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ORIGINAL REPORT

Factors Predictive of Tumor-Positive Nonsentinel Lymph Nodes After Tumor-Positive Sentinel Lymph Node Dissection for Melanoma

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ABSTRACT

Purpose

Approximately 20% of sentinel node (SN) positive melanoma patients have additional non-SN (NSN) metastasis. The rationale for this study was to identify the factors associated with additional nodal disease, as a method to determine which patients may most benefit from completion lymph node dissection (CLND).

Patients and Methods

During 1990 to 2002, 1,599 patients have undergone SN biopsy at our institute. 19.5% underwent CLND for tumor-positive SN. One hundred ninety-one of these patients had clinicopathologic information available for review. Univariate analyses used χ^2 test, Wilcoxson rank sum test, and χ^2 test for trend. Multivariate analyses used logistic regression and Wald test.

Results

Forty-six (24%) patients had tumor-positive NSN. Univariate analyses showed that primary thickness (Breslow and Clark), primary site, SN tumor size, and number of tumor-positive SNs were significantly associated with tumor-positive NSN. Multivariate analysis (167 patients), confirmed that Breslow and SN tumor size were independently predictive. Sex, histology, ulceration, mitotic index, and SN basin location were not predictive. Risk stratification by the number of prognostic factors present (Breslow $\geq$ 3 mm and SN tumor size $\geq$ 2 mm) showed that probability of finding tumor-positive NSN was 12.3% in the low-risk group (0 factors), 30.9% in the intermediate-risk group (1 factor), and 41.9% in the high-risk group (2 factors).

Conclusion

Thicker primary and larger SN tumor size are factors that correlate best with tumor-positive NSN. Although none of these factors are absolutely predictive of residual nodal disease, these factors must be strongly considered if the SN contains metastasis, as they provide enhanced risk assessment for NSN tumor-positivity.

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INTRODUCTION

Both incidence and mortality from melanoma continue to rise in the United States. In 1992, the projected annual incidence and mortality from melanoma were 32,000 and 6,700, respectively.[1] By 2003, these figures changed to 54,200 and 7,600, respectively.[2] The lifetime risk of developing melanoma has risen from 1:1500 in 1935 to 1:75 in 2000.[3] The mortality rate correlates with thickness of the primary lesion, presence of ulceration, and number of regional lymph node (LN) metastases. Whereas the estimated 10-year survival-rate for stage I melanoma patients is 85%, that of stage III melanoma patients is only approximately 35%.[4] Among stage III patients, 5-year

survival rate for patients with ≥ 4 tumor-positive lymph nodes is approximately half of that for similar patients with only a single tumor-positive LN.[5]

In 1892, Snow[6] first proposed performing routine elective lymph node dissection (ELND) based on the concept that melanoma spreads sequentially from the primary site to the regional LN basin. Thus, by empirically removing the regional LNs early in the metastatic process, disease would not progress to distant sites. Since then, multiple nonrandomized studies have supported the efficacy of ELND.[7-9] However, other studies argue that ELND offers no survival advantage and that LN dissection should be reserved for those with clinical evidence of LN metastasis.[10-12] The Intergroup Melanoma Surgical Trial adds more to the uncertainty as this study demonstrated no survival advantage for patients who underwent ELND, except for a subgroup of patients who were ≤ 60 years of age and had nonulcerated primary melanoma of 1 to 2 mm in thickness.[13] Given such uncertainty regarding the therapeutic efficacy of ELND, and considering the fact that only approximately 20% of patients with intermediate-thickness melanoma have regional LN metastasis, and thus benefit from ELND, it has become imperative to identify the patients who are unlikely to benefit from complete resection of the draining regional LNs.

Lymphatic mapping and sentinel lymphadenectomy (LM/SL) has now become widely accepted as a staging method for identifying tumor status of regional LN basins, essentially replacing ELND as a staging tool. By performing completion lymph node dissection (CLND) only on patients with tumor-positive sentinel nodes (SNs), we are now able to spare 75% to 80% of patients the cost and morbidity of ELND. Recent reports examining the frequency of non-SN (NSN) metastasis in SN-positive patients have shown that approximately 7% to 30% of patients with tumor-positive SN harbor additional tumor-positive LNs in the dissected LN basin.[14-22] The significance of this data becomes more evident when we consider that approximately 35% of patients with tumor-positive SNs die within 10 years despite undergoing CLND and receiving adjuvant treatments (data not shown). These findings raise significant doubt about the efficacy of CLND in preventing distant metastasis or extending survival in all patients, and also question the necessity of performing CLND in all patients with tumor-positive SN. The purpose of this study was to identify clinicopathologic factors that might correlate with NSN tumor positivity in patients with tumor-positive SNs, thus helping to identify patients who would most likely benefit from CLND.

PATIENTS AND METHODS

Data Acquisition

The John Wayne Cancer Institute (JWCI) melanoma database was queried to identify all patients who underwent LM/SL between the years 1990 to 2002, and were found to have a tumor-positive SN. During the past 13 years, 1,599 patients have undergone LM/SL at our institute for diagnosis of clinical stage I/II melanoma. Approximately 19.5% of these patients have had a tumor-positive SN, and of those, 191 had at least one of the clinicopathologic information of interest available for analysis after undergoing CLND. The data of interest were obtained from combination of computer query and from paper chart reviews. This study was approved by the JWCI/Saint John's Health Center Joint institutional review board.

SN Biopsy Technique and CLND

LM/SL was performed in a manner previously described.[23,24] In brief, preoperative lymphoscintigraphy using ^{99}mTc-labeled sulfur colloid was performed to identify the nodal basin at risk for metastases, followed by an intraoperative peritumoral intradermal injection of isosulfan blue dye (Lymphazurin; Tyco International, Norwalk, CT). The SN was localized by using a hand-held gamma probe and by visual inspection for the blue dye, which was considered the gold standard for identifying SNs.[25] The permanent sections of SNs were examined by conventional hematoxylin and eosin (H&E) staining and immunohistochemistry (IHC) to both HMB-45 and *S*-100. If the SN contained metastatic melanoma by either H&E or IHC, the patient subsequently underwent CLND of the involved nodal basin(s) in a standard fashion. The NSNs were evaluated by H&E alone.

Statistical Analysis

Information obtained for analysis were known and/or potential prognostic criteria, which included: (1) Patient characteristics—age at diagnosis (<30 years, 31-60 years, ≥ 61 years) and sex (male, female); (2) Primary tumor characteristics—Breslow thickness (continuous), Clark level (I, II, III, IV, V), primary site (head/neck, trunk, extremity, other), histologic type (SSM, NM, other), presence of ulceration or regression, degree of lymphocytic infiltration (absent, nonbrisk, brisk), lymphovascular invasion (absent, present), and mitotic index (low, moderate, high); and (3) LN tumor characteristics—number of tumor-positive SNs (1, 2, ≥ 3), size of SN tumor metastasis (< 2 mm, ≥ 2 mm, heavy—significant replacement of node by tumor), and SN basin location (neck/cervical, axilla, groin, other). Univariate analyses were done using χ^2 test, χ^2 test for trend, and Wilcoxon rank sum test. For multivariate analysis, a logistic regression model was developed to correlate the covariates with probability of having tumor-positive NSN. A stepwise procedure was used for covariate selection. The covariates included in the model were patient age, sex, primary site, Breslow thickness, Clark level, SN basin location, histological type, number of tumor-positive SNs, and SN metastasis size. Because data on lymphocytic infiltration, lymphovascular invasion, and regression were available for less than 70% of the patients (133 of 191), these variables were collected and presented (Table 1), but not included in the statistical analysis. Statistical significance was determined at $P < .05$.

RESULTS

The clinicopathologic features of the 191 patients and their tumors are shown in Table 1. Of the 191 patients, four had tumor-positive NSNs identified at the time of LM/SL and 46 (24%) had tumor-positive NSNs found at the time of CLND. The youngest patient with tumor-positive NSNs

Table 1. Clinicopathologic Feature of the 191 Patients and Their Primary Tumors and Sentinel Node Metastasis

	Mean	Median	Range	No. of Patients
Age, years	48	49	11-84	190
Breslow, mm	3.07	2.2	0.35-11	185
Clark level		IV	II-V	174
Sex				191
Male				105
Female				86
Ulceration				156
No				104
Yes				52
Unknown				35
Regression				107
No				103
Yes				4
Unknown				84
Lymphovascular invasion				54
No				42
Yes				12
Unknown				137
Lymphocytic infiltration				126
Absent				11
Nonbrisk				104
Brisk				11
Unknown				65
Histologic type				160
SSM				57
NM				71
LMM				1
ALM				13
Other/unknown				18/31
Mitotic index				134
Low				67
Moderate				12
High				55
Unknown				57
Tumor location				185
Head and neck				23
Trunk				69
Extremity				88
Other/unknown				5/6
SN location				186
Neck/cervical				21
Axilla				81
Groin				79
Other/unknown				5/5
Size of SN metastasis				172
< 2 mm				107
≥ 2 mm				61
Heavy*				4
Unknown				19
No. of tumor-positive SNs				181
1				134
2				38
≥ 3				9
Unknown				10

Abbreviations: SSM, superficial spreading melanoma; NM, nodular melanoma; LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma; SN, sentinel node.
*Heavy = significant replacement of SN by tumor.

was 23 years old; the thinnest lesion with NSN positivity was 0.65 mm and had Clark level of III; 1 of 3 patients who were found to have tumor-positive SNs only by IHC had tumor-positive NSNs. The univariate analyses (Table 2) show that patients with tumor-positive NSNs were significantly older ($P = .025$), had thicker primary lesions (Breslow $P = .001$; Clark $P < .001$), more tumor-positive SNs ($P = .016$), and larger SN metastasis ($P < .001$) with different primary site distribution than did patients with tumor-negative NSNs. The two groups were not significantly different regarding sex ($P = .174$), histologic subtype ($P = .138$), ulceration ($P = .597$), mitotic index ($P = .102$), or location of SN basin ($P = .685$). Figures 1 and 2 demonstrate striking correlations between the Breslow thickness and Clark level of the primary lesion and frequency of finding additional tumor-positive NSNs. Likewise, Figure 3 shows that increasing SN tumor burden correlates with the likelihood of finding tumor-positive NSNs. Additionally, as noted in Figures 4 and 5, both age at diagnosis and the number of tumor-positive SNs correlate with probability of finding additional NSN metastasis. The results of multivariate analysis are shown in Table 3. Of 167 patients included in the final model, 38 (23%) had NSN metastasis and 129 (77%) did not. Breslow thickness and SN metastasis size were noted to be significantly associated with patients having tumor-positive NSNs in our multivariate model.

The prespecified cutoff point of 3 mm for Breslow thickness comparing tumor-positive NSN group versus tumor-negative NSN group was chosen based on the studies of Haddad et al[26] (2.8 mm) and Wagner et al[15] (2.86 mm). The χ^2 test showed significant difference ($P = .002$) with relative risk (RR) of 2.96 (CI, 1.47 to 6.00) for NSN tumor-positivity. Similar results were noted when the data were analyzed in regards to SN tumor burden. Using 2 mm metastasis size as the cutoff point (commonly used definition of micrometastasis[27]), the χ^2 test shows a significant difference between tumor-positive and tumor-negative NSN groups ($P = .003$, RR = 2.93, CI, 1.42 to 6.06). Risk stratification was done using these independently significant factors that were identified in our multivariate analysis and prespecified cutoff points (Fig 6). The likelihood of NSN metastasis was 12.3% in the lowest risk group (0 factors) and 41.9% in the highest risk group (two factors).

DISCUSSION

The incidence of melanoma continues to rise, and prognosis remains poor for patients with advanced disease. The traditional treatment of early-stage disease by wide local excision (WLE) and ELND has been a subject of debate. While many surgeons advocated ELND, others preferred observation of the regional LNs and employed therapeutic lymph node dissection (TLND) only when patients

Table 2. Comparison of Risk Factors for Patients With and Without NSN Metastasis

Factor	NSN Metastasis: No — No. of Patients	No — %	Yes — No. of Patients	Yes — %	*P*
Sex (N = 191)					
Female	61	42	25	54	.174*
Male	84	58	21	46	
Age, years (n = 190)					
≤ 30	26	18	3	7	.025†
31-60	78	54	24	52	
≥ 61	40	28	19	41	
SN location (n = 186)					
Axilla	64	46	17	40	.685*
Groin	57	41	22	48	
Neck/cervical	16	11	5	11	
Other	3	2	2	4	
Breslow, mm (n = 185)					
Mean	2.78		3.98		.001‡
SD	2.28		2.93		
Median	2		3.5		
Range	0.35-10.2		0.65-11		
Primary site (n = 185)					
Extremity	69	49	19	42	.023*
Head and neck	16	11	7	16	
Trunk	54	39	15	33	
Other	1	1	4	9	
No. of tumor-positive SNs (n = 181)					
1	107	77	27	63	.016†
2	27	20	11	25	
≥ 3	4	3	5	12	
Clark level (n = 174)					
I	0	0	0	0	< .001†
II	7	5	0	0	
III	26	19	2	5	
IV	91	68	26	67	
V	11	8	11	28	
SN metastasis size (n = 172)					
< 2 mm	90	68	17	43	< .001†
≥ 2 mm	41	31	20	50	
Heavy§	1	1	3	7	
Histologic type (n = 160)					
NM	50	43	21	64	.138*
SSM	48	42	9	27	
Others	17	15	3	9	
Ulceration (n = 156)					
Absent	80	68	24	63	.597*
Present	38	32	14	37	
Mitotic index (n = 134)					
Low	53	54	13	38	.102†
Moderate	9	9	3	9	
High	37	37	18	53	

Abbreviations: NSN, nonsentinel node; SN, sentinel node; SD, standard deviation; NM, nodular melanoma; SSM, superficial spreading melanoma.
*χ^2.
†χ^2 test for trend.
‡Wilcoxon rank sum test.
§Heavy = significant replacement of SN by tumor.

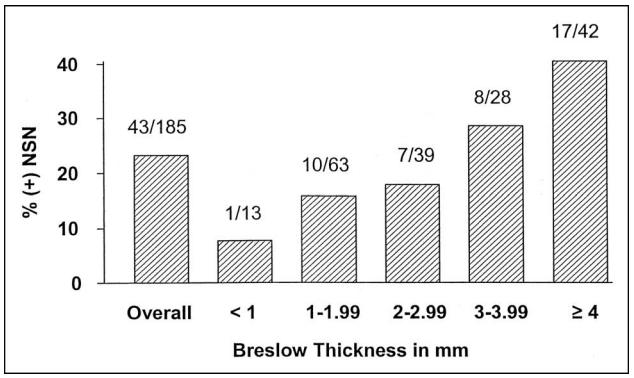

Fig 1. Correlation between the Breslow thickness (as ordered categoric variable) and the probability of finding tumor-positive non-sentinel nodes (NSN). Using 3 mm as the cutoff point, χ^2 test demonstrates significantly higher risk of patients having tumor-positive NSN with relative risk of 2.96 (CI, 1.47 to 6.00, $P = .002$).

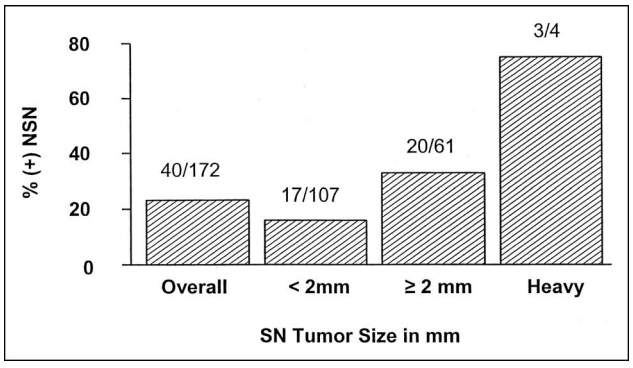

Fig 3. Correlation between the sentinel node (SN) tumor metastasis size and the probability of finding additional tumor-positive non-SNs (NSN). Using 2 mm as the cutoff point, χ^2 test shows a significant difference between the two groups (relative risk = 2.93, CI, 1.42 to 6.06, $P = .003$).

developed clinical evidence of nodal metastasis. Several retrospective studies have reported a survival advantage in patients undergoing ELND instead of observation followed by TLND.[7-9] These studies suggest that ELND may be associated with improved 5- to 10-year survival in a subgroup of melanoma patients. For example, Balch et al[28] reported improved survival in patients undergoing ELND, but only after 5 to 8 years of follow-up. In their subsequent study, the survival advantage was observed only in a group of patients with primary melanomas of 1.5 to 3.99 mm in thickness (for 0.76 to 1.5 mm group, mostly males benefited from ELND).[29] However, the prospective randomized trials of ELND versus TLND have failed to show a survival benefit for all patients undergoing ELND, but do suggest that some subgroups may benefit from ELND. Veronesi et al[30] and the WHO conducted a prospective randomized international trial and concluded that while not all patients did better after ELND, the patients with tumor-positive ELND tended to have better 10-year survival than those who underwent WLE and delayed lymph node dissection (~36% *v* ~23%, respectively). Results from the study of Cascinelli et al,[31] which compared immediate versus delayed regional lymphadenectomy, suggested that ELND mostly benefited patients with occult regional disease. Balch et al[13,32] from the Melanoma Intergroup Trial found no overall survival benefit of ELND, except in a subgroup of patients (1-2 mm thick melanoma, age < 60 years, and nonulcerated primaries). This group most likely represents the patients whose regional nodal disease is limited to the SN. Since LM/SL was not done on these patients, ELND achieved complete removal of the only tumor-involved LN. Accordingly, this data also suggest that if regional LNs are involved with melanoma metastases, then earlier removal of tumor-involved LNs may be beneficial to the patient. However, although the patients in the study done by Balch et al[13,32] were prospectively stratified and prerandomized, the subgroups found to have a survival benefit were not part of the original study design.[13] To summarize, both retrospective and prospective studies suggest that ELND likely has therapeutic value only when LN metastases are present. This concept is further supported by a report by Gershenwald et al,[33] which suggests that synchronously performing ELND on SN-negative patients does not improve survival.

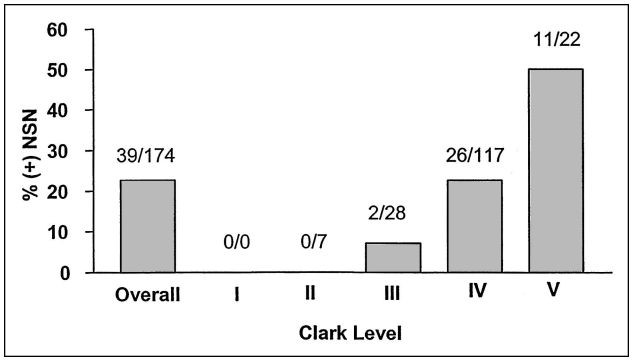

Fig 2. Relationship between Clark level of primary melanoma and probability of finding tumor-positive non-sentinel nodes (NSN).

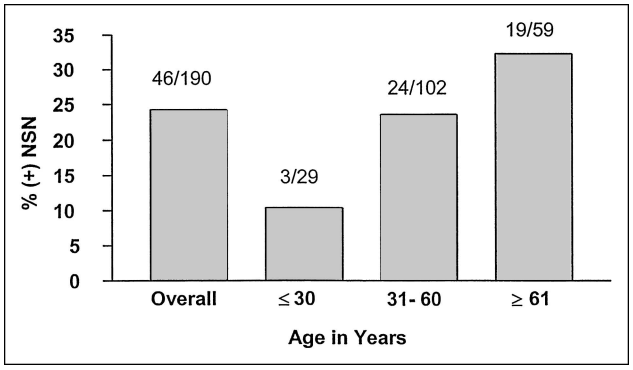

Fig 4. Correlation between patient age (intervals: ≤ 30, 31-60, > 60) and the probability of finding additional tumor-positive non-sentinel nodes (NSN).

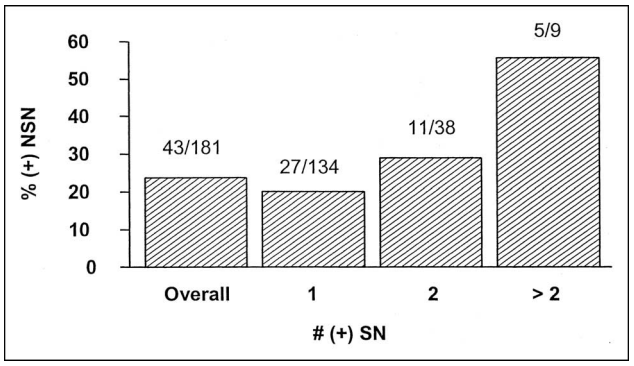

Fig 5. Correlation between number of tumor-positive sentinel nodes (SNs) and probability of finding additional tumor-positive non-SN (NSN).

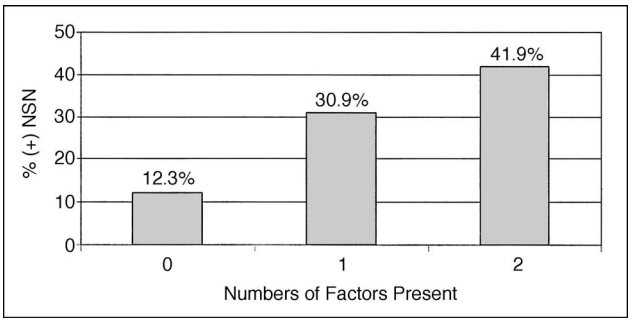

Fig 6. Risk stratification by using the number of prognostic factors present. The factors are Breslow ≥ 3 mm and sentinel node (SN) tumor metastasis size ≥ 2 mm. The low-risk group (0 factors) showed 12.3% probability non-SN (NSN) metastasis, whereas the intermediate-risk (1 factor) and high-risk group (2 factors) showed 30.9% and 41.9% probability of NSN metastasis, respectively.

Lack of definitive evidence regarding the efficacy of ELND in all patients has led to the advent of LM/SL. LM/SL has become widely accepted as a minimally invasive method of staging the regional LN basin. By performing CLND only in patients with a tumor-positive SN, we are able to spare approximately 75% to 80% of the patients who would otherwise receive ELND. However, recent studies indicate that only approximately 7% to 30% (21% ± 7.8%) of patients with tumor-positive SNs have additional NSN metastasis in the same nodal basin.[14-22] In our current series, approximately 24% of patients who underwent LM/SL followed by CLND for a tumor-positive SN had tumor-positive NSNs, which is well within the range of reported studies. This translates into potentially making 70% to 80% of the SN-positive patients free of nodal disease by performing LM/SL alone. The significance of this data becomes more evident when we consider the fact that approximately 35% of the patients with a tumor-positive SN die within 10 years despite undergoing CLND and receiving adjuvant treatments (data not shown). These results raise significant doubts as to the efficacy of CLND in preventing the development of distant metastases, as well as questioning the necessity of routinely performing CLND in all patients with tumor-positive SNs.

For these reasons, several investigators have examined clinical and pathologic factors that may be relevant in identifying subgroups of patients whose disease is confined to the SN and who therefore may not benefit from CLND.

Table 3. Multivariate Analysis of Factors Independently Predictive of NSN Positivity (N = 167)

Factor	Odds Ratio	95% CI	Wald Test *P*
Breslow, continuous	1.15	1.01 to 1.31	.038
SN metastasis size, < 2 mm *v* ≥ 2 mm and heavy*	2.55	1.19 to 5.48	.016

Abbreviations: NSN, nonsentinel node; SN, sentinel node.
*Heavy = significant replacement of SN by tumor.

Whereas Joseph et al[14] suggested the possibility of avoiding CLND in patients with primaries less than 1.5 mm thick, Haddad et al[26] suggested that CLND can be avoided in SN-positive patients with primaries less than 2.8 mm thick. McMasters et al[20] failed to find any factors that were associated with absence of NSN metastasis, thus adding to the confusion and controversy. Perhaps, the focus then should be on identifying a subset of patients who are most likely to harbor additional nodal disease after performing SN biopsy. Gershenwald et al[21] reported that tumor thickness more than 2 mm and SN tumor burden more than 2 mm^2 are independently predictive of NSN metastasis. Our study confirms the predictive significance of Breslow thickness and SN tumor burden. Contrary to the report of Reeves et al[22] on the importance of ulceration (as a part of size/ulceration scoring system) in predicting NSN status, we were unable to confirm ulceration as an independently predictive factor ($P = .597$). However, even in their study, ulceration alone failed to show significance in multivariate analysis ($P = .1$). In our study, the frequency of NSN metastasis correlated with increases in Breslow thickness (Fig 1). More specifically, Breslow thickness ≥ 3 mm was significantly associated with NSN metastasis (RR = 2.96). This result is in concordance with the report of Wagner et al,[15] which found 2.86 mm as the mean tumor thickness for patients with tumor-positive NSN, as well as 2.8 mm as the recommended cutoff for CLND, as suggested by Haddad et al[26] In addition, our data show a significant association between the SN tumor diameter ≥ 2 mm and the risk of NSN metastasis (RR = 2.93, $P = .003$), also in concordance with the report by Gershenwald et al[21] Furthermore, although age at diagnosis and presence of multiple tumor-positive SNs failed to achieve statistical significance in our multivariate analysis, these factors were highly suggestive of NSN metastasis. Prognostic significance of advancing age and multiple nodal involvements by the tumor has been reported in other studies, including various different types of cancers.[15,34-38]

It is worthy to note that factors predictive of NSN metastasis are similar to the prognostic factors for survival in melanoma patients. As mentioned earlier, in addition to Breslow thickness and the presence of LN metastasis, degree of regional lymph nodal involvement as measured by the number of tumor-positive LNs significantly influences survival.[5] It is not surprising, therefore, that Breslow thickness and SN tumor burden correlate with risk of NSN metastasis. This suggests an orderly progression of loco-regional spread of melanoma from the primary site to its draining lymph nodal basin. More specifically, thicker primaries show higher likelihood of SN metastases, greater SN tumor burden correlates with additional lymph nodal involvement, and multiple tumor-positive LNs are associated with worse prognosis. Reports by Starz et al[17,18] suggest that SN tumor burden (*S*-staging) is an independent predictive factor for development of NSN positivity, distant metastasis, and overall survival. More specifically, S3 stage (SN metastasis depth $>$ 1 mm) has been shown to carry relative risk ratios of 8.47 and 4.69 for development of distant metastasis and melanoma related death, respectively. Furthermore, they also concluded that risk of distant metastasis is best predicted by a combination of T-staging and *S*-staging. Cochran et al[39] report similar findings regarding prognostic utility of Breslow thickness and SN tumor burden. In their recent report, Breslow thickness, SN tumor area, and SN interdigitating dendritic cell density were all independently associated with frequency of NSN metastasis, melanoma recurrence, and melanoma-related survival. What is evident from these reports is that SN and regional lymph nodal tumor burdens correlate with risk of developing distant metastases, suggesting that regional LN basins may function as an "incubator" for melanoma, *en route* to eventual distant metastasis. This "incubator theory" provides compelling support for CLND as an effective therapeutic/prophylactic procedure. Conversely, the opponents of this theory may argue that given approximately 10% of stage I and 15% to 20% of stage II patients die within 5 years, subclinical distant metastasis may occur in absence of LN metastasis; in this case, regional lymph nodal dissection has minimal therapeutic role. However, this group constitutes a minority of melanoma patients. In addition, undetectable metastasis does not equate to absence of metastasis. More sensitive detection methods, such as reverse transcriptase polymerase chain reaction, are currently being evaluated in the multi-institutional Sunbelt Melanoma trial.[40] As clinicians, however, we cannot ignore the significant morbidity associated with loco-regional recurrences, and limited chance for a cure in some group of patients.

Regional lymphadenectomies carry substantial amount of health care costs, patient morbidity, and most importantly lost of productivity and long-term disability. Recent prospective studies failed to show a survival advantage of performing ELND in all patients with early-stage melanoma.[13,30-32] The advent of LM/SL has enabled us to spare approximately 80% of melanoma patients the morbidity associated with ELND. The question still remains however, does CLND after tumor-positive sentinel lymphadenectomy truly confer any therapeutic benefit in patients with clinically negative LNs but histologically positive SNs? If so, who would benefit most from it? Though our data do not show any single absolute predictive factor, the results suggest that patients with thicker primaries ($\geq$ 3 mm) and higher SN tumor burden ($\geq$ 2 mm in diameter) have a significantly higher risk of harboring additional metastasis in the SN lymph nodal basin, and therefore are most likely to benefit from CLND. More specifically, the low-risk group (0 factors) had a 12.3% rate of NSN metastasis, whereas the intermediate-risk (1 factor) and high-risk groups (2 factors) had corresponding rates of 30.9% and 41.9%. Enhanced risk stratification more accurately identifies patients who may harbor any additional nodal disease, and also enables us to better inform our patients the risk versus benefit ratio of CLND.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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