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Role for Lymphatic Mapping and Sentinel Lymph Node Biopsy in Patients With Thick (≥4 mm) Primary Melanoma

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Background: Historically, patients with thick (≥4 mm) primary melanoma have not been considered candidates for elective lymph node dissection, because their risk for occult distant disease is significant. Sentinel lymph node (SLN) biopsy offers an alternative approach to assess disease in the regional nodal basin, but no studies have specifically addressed the role for this technique in patients with thick melanoma. Although adjuvant therapy benefits patients who develop nodal metastases, data that supports its routine use in all patients with thick melanoma is both limited and controversial. This study was performed to determine whether pathological status of the SLN is an important risk factor in this heterogeneous group and, thus, provides a rationale for SLN biopsy.

Methods: The records of 131 patients with primary cutaneous melanoma whose primary tumors were at least 4 mm thick and who underwent lymphatic mapping and SLN biopsy were reviewed. Several known prognostic factors, i.e., tumor thickness, ulceration, Clark level, location, sex, as well as SLN pathological status were analyzed with respect to disease-free and overall survival.

Results: Lymphatic mapping and SLN biopsy was successful in 126 (96%) of 131 patients who underwent the procedure. In 49 patients (39%), the SLN biopsy was positive by conventional histology, although it was negative in 77 patients (61%). The median follow-up was 3 years. Although presence of ulceration and SLN status were independent prognostic factors with respect to disease-free and overall survival, SLN status was the most powerful predictor of overall survival by univariate and multivariate analyses.

Conclusions: Lymphatic mapping and SLN biopsy is a highly accurate method of staging lymph node basins at risk for regional metastases in patients with thick melanoma and identifies those patients who may benefit from earlier lymphadenectomy as well as patients with a more favorable prognosis. Pathological status of the SLN in these patients with clinically negative nodes is the most important prognostic factor for survival and is essential to establish stratification criteria for future adjuvant trials in this high-risk group.

Key Words: Lymphatic mapping—Prognostic factors—Sentinel lymph node biopsy.

Patients with thick (≥4 mm), clinically node-negative melanoma carry a high risk of both regional nodal micrometastatic (60%–70%) and occult systemic (70%) disease at the time of initial presentation.[1] It is thought the risk of distant microscopic metastases is so high in these patients that it may negate any potentially curative benefit of a regional operation. These patients have therefore not been considered candidates for elective lymph node dissection (ELND) but have been targeted for adjuvant therapy. Although adjuvant therapy benefits patients who develop nodal metastases, data that support its routine use in all patients with thick melanoma are both limited and controversial.

Recent studies in patients with thick melanoma suggest that this group is heterogeneous in prognosis and have demonstrated that certain prognostic factors, especially tumor ulceration and nodal disease, can discriminate favorable from unfavorable prognostic subsets. Sen-

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tinel lymph node (SLN) biopsy rather than ELND offers a selective approach to assess the regional nodal basin, but no studies have specifically addressed the role for this technique in patients with thick melanoma. Our study was performed to determine if pathological status of the SLN is an important risk factor for recurrence or survival and, thus, provide a rationale for SLN biopsy in this high-risk group.

PATIENTS AND METHODS

Patients

From 1991 to mid-1998, 131 patients with thick primary cutaneous melanoma underwent lymphatic mapping and SLN biopsy at The University of Texas M. D. Anderson Cancer Center. Patients were included in this analysis if the primary tumor was at least 4 mm thick and there was no evidence of metastatic melanoma in regional lymph nodes and distant sites by physical examination and staging evaluation (chest x-ray and alkaline phosphatase and lactate dehydrogenase concentrations). Several known prognostic factors, i.e., age, sex, tumor thickness, Clark level, axial location, presence of ulceration, as well as pathological status of the SLN, were documented for each patient.

SLN Mapping Technique

Lymphatic mapping and SLN biopsy were performed as previously described.[2,3] Most patients underwent preoperative lymphoscintigraphy with intradermally administered ^{99m}Tc sulfur colloid to establish lymphatic drainage patterns and identify those basins at risk for metastatic melanoma. Lymphatic mapping and SLN biopsy were performed after the intradermal administration of 1 to 3 ml of isosulfan blue dye around the intact tumor or biopsy site immediately before the procedure. More recently (November 1994 to the present), patients also received an intradermal injection of 0.5 to 1.0 mCi of unfiltered technetium ^{99m}Tc sulfur colloid 1 to 4 hours before surgery; lymphatic mapping was then performed with the aid of a handheld gamma counter (RIGS model 1001; Neoprobe Corporation, Dublin, OH). Each SLN was excised and submitted for pathological analysis. All patients underwent wide local excision of the primary melanoma with margins appropriate for tumor thickness.[4,5]

Excised SLNs were analyzed by conventional histological staining (hematoxylin and eosin) of bisected specimens. More recently, pathological evaluation of SLNs included a serial section of each node if no metastatic disease was identified by standard sectioning, as described in detail previously.[6] In some cases, immunohistochemical staining was performed by using antisera to the S-100 protein and the melanoma antigen HMB-45 to clarify equivocal findings.

Patients with a positive SLN were not routinely offered adjuvant therapy because no standard treatment was available during most of the study period. However, patients were offered participation in prospective clinical trials that evaluate adjuvant therapy regimens.

A surgical melanoma database and patient charts were reviewed to determine relevant clinical information and to identify sites of recurrence. Disease-free survival and time to most recent follow-up (or death) were calculated from the date of primary melanoma diagnosis.

Statistical Analysis

Standard statistical techniques were used. Categorical variables were analyzed by χ^2 test and continuous data by Student's *t*-test or Wilcoxon rank-sum test whenever appropriate. Multivariate analyses used to associate covariates to timed event end points such as disease-free and overall survival were performed by using the Cox proportional hazard regression model. Tumor thickness was treated as a continuous variable for both univariate and multivariate analyses.

RESULTS

SLN Identification Rate and Histological Status of SLN

Of the 131 patients who underwent lymphatic mapping and attempted SLN biopsy, at least one SLN was identified in 126 (96%); these patients constitute the study population. By histological analysis, a positive SLN was identified in 49 of 126 successfully mapped patients (39%). All these patients were offered and underwent therapeutic lymphadenectomy.

Patient Characteristics, Prognostic Factors, and Adjuvant Therapy

Clinical and pathological characteristics of these patients are listed in Table 1. The median and mean tumor thicknesses were 5.0 and 6.3 mm, respectively. The median age was 57 years, and 63% of patients were male. In addition, 63 patients (50%) had ulcerated primary tumors.

The distribution of prognostic factors grouped by histological status of the SLN is illustrated in Table 2. Patients with a positive SLN were statistically more likely to have primary tumors that were ulcerated. Patient age, sex, Clark level, tumor thickness, and tumor location were not significantly different between SLN groups.

TABLE 1. *Clinical and pathological characteristics (n = 126)*

Characteristic	
Sex, n (%)	
Male	79 (63)
Female	47 (37)
Age (y)	
Median	57
Range	7–84
Site of primary, n (%)	
Trunk	65 (52)
Extremity	56 (43)
Upper	17 (13)
Lower	39 (31)
Head or neck	5 (4)
Thickness (mm)	
Median	5.0
Mean	6.3
Range	4–22
Clark level, n (%)	
II/III	15 (12)
IV/V	103 (82)
Unknown	8 (6)
Ulceration, n (%)	
Present	63 (50)
Absent	61 (48)
Unknown	2 (2)
Status of SLN, n (%)	
Positive	49 (39)
Negative	77 (61)

SLN, sentinel lymph node.

In patients with at least one histologically positive SLN, 51% received no adjuvant therapy and 49% received adjuvant therapy, as follows: interferon, 38%; vaccine, 3.5%; and biochemotherapy, 5.5%. In addition, 6% of patients with histologically negative SLNs also received adjuvant therapy, i.e., all received interferon.

Survival Analysis

Analysis with respect to prognostic factors and disease-free and overall survival was limited to the 116 patients in whom successful lymphatic mapping and SLN biopsy was performed and all variables were assessable. The median follow-up was 36 months. The 3-year disease-free and overall survival of the entire cohort was 72% and 80.2%, respectively (Fig. 1). The 5-year overall survival was 58%.

TABLE 2. *Distribution of prognostic factors according to histological status of the SLN*

Prognostic factor	Negative (n = 77)	Positive (n = 49)	*P*
Age (mean years)	57	53	NS
Male (%)	62	63	NS
Tumor thickness (mm)			
Median	5.0	5.0	–
Mean	6.43	6.11	NS
Clark level > III (%)	89	85	NS
Axial location (%)	60	49	NS
Ulceration (%)	40	63	.01

SLN, sentinel lymph node; NS, not significant.

The results of univariate analyses of several known prognostic factors with respect to disease-free survival are shown in Table 3. Positive SLN status and presence of ulceration were both statistically significant prognostic factors by univariate analysis. The 3-year disease-free survival for negative and positive SLN patients was 82.4% and 58%, respectively ($P < .03$) (Fig. 2A). In addition, the 3-year disease-free survival for patients without and with evidence of tumor ulceration was 80.3% and 65.9%, respectively ($P = .011$) (Fig. 3A). When both SLN status and presence of ulceration were combined in the univariate analysis, the 3-year disease-free survival for patients with both favorable factors (i.e., ulceration absent and negative SLN; n = 44) vs. those patients with both adverse factors (i.e., ulceration present and positive SLN; n = 31) was 82.4% and 49.9%, respectively ($P < .003$) (Fig. 4A). Although a positive

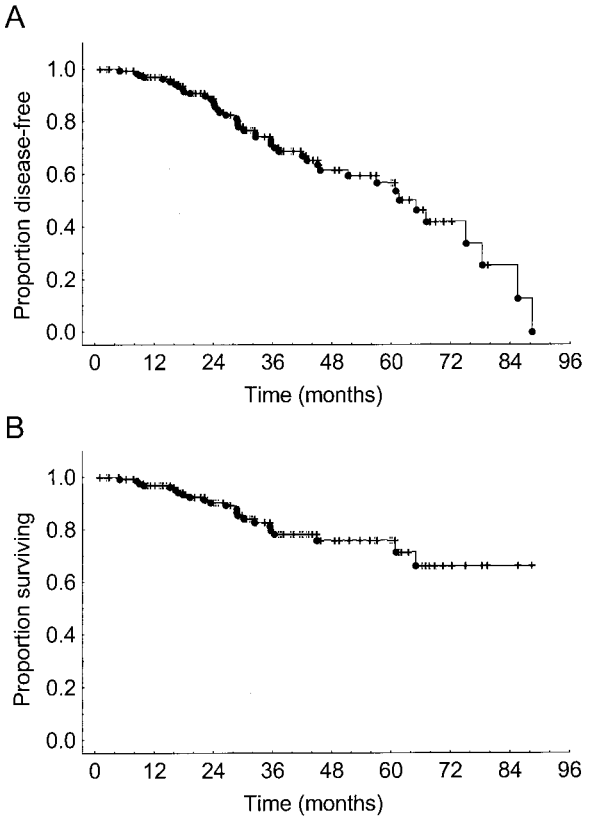

FIG. 1. Kaplan-Meier survival for patients undergoing successful lymphatic mapping and sentinel lymph node (SLN) biopsy (n = 126). The 3-year disease-free (**A**) and overall (**B**) survivals were 72.0% and 80.2%, respectively.

TABLE 3. *Prognostic factors influencing disease-free and overall survival, all patients*

	Disease-free survival				Overall survival			
		Multivariate				Multivariate		
Prognostic factor	Univariate *P*	HR	CI	*P*	Univariate *P*	HR	CI	*P*
Age	NS	–	–	NS	NS	–	–	NS
Sex	NS	–	–	NS	NS	–	–	NS
Tumor thickness	NS	–	–	NS	NS	–	–	NS
Clark level > III	NS	–	–	NS	NS	–	–	NS
Axial location	NS	–	–	NS	NS	–	–	NS
Ulceration	.011	2.43	1.69–3.17	.002	.038	2.76	1.76–3.76	.047
SLN status	.029	2.03	1.36–2.70	.039	.006	3.24	2.26–4.21	.018

HR, hazard ratio; CI 95% confidence interval for hazard ratio; NS, not significant; SLN, sentinel lymph node.

SLN and presence of ulceration remained significant by multivariate analysis, the presence of ulceration was the strongest predictor (Table 3).

Univariate analyses of the several known prognostic factors with respect to overall survival are also shown in Table 3. The same two factors were again statistically significant. The 3-year overall survival for negative and positive SLN patients was 89.8% and 64.4%, respectively ($P = .006$) (Fig. 2B). When stratified by the

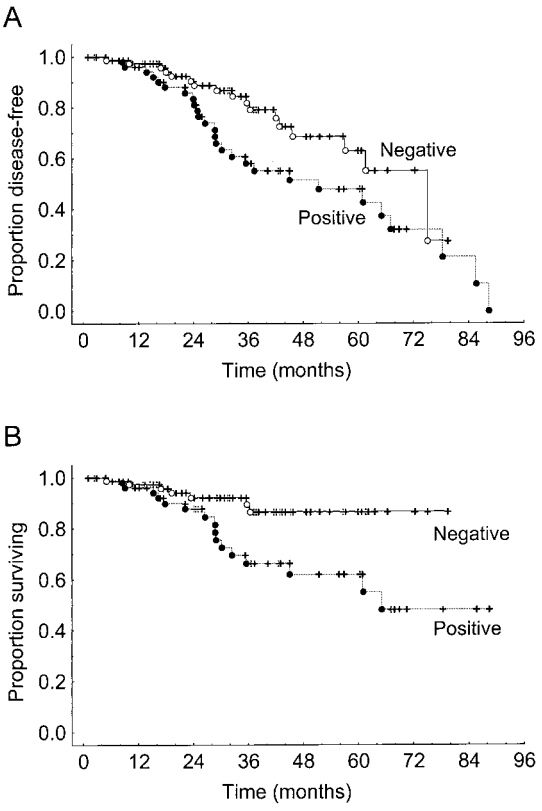

FIG. 2. Kaplan-Meier survival for patients undergoing successful lymphatic mapping and sentinel lymph node (SLN) biopsy stratified by SLN status. (**A**) The 3-year disease-free survivals for negative SLN patients (n = 77) and positive SLN patients (n = 49) were 82.4% and 58.0%, respectively. (**B**) The 3-year overall survivals for negative SLN and positive SLN patients were 89.8% and 66.4%, respectively. Disease-free and overall survivals were significantly better for patients with a negative SLN biopsy ($P < .03$ and $P = .006$, respectively).

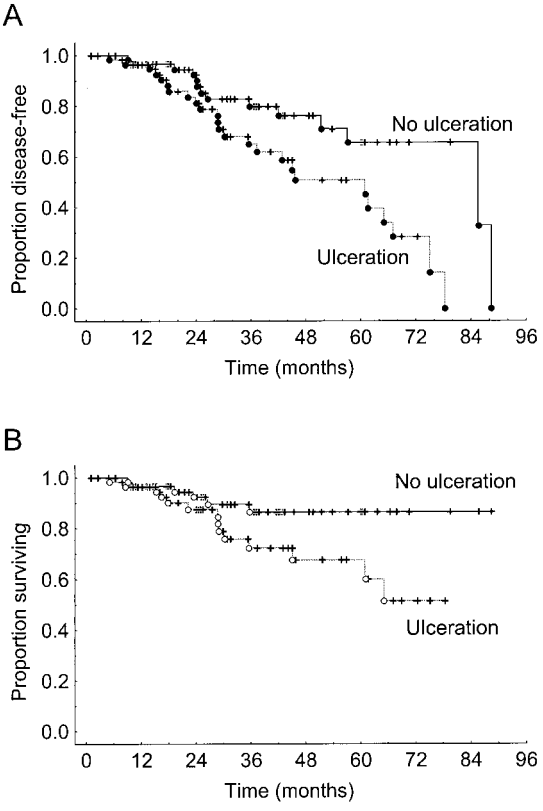

FIG. 3. Kaplan-Meier survival for patients undergoing successful lymphatic mapping and sentinel lymph node (SLN) biopsy stratified by presence of ulceration. (**A**) The 3-year disease-free survivals for patients without ulceration (n = 61) and patients with ulceration (n = 63) were 80.3% and 65.9%, respectively. (**B**) The 3-year overall survivals for patients without and with ulceration were 86.7% and 73.1%, respectively. Disease-free and overall survivals were significantly better for patients without evidence of tumor ulceration ($P = .011$ and $P = .038$, respectively).

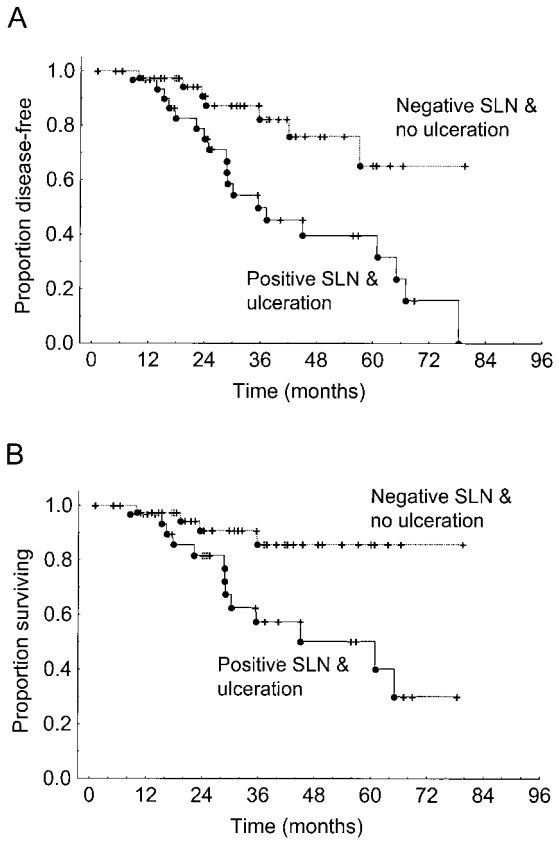

FIG. 4. Kaplan-Meier survival for patients undergoing successful lymphatic mapping and sentinel lymph node (SLN) biopsy stratified by both SLN status and presence or absence of ulceration. (**A**) The 3-year disease-free survival for patients with a negative SLN and without ulceration (n = 44) compared with patients who had a positive SLN and with ulceration (n = 31) was 82.4% and 49.9%, respectively. (**B**) The 3-year overall survival for patients with a negative SLN and without ulceration (n = 44) compared with patients who had a positive SLN and with ulceration (n = 31) was 85.9% and 57.3%, respectively. Disease-free and overall survivals were significantly better for patients with a negative SLN and absence of tumor ulceration (both $P < .003$).

absence or presence of tumor ulceration, the 3-year overall survival was 86.7% and 73.1%, respectively ($P < .003$) (Fig. 3B). When both SLN status and presence of ulceration were combined in the univariate analysis, the 3-year overall survival for patients with both favorable factors vs. those patients with both adverse factors was 85.9% and 57.3%, respectively ($P < .003$) (Fig. 4B). Although positive SLN status and presence of ulceration remained significant by multivariate analysis, positive SLN status was the strongest predictor (Table 3).

DISCUSSION

The management of patients with clinically localized, thick melanoma represents a challenge for the surgeon. Because these patients have a high risk of distant failure, contemporary thinking suggests that treatment of the clinically negative regional nodal basin as part of the initial management does not provide any survival benefit.[1] Therefore, regional lymph node dissection in patients with thick primary melanomas has generally been deferred until nodal metastases become clinically evident. However, several contemporary studies demonstrate that long-term survival is not universally poor, with overall 5-year survival rates of 47% to 62%.[7–10] In this study, 5-year overall survival was 58%.

Prognostic factor analysis demonstrates that this population actually represents a heterogeneous group. Heaton et al.[9] demonstrated that nodal status, as determined by ELND or the development of clinically apparent disease, was the most important prognostic factor in these patients, whereas presence of tumor ulceration was also an independent predictor of overall survival by multivariate analysis. The importance of tumor ulceration and nodal status was confirmed in a recent report by Kim et al.,[8] who demonstrated that nodal status, presence of ulceration, and increasing tumor thickness were all independent predictors of survival in patients with thick melanoma. Given that recent data suggest that patients with nodal disease may benefit from,[11] or at least be candidates for, adjuvant therapy protocols, proper staging of the nodal basin is essential.

The availability of lymphatic mapping and sentinel node biopsy led us to evaluate the role for this technique in the management of patients with thick melanoma. Our 96% SLN identification rate compares favorably with other reported series and includes some patients who underwent this procedure earlier in our experience, 1991 to 1994, before we used the handheld gamma probe.[12–14] The overall frequency of a positive SLN in successfully mapped patients in this study was 39%, which is consistent with previous reports of primary nodal basin status after both SLN biopsy and ELND.[12,15] In a large retrospective analysis, Slingluff et al.[15] reported that a nearly identical 36% of patients with melanoma at least 4 mm thick had positive lymph nodes by ELND. Because routine histological techniques were used for most patients, it is not surprising that these rates are similar.

The present study confirms by multivariate analysis that SLN biopsy provides essential prognostic information in this patient population. Compared with a positive SLN biopsy, a negative SLN biopsy was associated with 42% and 35% increases in 3-year disease-free and overall survival, respectively, in this cohort of patients. In addition, this study corroborated previous studies in that ulceration is clearly an important prognostic factor in this patient population.[8,9] It is interesting that if SLN status

and ulceration are combined, relatively homogeneous subgroups can be identified that have favorable or unfavorable biology. In fact, compared with patients who have both ulceration and a histologically positive SLN, those patients without either had a 50% better 3-year overall survival (85.9% vs. 57.3%; $P < .003$) (Fig. 4). These findings are critical, considering the current controversy regarding the use of adjuvant therapy for the entire population of patients with thick melanoma, and they provide additional support for including ulceration as well as SLN status in the staging of these patients. It is also noteworthy that tumor thickness did not provide additional prognostic information, which suggests that differences in tumor thickness in this group of patients do not represent major differences in biological behavior.

Data from the Eastern Cooperative Oncology Group 1684 trial published in 1996 demonstrated an overall survival benefit for node-positive patients treated with interferon.[11] However, no data exist to support this relatively aggressive approach for the node-negative thick melanoma group, because only 31 patients in this trial were a pathological stage T4N0, and no survival benefit to high-dose interferon was reported for this subset. Although these patients have been characterized as high risk, the present study suggests that many such patients have a more favorable prognosis. These data also support an integral role for SLN biopsy in the management of patients with thick melanoma, because accurate nodal staging can help determine which patients may benefit from adjuvant therapy and may provide the most relevant patient stratification for future adjuvant trials. In this way, patients who have thick melanoma and occult nodal disease can undergo therapeutic node dissection, with the hope to achieve durable regional nodal control and, therefore, become better candidates for adjuvant therapy protocols, because they would receive therapy after all known disease was removed first. The SLN-negative patients may be spared the morbidity of potentially unnecessary lymphadenectomy and either followed by observation or enrolled in adjuvant therapy trials that evaluate potentially less toxic regimens.

In conclusion, although ELND may not be appropriate for the thick melanoma group, the information gained from SLN biopsy provides valuable staging information and should be incorporated into the routine management of these patients.

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