Microscopic Tumor Burden in Sentinel Lymph Nodes Predicts Synchronous Nonsentinel Lymph Node Involvement in Patients With Melanoma

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A B S T R A C T

Purpose

We and others have demonstrated that additional positive lymph nodes (LNs) are identified in only 8% to 33% of patients with melanoma who have positive sentinel LNs (SLNs) and undergo complete therapeutic LN dissection (cTLND). We sought to determine predictors of additional regional LN involvement in patients with positive SLNs.

Patients and Methods

Patients with clinically node-negative melanoma who underwent SLN biopsy (1991 to 2003) and had positive SLNs were identified. Clinicopathologic factors, including extent of microscopic disease within SLNs, were evaluated as potential predictors of positive non-SLNs.

Results

Overall, 359 (16.3%) of the 2,203 patients identified had a positive SLN. Positive non-SLNs were identified in 48 (14.0%) of the 343 patients with positive SLNs who underwent cTLND. On univariate analysis, several measures of SLN microscopic tumor burden, one versus three or more SLNs harvested, tumor thickness more than 2 mm, age older than 50 years, and Clark level higher than III were predictive of positive non-SLNs; primary tumor ulceration and number of positive SLNs had no apparent impact. On multivariable logistic regression analysis, measures of SLN microscopic tumor burden were the most significant independent predictors of positive non-SLNs; tumor thickness more than 2 mm and number of SLNs harvested also predicted additional disease. A model was developed that stratified patients according to their risk for non-SLN involvement.

Conclusion

In melanoma patients with positive SLNs, SLN tumor burden, primary tumor thickness, and number of SLNs harvested may be useful in identifying a group at low risk for positive non-SLNs and be spared the potential morbidity of a cTLND.

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INTRODUCTION

Although most patients with invasive melanoma present with clinically negative nodal basins, many patients harbor occult regional lymph node metastases. Intraoperative lymphatic mapping (IOLM) and sentinel lymph node (SLN) biopsy have become standard methods for determining the pathologic status of the clinically negative regional lymph node basin in patients with cutaneous melanoma.¹⁻¹⁰ SLN status is the most important predictor of survival in clinically node-negative melanoma patients.^{1,2,6,7,11,12}

Standard practice consists of observation of the mapped nodal basin if all identified SLNs are negative for disease and complete therapeutic lymph

node dissection (cTLND) if any SLN contains melanoma. The rationale for cTLND includes the possibility that patients will derive a survival benefit and improved regional nodal control compared with patients in whom lymphadenectomy is delayed until nodal disease becomes clinically apparent.^{13,14} Moreover, multivariate analyses have demonstrated that the number of nodes involved is an important predictor of survival.¹² However, because cTLND can be associated with significant morbidity¹⁵⁻¹⁷ and because positive non-SLNs are identified in only 8% to 33% of cTLND specimens,^{1,9,10,18-42} some argue that cTLND may not be required in all patients with a positive SLN.

We sought to determine which of the clinicopathologic prognostic factors—tumor thickness,

ulceration, Clark level, age, and sex—and which measures of tumor burden within SLNs could be used to predict the presence of positive non-SLNs. Our decision to examine multiple measures of SLN tumor burden was based in part on the extensive revision of the American Joint Committee on Cancer melanoma staging system in 2002,^{12,43} in which independent predictors of adverse survival in patients with stage III disease include, in addition to the total number of lymph nodes involved, whether the lymph node involvement is microscopic (ie, identified by SLN biopsy or elective lymph node dissection) or macroscopic (ie, clinically or radiographically detectable). Interestingly, our own preliminary data⁴⁴⁻⁴⁶ as well as published reports^{8,30,47} suggest that the extent of SLN tumor burden is associated with recurrence and survival. We therefore hypothesized that patients with greater microscopic SLN tumor burden would be at increased risk for non-SLN disease in their cTLND specimen and that a subset of patients could be identified in whom the risk of positive non-SLNs is sufficiently low that patients may be spared the morbidity of cTLND.

PATIENTS AND METHODS

Patients

Permission to perform the study and a waiver of informed consent were obtained from our institutional review board. Using a melanoma database, we identified all patients with primary cutaneous melanoma who underwent IOLM/SLN biopsy between January 1991 and June 2003 and had a positive SLN identified. Patients were offered SLN biopsy as previously described.⁴⁸

The patients' records were reviewed for information about patient and primary tumor characteristics and measures of SLN tumor burden.

SLN Mapping Technique

IOLM/SLN biopsy was performed as described previously.^{1,2,48,49} From 1991 to 1994, IOLM/SLN biopsy was performed using isosulfan blue dye only.² From November 1994 through June 2003, the period during which the majority of patients in our series were treated, most patients also underwent intradermal injection of Tc 99m sulfur colloid 1 to 4 hours before mapping and intraoperative use of a handheld gamma counter.⁴⁸

Table 1. Clinical and Pathologic Characteristics in SLN-Positive Patients Who Underwent Complete Therapeutic Lymph Node Dissection (N = 343)

Characteristic	All Patients (N = 343)	SLN Biopsy Before 1996 (n = 56)	SLN Biopsy During or After 1996 (n = 287)	P
Tumor thickness, mm				
Median	2.8	3.5	2.5	.006
Mean	3.5	3.8	3.4	
Range	0.37-22.0	0.73-9.00	0.37-22.0	
Ulceration, No.	145	29	116	.14
%	42	52	40	
Clark level > III, No.*	241	40	201	.99
%	72	73	72	
Age, years				.44
Median	49	46	49	
Mean	49.5	48.2	49.7	
Range	7-86	7-78	9-86	.23
Male sex, No.	207	38	169	
%	60	68	59	
Total No. of SLNs				< .0001
Median	2	2	3	
Mean	3.01	2.23	3.16	
Range	1-12	1-9	1-12	.23
No. of positive SLNs				
Median	1	1	1	
Mean	1.34	1.23	1.36	.003
Range	1-6	1-3	1-6	
Measures of SLN tumor burden				.001
Largest SLN metastatic focus,† mm				
Median	1.5	2.20	1.20	
Mean	3.14	4.27	2.90	.008
SLN tumor square area,‡ mm ²				
Median	1	2.67	0.74	
Mean	15.38	23.33	13.62	.008
No. of metastatic foci§				
Median	1	2	1	
Mean	2.24	2.96	2.01	

Abbreviation: SLN, sentinel lymph node.

*Information available for 335 patients.

†Information available for 309 patients.

‡Information available for 291 patients.

§Information available for 206 patients.

Patients underwent wide excision of the primary lesion with margins appropriate for tumor thickness.^{50,51} Patients with a positive SLN were offered cTLND. Initially, SLNs were bisected and analyzed by conventional hematoxylin and eosin staining. In cases of equivocal findings, immunohistochemistry using antisera to S-100 protein and HMB-45 antigen was performed. By the end of the study period, our histologic assessment included both gross specimen serial sectioning (since 1996) and immunohistochemical staining for HMB-45 and/or MART-1 if the initial analysis failed to identify the presence of metastases (since 1999), as described previously.⁵² cTLND specimens were analyzed following standard procedures.

Statistical Methods

Clinicopathologic factors (age, sex, tumor thickness, ulceration, and Clark level) and several measures of SLN tumor burden (defined below) were assessed as potential predictors of non-SLN involvement in cTLND specimens. The measures of SLN tumor burden in cTLND specimens included: largest SLN metastatic focus (mm), SLN tumor square area, defined as the sum of the cross-sectional areas of all SLN metastatic foci (mm²); number of SLN metastatic foci; location of SLN metastasis (subcapsular, intramedullary, or both); and presence or absence of extracapsular extension. These surrogate measures of tumor burden were obtained by review of original SLN pathologic material by two dermatopathologists (V.G.P., A.H.D.) and were available for more than 90% of the patients.

Cut points for each tumor-burden parameter were defined by recursive partitioning procedures in addition to a review of published literature. Using these cut points, univariable and multivariable logistic regression models were assessed.⁵³ The association of clinicopathologic factors with non-SLN involvement in cTLND specimens was evaluated using a χ^2 or Fisher's exact test, as appropriate. Nodal factors with a significant univariate association ($P < .05$) were then further evaluated in multivariate models. Number of SLNs harvested, number of positive SLNs, number of nodal basins mapped, and number of nodal basins with positive SLNs were also explored as potential predictors of positive non-SLNs. A working model was developed using a scoring system to attempt to stratify patients according to risk of positive non-SLNs in cTLND specimens. All reported P values are two sided. Analyses were performed using S-PLUS (Mathsoft Inc, Seattle, WA) and SAS (SAS Institute, Cary, NC).

RESULTS

Clinicopathologic Factors and SLN Tumor Factors

Overall, 359 (16.3%) of the 2,203 patients had at least one pathologically positive SLN, and 343 patients (96%) underwent cTLND. The clinical and pathologic characteristics of these 343 patients are listed in Table 1. The vast majority of patients ($n = 287$; 84%) were treated 1996 or later. Among the 343 patients who underwent cTLND, the majority (72%) had only one positive SLN; 24% and 4% of patients, respectively, had two or at least three positive SLNs.

Incidence of Metastatic Disease in Non-SLNs

Among the 343 patients who underwent cTLND, 48 (14.0%) had a pathologically positive non-SLN. When both SLNs and non-SLNs (ie, from the cTLND specimen) were analyzed together, 64%, 24%, and 12% of patients had one, two, or three or more positive nodes overall. Interestingly, 18 (32.1%) of the 56 patients treated before 1996 but only 30 (10.5%) of the 287 patients treated during 1996 or later had at least one pathologically positive non-SLN ($P < .0001$).

Predictors of Metastatic Disease in Non-SLNs

Patients who had only one SLN harvested had a significantly increased risk of harboring positive non-SLNs compared with patients who had at least three SLNs harvested (Table 2). This was also ob-

Table 2. Predictors of Positive Non-SLNs: Impact of No. of SLNs Harvested and No. of Positive SLNs (N = 343)

Table 1. Patient Characteristics and Results of SLN Harvesting (N = 100)						
Variable	Patients			OR	95% CI	P
	No.	%	% With Positive Non-SLN			
No. of SLNs harvested						
≥ 3	170	49.6	8.2	1.00		
2	92	26.8	15.2	2.00	0.91 to 4.40	.09
1	81	23.6	24.7	3.65	1.74 to 7.69	.0006
No. of positive SLNs						
1	248	72.3	12.1	1.00		
2	81	23.6	17.3	1.52	0.76 to 3.03	.24
≥ 3	14	4.1	28.6	2.91	0.86 to 9.85	.09

Abbreviations: SLN, sentinel lymph node; OR, odds ratio.

served in the 287 patients treated during 1996 or later (16.7% v 7.1%; $P = .047$). There was a trend for higher number of positive SLNs to predict non-SLN involvement in the overall group ($P = .09$; Table 2) and the 287 patients treated during 1996 or later ($P = .08$).

The results of univariate analyses are presented in Table 3. Age older than 50 years, tumor thickness more than 2 mm, and Clark level higher than III were all statistically significant prognostic factors; sex and ulceration did not predict positive non-SLNs. Location of the primary melanoma also predicted non-SLN involvement. Primary melanomas located on the head and neck, upper extremity, and trunk had non-SLN involvement in 9.8% to 10.2% of cases, compared with 22.6% in melanomas of the lower extremity ($P = .03$). Several measures of tumor burden in the SLN were also examined (Table 4). By univariate analysis, all measures of SLN tumor burden predicted positive non-SLNs. The most significant stratification occurred when the

Table 3. Predictors of Positive Non-SLNs: Impact of Patient and Primary Tumor Factors

Factor	Patients*			<i>P</i>
	No.	%	% With Positive Non-SLN	
Sex				
Male	207	60.3	11.6	.15
Female	136	39.7	17.7	
Age, years				
≤ 50	183	53.3	9.8	.02
> 50	160	46.7	18.8	
Tumor thickness, mm				
≤ 2	125	36.7	4.8	.0001
> 2	216	63.3	19.0	
Clark group				
II or III	94	28.1	6.4	.01
IV or V	241	71.9	16.6	
Ulceration				
Absent	198	57.7	12.6	.43
Present	145	42.3	15.9	

Abbreviation: SLN, sentinel lymph node.

*Numbers in some groups do not total 343 because data were not available for all patients.

Table 4. Predictors of Positive Non-SLNs: Impact of Nodal Factors

Factor	Patients*			P
	No.	%	% With Positive Non-SLN	
Largest focus in SLN, mm				
≤ 0.5	94	30.4	5.3	< .0001
> 0.5 to ≤ 2	103	33.3	10.7	
> 2 to ≤ 10	92	29.8	25.0	
> 10	20	6.5	45.0	
SLN tumor square area, mm ²				
≤ 0.1	81	27.8	3.7	< .0001
> 0.1 but ≤ 2	89	30.6	11.2	
> 2.0 but ≤ 10	54	18.6	16.7	
> 10	67	23.0	34.3	
Location of disease in SLN				
Subcapsular	184	62.4	9.8	—†‡
Intramedullary	30	10.2	10.0	—†§
Both	81	27.5	29.6	—‡§
Extracapsular extension in SLN				
Absent	270	86.0	11.9	.0001
Present	44	14.0	36.4	
No. of SLN metastatic foci				
1	98	49.3	13.3	.004
2-5	84	42.2	19.0	
≥ 6	17	8.5	47.1	

Abbreviation: SLN, sentinel lymph node.

*Numbers in some groups do not total 343 because data were not available for all patients.

†P = .99 subcapsular v intramedullary.

‡P < .0001 subcapsular v both.

§P = .04 intramedullary v both.

largest metastatic focus was used; the incidence of non-SLN involvement was 5.3% to 45.0% in patients whose single largest SLN deposit was ≤ 0.5 mm to larger than 10 mm in greatest diameter, respectively ($P < .0001$).

To further explore these prognostic factors, we performed univariable and multivariable logistic regression analyses of the SLN tumor burden predictors, the number of SLNs harvested, and the strongest two patient and primary tumor predictors of positive non-SLNs—tumor thickness and patient age (both as dichotomous variables). Fifty years was used as the cut point for age. All measures of microscopic SLN tumor burden retained their independent prognostic significance even when both tumor thickness and age were entered into the model. Tumor thickness and the number of SLNs harvested also retained their independent prognostic significance in all analyses. In contrast, age was not an independent predictor of positive non-SLNs in all analyses, although there was at least a trend (Table 5).

On the basis of these analyses demonstrating that tumor thickness, the number of SLNs harvested and SLN tumor burden each predicted non-SLN involvement, a working model was developed in an attempt to predict the risk of non-SLN involvement. Four distinct risk strata were identified (Table 6).

DISCUSSION

Our findings indicate that SLN tumor burden, the number of SLNs harvested, and primary tumor thickness may be useful in predicting the risk of synchronous non-SLN involvement in melanoma patients

with positive SLNs. The ability to identify patients at lowest risk for positive non-SLNs may allow such patients to be spared cTLND and associated morbidity.

The incidence of non-SLN involvement in our study—14.0%—is similar to that reported in other studies.^{18-29,31,33-36,38-42} Importantly, we found that the incidence differed by treatment era: it was only 10.5% among the 287 patients treated during 1996 or later, compared with 32.1% ($P < .0001$) among the 56 patients treated before 1996. Moreover, the median number of SLNs harvested was greater and all measures of SLN tumor burden were smaller in the later series. These observations most likely reflect improvements in technique, including use of preoperative lymphoscintigraphy, the intraoperative gamma probe, and enhanced SLN pathologic analysis. Taken together with an expansion of indications for IOLM/SLN biopsy to include patients with thinner melanomas, who have a decreased risk of lymph node metastases and non-SLN involvement, these findings may not only explain the difference in non-SLN involvement in patients treated earlier versus later in our study, but may also have significant implications for future clinical trial design, which should account for contemporary SLN positivity rates.

Our study is not the first to evaluate predictors of non-SLN involvement in patients with melanoma, but to our knowledge represents the largest such study to include a detailed examination of the predictive value of multiple measures of SLN tumor burden. Previous studies of the utility of primary tumor characteristics and SLN tumor burden in predicting non-SLN involvement have yielded conflicting results. In one of the first such studies, Starz et al²⁵ classified SLN metastasis according to centripetal depth of spread (in millimeters) and the number of 1-mm sections in which metastases were identified. Using data from a relatively small cohort of 39 assessable patients who underwent cTLND after identification of a positive SLN (a subset of the 62 patients overall who had a positive SLN), the authors found that the risk of positive non-SLNs ranged from 0% to 60%. The same group published a follow-up study in 2004 that described a modified classification-based analysis of 45 patients who had a cTLND (from among the 65 of 324 patients undergoing SLN biopsy who had at least one histologically positive SLN).³⁵ The authors concluded that this modified classification also predicted non-SLN involvement by univariate logistic regression analysis of the classes. In this analysis, however, minimal centripetal SLN spread (ie, ≤ 0.3 mm) was no longer associated with a trivial risk of non-SLN involvement, nor was there any apparent difference in the incidence of non-SLN involvement between patients with depth of SLN invasion ≤ 0.3 mm (group S1, one of 12 patients; 8.3%) and patients with depth of SLN invasion 0.31 mm to 1 mm (group S2, two of 17 patients; 11.8%).

Scolyer et al²⁷ assessed multiple measures of SLN tumor burden in 140 patients. The presence of non-SLN metastases correlated significantly with SLN tumor penetration depth more than 2 mm, deposit size more than 10 mm², presence of melanoma cells in perinodal lymphatics, and effacement of SLN nodal architecture by metastatic melanoma cells. In contrast to Starz et al³⁵ who found non-SLN involvement in cTLND specimens in 60% of patients with a SLN centripetal depth of more than 1 mm, Scolyer et al found non-SLN involvement in only 19% of patients in that group. Scolyer et al also found that 28% of patients with a SLN tumor penetration depth of more than 2 mm had non-SLN involvement.

Table 5. Predictors of Positive Non-SLNs According to Measures of SLN Tumor Burden

Variable	Univariate			Multivariate		
	<i>P</i>	OR	95% CI	<i>P</i>	OR	95% CI
Analysis 1						
Largest SLN metastatic focus, mm						
≤ 0.5	—	1.00	—	—	1.00	—
> 0.5 ≤ 2	.18	2.13	0.71 to 6.37	.37	1.68	0.54 to 5.22
> 2 ≤ 10	.0006	5.93	2.15 to 16.40	.0038	4.79	1.66 to 13.82
> 10	< .0001	14.56	4.13 to 51.34	.0003	12.41	3.22 to 47.81
Tumor thickness, > 2 mm	.0007	4.65	1.91 to 11.29	.034	2.78	1.08 to 7.12
Total No. of SLNs harvested						
1 v ≥ 3 SLNs harvested	.0006	3.65	1.74 to 7.69	.0004	4.53	1.95 to 10.50
2 v ≥ 3 SLNs harvested	.09	2.00	0.91 to 4.40	.16	1.88	0.79 to 4.52
Age > 50 years	.019	2.11	1.13 to 3.96	.037	2.13	1.05 to 4.34
Analysis 2						
SLN tumor square area, mm ²						
≤ 0.1	—	1.00	—	—	1.00	—
> 0.1 ≤ 2	.079	3.29	0.87 to 12.41	.086	3.29	0.85 to 12.81
> 2 ≤ 10	.017	5.20	1.34 to 20.20	.082	3.51	0.85 to 14.47
> 10	< .0001	13.59	3.86 to 47.84	.0003	10.71	2.94 to 39.10
Tumor thickness, > 2 mm	.0007	4.65	1.91 to 11.29	.03	3.19	1.14 to 8.93
Total No. of SLNs harvested						
1 v ≥ 3 SLNs harvested	.0006	3.65	1.74 to 7.69	.003	3.74	1.56 to 8.96
2 v ≥ 3 SLNs harvested	.09	2.00	0.91 to 4.40	.18	1.85	0.75 to 4.55
Age > 50 years	.019	2.11	1.13 to 3.96	.054	2.07	0.99 to 4.35
Analysis 3						
No. of SLN metastatic foci						
1	—	1.00	—	—	1.00	—
2-5	.29	1.54	0.69 to 3.42	.93	0.96	0.40 to 2.31
≥ 6	.002	5.81	1.90 to 17.76	.004	6.66	1.83 to 24.29
Tumor thickness, > 2 mm	.0007	4.65	1.91 to 11.29	.008	5.77	1.58 to 21.04
Total No. of SLNs harvested						
1 v ≥ 3 SLNs harvested	.0006	3.65	1.74 to 7.69	.0046	4.12	1.55 to 10.96
2 v ≥ 3 SLNs harvested	.09	2.00	0.91 to 4.40	.11	2.38	0.83 to 6.82
Age > 50 years	.019	2.11	1.13 to 3.96	.043	2.33	1.03 to 5.29
Analysis 4						
Location						
Subcapsular or intramedullary	—	1.00	—	—	1.00	—
Both	< .0001	3.87	2.01 to 7.46	.001	3.19	1.58 to 6.46
Tumor thickness, > 2 mm	.0007	4.65	1.91 to 11.29	.016	3.42	1.25 to 9.35
Total No. of SLNs harvested						
1 v ≥ 3 SLNs harvested	.0006	3.65	1.74 to 7.69	.003	3.70	1.59 to 8.64
2 v ≥ 3 SLNs harvested	.09	2.00	0.91 to 4.40	.073	2.22	0.93 to 5.30
Age > 50 years	.019	2.11	1.13 to 3.96	.071	1.94	0.95 to 3.97
Analysis 5						
Extracapsular extension						
No	—	1.00	—	—	1.00	—
Yes	< .0001	4.25	2.08 to 8.70	.0017	3.56	1.61 to 7.87
Tumor thickness, > 2 mm	.0007	4.65	1.91 to 11.29	.007	3.54	1.41 to 8.88
Total No. of SLNs harvested						
1 v ≥ 3 SLNs harvested	.0006	3.65	1.74 to 7.69	.0007	4.08	1.81 to 9.19
2 v ≥ 3 SLNs harvested	.09	2.00	0.91 to 4.40	.068	2.21	0.94 to 5.16
Age > 50 years	.019	2.11	1.13 to 3.96	.19	1.58	0.79 to 3.15

Abbreviations: SLN, sentinel lymph node; OR, odds ratio.

Some authors have reported that size of SLN metastasis did not predict non-SLN involvement.^{31,34} In their analysis of 98 patients with positive SLNs, Reeves et al²⁶ found that SLN metastatic size was not an independent predictor of non-SLN metastases and that the only independent predictor of non-SLN metastases was a combined size/ulceration (SU) score. In this score, 1 point was

assigned for primary tumor ulceration and 1 point for a SLN containing a metastasis more than 2 mm in diameter. None of the 21 patients with a SU score of 0 had a positive non-SLN, whereas eight (31%) of the 26 patients with a SU score of 2 had a positive non-SLN (odds ratio, 2.9). Gietema et al⁵⁴ used the SU score and found, contrary to Reeves et al,²⁶ that eight (18%) of 44 patients

Table 6. Working Model for Predicting Risk of Additional Positive Non-SLNs

Total Score*	No. of Patients in Group	Additional Positive Non-SLNs	
		No.	%
0	25	0	0
1-2	126	5	4.0
3-4	126	28	22.2
5-6	30	14	46.7

Abbreviation: SLN, sentinel lymph node.

*Sum of scores for tumor thickness (0 or 1 for tumor thickness of ≤ 2 mm or > 2 mm, respectively), largest SLN metastatic focus (0, 1, 2, or 3 for largest metastatic focus ≤ 0.5 , > 0.5 to ≤ 2 , > 2 to ≤ 10 , or > 10 mm, respectively), and number of SLNs harvested (0, 1, or 2 for ≥ 3 , 2, 1, respectively). All data available for 307 of 343 patients.

with a SU score of 0 had positive non-SLNs. Dewar et al²⁹ found similar results in their analysis of 146 patients: six (25%) of 24 patients with a SLN metastasis of less than 2 mm had positive non-SLNs. In addition, the authors observed that the microanatomic location within SLNs was more predictive of non-SLN involvement than was metastasis size or depth of invasion alone. None of the 38 patients (26%) with SLN metastasis confined to the subcapsular area alone had non-SLN involvement.

In this study, we built on the work of others to thoroughly examine the potential role of SLN tumor burden as a predictor of non-SLN metastases. A striking observation was that by univariate analysis, all measures of SLN tumor burden were associated with an increased risk of positive non-SLNs. Among these factors, largest SLN metastatic focus was the most significant (Table 4). The impact of SLN tumor size was previously noted by Reeves et al,²⁶ who found that SLN tumor size more than 2 mm was a significant predictor of positive non-SLNs by univariate but not multivariate analysis. We created several strata for the SLN tumor burden variables to permit identification of the relative risk of positive non-SLNs associated with various sizes of SLN tumor foci. Interestingly, patients in the two categories with relatively limited tumor burden (ie, largest SLN metastatic focus ≤ 2 mm) had essentially similar risk, while patients in the two categories with greater tumor burden had significantly increased risk (odds ratios, 5.93 and 14.56, respectively, compared with that of patients with SLN focus ≤ 0.5 mm). Other measures of SLN tumor burden revealed similar trends.

Our finding that primary tumor thickness (≤ 2 v > 2 mm) predicted positive non-SLNs on univariate analysis (Tables 3 and 5) agrees with the findings of Lee et al,²⁸ who reported a higher incidence of positive non-SLNs in patients with tumor thickness ≥ 3 mm. Other studies on the association between primary tumor thickness and non-SLN involvement have reported conflicting findings.^{8,9,18,38,55}

While ulceration has repeatedly been shown to be a predictor of survival and SLN positivity, we found—as have most previous studies^{27,28,55}—that ulceration did not predict non-SLN involvement. These data contrast with findings from the study by Reeves et al,²⁶ which included ulceration as a component of the SU scoring system, and with findings from the University of Michigan.¹⁸

In our study, among patients with positive SLNs, patients who had only one SLN harvested had a significantly greater incidence of additional positive nodes than did patients who had three or more

SLNs harvested (25% v 8%; $P = .0006$; Table 2). At least some of the positive non-SLNs may actually have been SLNs that were missed when only blue dye was used. With the current technique of IOLM/SLN biopsy, which uses blue dye and technetium-labeled sulfur colloid, the number of SLNs harvested is greater than that when blue dye is used alone ($P < .003$ in this study). Interestingly, when we included this factor in the multivariable regression analysis, the number of SLNs harvested was an independent predictor of non-SLN involvement, thus underscoring the importance of performing a complete sentinel lymphadenectomy. Our findings indicate that overall, in patients with at least one positive SLN, SLN tumor burden, primary tumor thickness, and number of SLNs harvested may be useful in identifying a group at low risk for positive non-SLNs. Using these criteria, patients are stratified according to rather heterogeneous risk (0% to 47%; Table 6); of these, nearly one half have an estimated risk of non-SLN involvement of 4% or less. Further study of SLN tumor burden and other factors in larger multi-institutional data sets is warranted to determine the feasibility of a selective cTLND approach.

A potential criticism of our study is that the cTLND specimens were examined according to current pathology standards of care and were not subjected to the intense histologic scrutiny that is in widespread practice for SLN analysis; therefore, some disease in cTLND specimens may have remained undetected.

A decision not to perform cTLND should be made cautiously and probably only as part of a clinical trial based on inclusion of low-risk groups as outlined in this study. Preliminary observations of the minority of patients in our database with a positive SLN who did not undergo cTLND indicate that seven (44%) of 16 patients have had a recurrence and that three patients (19%) had a recurrence in the nondissected lymph node basin. In a multi-institutional study with a median follow-up of 20 months, Wong et al⁵⁶ reported that regional nodal basin failure was a component of the first site of recurrence in 20 (15%) of 134 patients with positive SLNs who did not undergo cTLND. Most likely, additional nodal recurrences will be observed with additional follow-up.

There is currently no consensus regarding what degree of risk of non-SLN involvement indicates that it is safe to forego cTLND. In this study, only 14% of SLN-positive patients had positive non-SLNs. Identification and incorporation of additional biomarkers reflective of melanoma biology may allow us to identify a much higher proportion of the patients with positive SLNs who do not harbor clinically relevant microscopic non-SLN involvement.

Interim results of the Multicenter Selective Lymphadenectomy Trial demonstrated a survival advantage in patients with SLN-positive melanoma who underwent immediate cTLND compared with patients who were initially randomly assigned to wide excision alone, did not undergo SLN biopsy, and underwent TLND when regional nodal metastases became clinically evident.⁵⁷ Before elimination of cTLND can be advocated, prospective clinical trials designed to assess the safety of omitting formal cTLND with respect to survival and locoregional control in low-risk groups are needed. The ongoing Multicenter Selective Lymphadenectomy Trial II,⁵⁸ which compares cTLND versus close observation with sonography and clinical examination for patients with a positive SLN, should provide valuable information about which patients might be spared a cTLND and can be used to further validate the proposed model.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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