risk of occult regional disease is high among patients with thick melanoma (39.1% in the current study), our subset analysis of patients with desmoplastic histology (pure, mixed, and not otherwise specified) who underwent SLNB (47 patients) demonstrated a lower SLNB-positive rate (6.4%) compared with patients with superficial spreading melanoma that was statistically significant on both univariable and multivariable analysis (OR, 0.09; $P < .001$). The other histologic subtypes did not demonstrate an increased or decreased risk of SLN positivity compared with superficial spreading. This lower lymph node disease rate mirrors previous studies evaluating SLNB positivity among patients with this histologic subtype,²⁵⁻²⁷ and further studies with larger numbers of patients with

desmoplastic histology are warranted to more fully define the value of SLNB in this subset of individuals. Based on a prior analysis involving a larger number of patients with (intermediate and thick) desmoplastic melanoma who had undergone SLNB, we continue to advocate its use in the majority of cases.²⁷

The results of the current study found that patients presenting with thick melanoma (≥ 4 mm in Breslow thickness) and a negative SLNB experience longer OS, DSS, and RFS compared with patients with a positive SLNB. In addition, patients with positive SLN (occult) disease experience longer OS, RFS, and DSS compared with those with clinically evident lymph node disease. With a relative high risk of lymph node disease, an acceptably low FNR, and significant prognostic information relative to survival, we believe that SLNB is indicated in patients with clinically lymph node-negative, thick, cutaneous melanoma.

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Figure 1.

Breakdown of 571 patients with melanoma is shown based on lymph node status at the time of presentation. TLND indicates therapeutic lymph node dissection; SLNB, sentinel lymph node biopsy.

Figure 2.

Kaplan-Meier curves are shown for (*Top*) overall survival, (*Middle*) disease-specific survival, and (*Bottom*) recurrence-free survival. Clinically positive (TLND) indicates patients with clinically positive regional disease at the time of presentation who underwent therapeutic lymph node dissection; SLN, sentinel lymph node.

TABLE 1

Characteristics of 571 Patients With Thick Cutaneous Melanoma

Characteristic		No. (%)
Age, y	Median	66
	Range	12-98
Sex	Male	401 (70.2)
	Female	170 (29.8)
Breslow thickness, mm	Median	6.2
	Range	4-25
Site of primary tumor	Extremities	231 (40.5)
	Trunk	187 (32.7)
	Head and neck	153 (26.8)
Histologic subtype	Nodular	259 (45.4)
	Desmoplastic (pure, mixed, NOS)	82 (14.4)
	Acral lentiginous	44 (7.7)
	Superficial spreading	43 (7.5)
	Other/unknown	143 (25.0)
Ulceration	Present	312 (54.6)
	Absent	205 (35.9)
	Unknown	54 (9.5)
Mitotic rate, mitoses/mm ²	Median	5
	Range	0-60
Satellitosis	Present	54 (9.5)
	Absent	517 (90.5)

Abbreviation: NOS, not otherwise specified.

TABLE 2

Associations With Positive SLNB in Patients With Thick Cutaneous Melanoma Using Logistic Regression

	Univariable Analysis		Multivariable Analysis	
	OR (95% Wald CI)	P	OR (95% Wald CI)	P
Age (>66 y vs ≤66 y)	0.71 (0.47-1.06)	.093		
Sex (female vs male)	1.16 (0.76-1.78)	.484		
Location				
Trunk vs head/neck	4.05 (2.20-7.45)	<.0001	4.60 (2.03-10.42)	.0003
Extremities vs head/neck	2.83 (1.56-5.12)	.001	3.17 (1.35-7.42)	.008
Breslow thickness (≥6 mm vs <6 mm)	1.21 (0.81-1.80)	.351		
Histology				
Desmoplastic vs superficial spreading	0.07 (0.02-0.26)	<.0001	0.09 (0.02-0.36)	.001
Acral lentiginous vs superficial spreading	0.83 (0.32-2.15)	.706	0.79 (0.28-2.25)	.657
Nodular vs superficial spreading	0.89 (0.44-1.82)	.751	0.82 (0.39-1.76)	.615
Vertical growth phase	0.78 (0.07-8.67)	.838		
Tumor regression (absent vs present)	0.59 (0.24-1.44)	.25		
Ulceration (present vs absent)	1.66 (1.09-2.54)	.019	1.43 (0.83-2.45)	.194
Mitotic rate, mitoses/mm ² (≤5 vs >5)	1.06 (0.69-1.65)	.784		
Satellitosis (present vs absent)	4.63 (1.77-12.11)	.002	10.31 (1.98-53.83)	.006

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio; SLNB, sentinel lymph node biopsy.

TABLE 3
Factors Associated With Recurrence of Melanoma Using Cox Proportional Hazard Models

		Univariable Analysis		Multivariable Analysis	
		HR (95% CI)	P	HR (95% CI)	P
Lymph node status	SLNB negative				
	SLNB positive	1.71 (1.33-2.19)	<.001	1.39 (1.03-1.86)	.029
	Clinically positive	3.93 (2.77-5.59)	<.001	4.36 (2.88-6.61)	<.0001
Ulceration	Absent				
	Present	1.33 (1.06-1.66)	.012	1.07 (0.83-1.39)	.599
Mitotic rate	<5 mitoses/mm ²				
	5 mitoses/mm ²	1.45 (1.15-1.84)	.002	1.43 (1.11-1.84)	.006
Satellitosis	Absent				
	Present	2.14 (1.56-2.93)	<.001	1.30 (0.86-1.96)	.212

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; SLNB, sentinel lymph node biopsy.

Selected Studies Evaluating SLNB in Patients With Thick Cutaneous Melanoma

TABLE 4

Study	Institution	Breslow Thickness, mm	No. of Patients	Positive Versus Negative SLN, %	3-Year OS Rate	3-Year RFS Rate	5-Year OS Rate	5-Year RFS Rate	Median RFS, Months	Median OS, Months
Gershenwald 2000 ⁸	MDACC	4	126	+SLN: 39% −SLN: 61%	66.4% (<i>P</i> < .006)	58% (<i>P</i> < .03)				
Cherpelis 2001 ²²	H. Lee Moffitt Cancer Center and Research Institute	>3	201	+SLN: 25% −SLN: 75%	70% (<i>P</i> = .08)	37% (<i>P</i> = .02)				
Ferrone 2002 ⁹	MSKCC	>4 or Clark level V	126	+SLN: 30% −SLN: 70%	82%	73%		32% (<i>P</i> = .0008)		
Essner 2002 ²³	John Wayne Cancer Institute	4	113	+SLN: 35% −SLN: 65%			50% (<i>P</i> = .159)	34% (<i>P</i> = .012)		
Thompson & Shaw 2002 ¹⁴	SMU	4	172	+SLN: 30% −SLN: 70%	66% (<i>P</i> = .005)	38% (<i>P</i> < .0001)	41% (<i>P</i> = .0005)	29% (<i>P</i> < .0001)		
Gajdos 2009 ¹⁵	Michigan	4	227	+SLN: 47% −SLN: 53%	88%	77%	47% (<i>P</i> < .0001)	68%		
Scoggins 2010 ¹³	Sunbelt Melanoma Trial	>4	240	+SLN: 41.7% −SLN: 58.3%			80%		31.0 (<i>P</i> = .04)	43.0 (<i>P</i> = .004)
Mozzillo 2013 ²⁴	Italy		298	+SLN: 39.3% −SLN: 60.7%			49%		46.5	55.5
Morton 2014 ⁵	MSLT-I	>3.5	173	+SLN: 32.9% −SLN: 67.1%			56% (<i>P</i> = .005)			
							60.8% ^a			
							70.2% ^a (<i>P</i> = .03)			
Current study	H. Lee Moffitt Cancer Center and Research Institute	4	412 ^b	+SLN: 39.1% −SLN: 60.9%					14.3 (<i>P</i> < .0001)	32.4 (<i>P</i> < .0001)
									34.7	53.4

Abbreviations: +, positive; −, negative; MDACC, The University of Texas MD Anderson Cancer Center; MSKCC, Memorial Sloan-Kettering Cancer Center; MSLT-I, Multicenter Selective Lymphadenectomy Trial-I; OS, overall survival; RFS, recurrence-free survival; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; SMU, Sydney Melanoma Unit.

^aResults are shown for 5-year melanoma-specific survival.

^bIncludes only those patients undergoing SLNB.