PAPER

Prognostic Information From Sentinel Lymph Node Biopsy in Patients With Thick Melanoma

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Hypothesis: Sentinel lymph node (SLN) biopsy provides valuable prognostic information for patients with thick (T4) melanoma.

Design: Post hoc analysis of data from a prospective, randomized trial.

Setting: Academic and private hospitals.

Patients: Data of 240 patients with melanoma thicker than 4 mm were analyzed. Patients with tumor-positive SLNs underwent completion lymphadenectomy. Disease-free and overall survival were evaluated by Kaplan-Meier analysis. Univariate and multivariate analyses were performed to evaluate factors predictive of tumor-positive SLNs and disease-free and overall survival.

Results: Median thickness of melanoma was 5.6 mm, and patients were followed up for a median of 50 months. The SLNs were tumor positive in 100 patients (41.7%); 18% of these had additional positive nodes on completion lymphadenectomy. Extremity tumor location (risk ratio, 1.66; 95% confidence interval, 1.24-2.24; $P=.001$), Clark level (1.95; 1.33-2.87; $P=.02$), and lymphovascular invasion (1.57; 1.13-2.17; $P=.01$) were associated with a greater risk of tumor-positive SLNs. The patients with tumor-negative SLNs had significantly better median disease-free survival (46.5 vs 31.0 months; $P=.04$) and overall survival (55.5 vs 43.0 months; $P=.004$) compared with patients with tumor-positive SLNs. On multivariate analysis, male sex (risk ratio, 1.59; 95% confidence interval, 1.05-2.50; $P=.02$), increasing Breslow thickness (1.58; 1.10- 2.30; $P=.03$), ulceration (1.73; 1.18-2.59; $P=.02$), and tumor-positive SLNs (1.68; 1.17-2.43; $P=.009$) were associated with worse overall survival.

Conclusion: The SLN biopsy provides useful prognostic information for patients with T4 melanoma.

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THE PROGNOSIS OF PATIENTS with intermediate-thickness melanoma is determined by several clinicopathologic factors such as Breslow thickness,[1,2] ulceration,[2,3] sex,[4] and regional nodal status.[5,6] Indeed, the presence of regional nodal metastases is the single most important factor predicting recurrence and survival for these patients.[5] For patients with intermediate-thickness melanoma, sentinel lymph node (SLN) biopsy has become the standard method of determining the pathologic status of the regional nodal basin.[5] This minimally invasive technique allows for staging in patients with clinically negative nodes with less morbidity than elective lymph node dissection.[3]

Given the effect that the regional nodal basin status has on survival, an understanding of the factors that influence nodal metastasis is important to the clinician. During the past several years, several factors have emerged as independent predictors of nodal status, including those inherent to the tumor. For example, patients with ulcerated primary melanoma tumors have a higher risk of nodal metastasis.[2,3] The most important predictor of nodal status, however, is the Breslow thickness.[2,7,8] For patients with thin melanoma (<1 mm), the risk of nodal metastasis is low (<5%).[5] In the absence of other factors (ie, ulceration, mitotic activity), many authorities do not recommend routine SLN biopsy for patients with thin melanoma. The role of SLN biopsy is more clearly defined for patients with intermediate-thickness melanoma (1-4 mm thick).

The risk of nodal metastasis for patients with intermediate-thickness melanoma ranges from 15% to 30%.[5,9] For these patients, SLN biopsy allows accurate staging of the draining nodal basin, thus avoiding a full lymphadenectomy for most of the patients. The risk of nodal disease is even greater for patients with thick melanoma (>4 mm thick).[10] Furthermore, with increasing thickness, the risk of systemic metastatic disease also increases, making this the highest-risk group. Given the high probability for distant metastatic disease, the role of SLN biopsy in patients with thick melanoma is controversial.

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Because most patients with thick melanoma do not present with clinical evidence of nodal metastasis, there might be a role for SLN biopsy in these patients. Sentinel lymph node status not only affects prognostic discussions between clinician and patient, it also influences further treatment choices. The goals of treatment of the regional lymph nodes are cure and regional disease control. Currently, most patients found to have tumor-bearing nodes at the time of SLN biopsy are treated with completion lymph node dissection (CLND) and are candidates for adjuvant therapy. Despite the high risk for disseminated disease in patients with thick melanoma, evaluation of the regional nodal basin for those who lack clinical evidence of nodal disease might provide useful information. Although some might argue that treatment of the regional lymph nodes in patients with thick melanoma is futile (given the high risk of distant metastatic disease) and that these patients should receive adjuvant therapy without nodal staging, others have shown that patients with node-negative thick melanoma have a better prognosis and may reasonably consider foregoing adjuvant therapy.[10-13] Furthermore, there is nothing absolute about the 4.0-mm Breslow thickness level; likely there is a group of patients with T4 melanoma who may benefit in terms of regional disease control and cure by resection of tumor-bearing nodes. Therefore, we hypothesized that SLN biopsy might provide useful prognostic information for patients with thick melanoma who lack clinical evidence of metastatic disease.

METHODS

The Sunbelt Melanoma Trial is a prospective, randomized trial involving 79 centers in North America. The institutional review board of each participating institution approved this study. Patients aged 18 to 70 years with cutaneous melanoma of 1-mm Breslow thickness or more and without clinical evidence of regional or distant metastasis were eligible. The details of the Sunbelt Melanoma Trial's randomization and treatment schema have been published elsewhere.[3] Some patients were registered in the study before SLN biopsy but did not proceed to randomization in the study; most of these patients were followed up even if not randomized and were included in this analysis. After informed consent, patients were registered and underwent wide local excision of the primary melanoma and SLN biopsy with peritumoral intradermal injection of technetium Tc 99m sulfur colloid; intradermal isosulfan blue dye was also used in most cases. All of the SLNs were identified and excised per previously published guidelines.[14]

The SLNs were processed with serial sectioning (≥5 sections per block) with hematoxylin-eosin staining and immunohistochemistry for S-100 protein. Some institutions also performed immunohistochemical analysis for HMB-45, but this was not a requirement per protocol. A histologically positive SLN was defined as evidence of metastatic tumor cells identified by hematoxylin-eosin staining or immunohistochemistry. A central pathology review committee evaluated the first 10 cases from each participating institution, as well as all cases of SLNs containing metastases. There was an independent data safety and monitoring committee for this study.

Patients with evidence of metastasis to SLNs underwent a staging evaluation before CLND. The required staging evaluation included chest radiography and abdominal/pelvic computed tomography; other tests were obtained as deemed appropriate by the treating physicians. Patients with documented distant metastatic disease were excluded from the randomized adjuvant therapy protocols of the Sunbelt Melanoma Trial; however, their data were collected and included in the trial database after registration, regardless of randomization status.

Table 1. Clinicopathologic Characteristics of Patients With Thick Melanoma[a]

	Tumor-Negative SLN	Tumor-Positive SLN	*P* Value
No. of patients	140 (58.3)	100 (41.7)	
Mean age, y	51.9	51.7	.88
Male sex	100 (71.4)	70 (70.0)	.81
Clark level IV or V	133 (98.5)	88 (92.6)	.02
Ulcerated tumor	74 (54.0)	65 (65.7)	.07
Superficial spreading histologic subtype	18 (13.2)	19 (19.4)	.20
Regression	20 (15.7)	14 (16.3)	.92
Extremity tumor site	44 (31.4)	53 (53.0)	.001
Vertical growth phase	101 (84.9)	75 (86.2)	.79
Lymphovascular invasion	17 (14.0)	24 (27.9)	.01

Abbreviation: SLN, sentinel lymph node.
[a] Unless otherwise indicated, data are expressed as number (percentage) of patients. The number of patients may not equal the total number of the cohort because of missing data.

For this post hoc analysis, enrolled patients with primary tumors thicker than 4 mm underwent analysis. Clinicopathologic factors were analyzed with regard to their relationship with SLN status, including age, sex, Clark level, ulceration, histologic subtype, regression, tumor site, vertical growth phase, and presence of lymphovascular invasion. Because mitotic rate was not recognized as being important during the development of the Sunbelt Melanoma Trial and therefore not collected, these data were not included in this analysis. We generated disease-free survival (DFS) and overall survival (OS) curves using the Kaplan-Meier method. Disease-free survival was defined as the time from definitive surgical therapy to the development of recurrent disease. Overall survival was defined as the time from definitive surgical therapy to death. A Cox proportional hazards model was then used to determine which clinicopathologic variables, including SLN status, were independent predictors of DFS and OS in this population of patients with thick melanoma. All analyses were performed with commercially available software (JMP; SAS Institute Inc, Cary, North Carolina).

RESULTS

We identified a total of 240 patients with thick melanoma (>4 mm). All of the patients underwent local excision of the primary tumor and SLN biopsy. The median follow-up was 50 months. The median age was 51 (range, 24-71) years, and 170 (70.8%) were men. Because this cohort consisted only of patients with thick primary tumors, there were a large proportion of patients with adverse clinicopathologic features. Nearly all (96.1%) were determined to have Clark level IV or V tumors, and 58.9% had an ulcerated primary tumor.

Of the entire cohort, 100 (41.7%) had evidence of metastatic melanoma within the SLNs. The Clark level ($P=.02$), extremity primary tumor site ($P=.001$), and presence of lymphovascular invasion ($P=.01$) were the only factors associated with a tumor-positive SLN in this cohort (**Table 1**). Primary tumor ulceration, although numerically more

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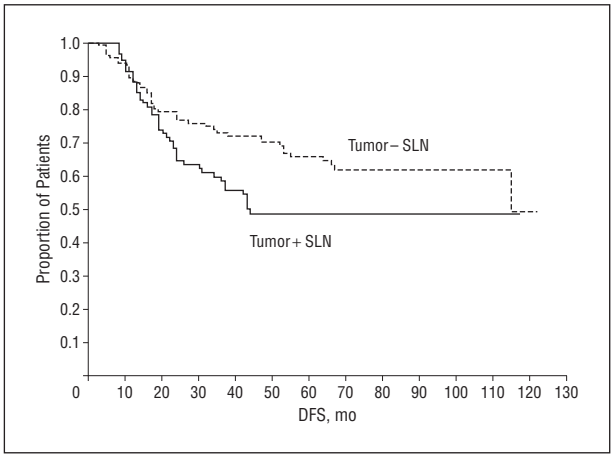

Figure 1. Disease-free survival (DFS) for patients with thick melanoma. SLN indicates sentinel lymph node; –, negative; and +, positive. $P=.04$.

prevalent in the patients with node-positive disease, was not statistically associated with SLN status ($P=.07$).

Of the 100 patients found to have tumor-positive SLNs, 71 underwent CLND. Of these patients, 58 (82%) had metastatic melanoma confined to the SLN; no additional positive nodes were detected at CLND. Furthermore, when the total number of metastatic nodes was considered, 38 (54%) of the patients who underwent CLND had only 1 positive lymph node; 15 (21%) had 2 positive lymph nodes, 2 (3%) had 3 positive lymph nodes, and 4 (6%) had more than 3 positive lymph nodes. The major reason some patients with tumor-positive SLNs did not undergo CLND was refusal to undergo randomization into one of the various treatment arms. Furthermore, 2 patients were found to have pulmonary metastases during the staging workup and thus did not undergo CLND.

The median DFS for the entire cohort was 37 months; the 5-year DFS rate was 59.1%. During follow-up, 88 patients developed recurrent melanoma. Patients with a tumor-positive SLN had a shorter median DFS than those with a tumor-negative SLN (31.0 vs 46.5 months, respectively; $P=.04$; **Figure 1**). Only the following 2 clinicopathologic factors were found to significantly predict DFS on univariate analysis: tumor thickness greater than the median thickness for the entire cohort (>5.6 mm; $P=.03$) and a tumor-positive SLN ($P=.04$). Both factors remained significant on multivariate analysis (**Table 2**). Patient age, sex, and ulceration had no effect on DFS for patients with thick melanoma.

We then conducted an analysis of the patterns of recurrence. Recurrent melanoma was detected in 45 of 140 patients (32.1%) with tumor-negative SLNs vs 43 of 100 (43.0%) of those with tumor-positive SLNs ($P=.09$). When we compared patients with tumor-negative vs tumor-positive SLNs, the patterns of recurrence were as follows: distant metastasis (77.8% vs 72.1%; $P=.54$); local/in-transit recurrence (28.9% vs 39.5%; $P=.29$), and recurrence within the previously mapped nodal basin (13.3% vs 0%; $P=.01$). No patient found to have a tumor-positive SLN who subsequently underwent a CLND developed recurrence within the dissected basin. Although 6 of the 29 patients with tumor-positive SLNs who did not undergo CLND developed recurrent disease, none had a recurrence in a previously mapped nodal basin.

Table 2. Factors Associated With Disease-Free Survival for Patients With Thick Melanoma

Variable	No. (%) of Patients[a]	RR (95% CI)	*P* Value: Univariate	*P* Value: Multivariate
Breslow thickness, mm				
>5.6	120 (50.0)	1.60 (1.06-2.46)	.03	.03
≤5.6	120 (50.0)			
SLN result				
Positive	100 (41.7)	1.54 (1.01-2.34)	.04	.045
Negative	140 (58.3)			
Age, y				
>51	118 (49.2)	1.07 (0.71-1.63)	.75	
≤51	122 (50.8)			
Sex				
Male	170 (70.8)	1.45 (0.91-2.43)	.12	
Female	70 (29.2)			
Clark level				
I-III	9 (3.9)	1.18 (0.36-2.83)	.76	
IV or V	221 (96.1)			
Ulceration				
Present	139 (58.9)	1.39 (0.91-2.16)	.13	
Absent	97 (41.1)			
Histologic subtype				
Superficial spreading	37 (15.8)	0.95 (0.50-1.65)	.86	
Other	197 (84.2)			
Regression				
Present	34 (16.0)	1.03 (0.53-1.84)	.92	
Absent	179 (84.0)			
Site				
Nonextremity	143 (59.6)	1.20 (0.78-1.86)	.41	
Extremity	97 (40.4)			
Vertical growth phase				
Present	176 (85.4)	1.65 (0.81-3.96)	.18	
Absent	30 (14.6)			
Lymphovascular invasion				
Present	41 (19.8)	1.02 (0.59-1.90)	.95	
Absent	166 (80.2)			

Abbreviations: CI, confidence interval; RR, risk ratio; SLN, sentinel lymph node.

[a] The number of patients may not equal the total number of the cohort because of missing data.

The median OS for the entire cohort was 50 months; the 5-year OS rate was 55.5%. Of those patients who died during follow-up, the median time to death was 30 months. Patients with tumor-positive SLNs had a shorter median OS rate compared with those with tumor-negative SLNs (43.0 vs 55.5 months; $P=.004$) (**Figure 2**). On multivariate analysis, the following 4 factors were found to predict OS: Breslow thickness ($P=.03$), SLN status ($P=.009$), male sex ($P=.02$), and primary tumor ulceration ($P=.02$; **Table 3**). For the patients with a tumor-positive SLN, primary tumor ulceration significantly affected OS ($P=.03$; **Figure 3**).

COMMENT

The purpose of this analysis was to determine the value of SLN biopsy for patients with thick melanoma. As a staging tool, SLN biopsy has been shown to be accurate[15-17] and safe.[18] In addition, SLN biopsy provides the single most valuable piece of information in the staging of clinically node-negative melanoma.[2,5] Although its role in staging of thin melanoma

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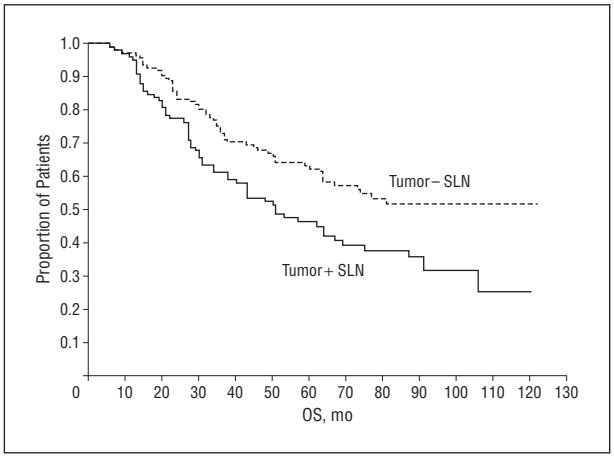

Figure 2. Overall survival (OS) for patients with thick melanoma. SLN indicates sentinel lymph node; –, negative; and +, positive. *P*=.004.

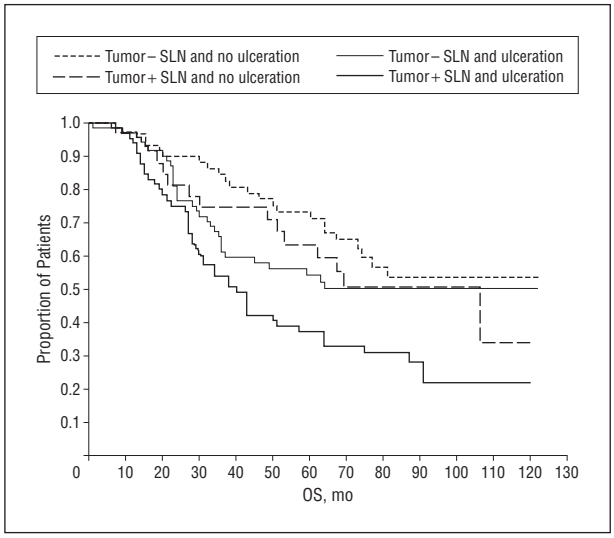

Figure 3. Overall survival (OS) for patients with thick melanoma stratified by nodal status and primary tumor ulceration. SLN indicates sentinel lymph node; –, negative; and +, positive. *P*=.03.

Table 3. Factors Associated With Overall Survival for Patients With Thick Melanoma

Variable	No. (%) of Patients[a]	RR (95% CI)	*P* Value Univariate	*P* Value Multivariate
Breslow thickness, mm				
>5.6	120 (50.0)	1.58 (1.10-2.30)	.01	.03
≤5.6	120 (50.0)			
SLN result				
Positive	100 (41.7)	1.68 (1.17-2.43)	.005	.009
Negative	140 (58.3)			
Age, y				
>51	118 (49.2)	1.41 (0.98-2.04)	.07	
≤51	122 (50.8)			
Sex				
Male	170 (70.8)	1.59 (1.05-2.50)	.03	.02
Female	70 (29.2)			
Clark level				
I-III	9 (3.9)	1.49 (0.58-3.12)	.37	
IV or V	221 (96.1)			
Ulceration				
Present	139 (58.9)	1.73 (1.18-2.59)	.004	.02
Absent	97 (41.1)			
Histologic subtype				
Superficial spreading	37 (15.8)	1.06 (0.62-1.72)	.81	
Other	197 (84.2)			
Regression				
Present	34 (16.0)	1.20 (0.69-1.96)	.50	
Absent	179 (84.0)			
Site				
Nonextremity	143 (59.6)	1.19 (0.82-1.74)	.37	
Extremity	97 (40.4)			
Vertical growth phase				
Present	176 (85.4)	1.12 (0.64-2.10)	.71	
Absent	30 (14.6)			
Lymphovascular invasion				
Present	41 (19.8)	0.83 (0.51-1.39)	.46	
Absent	166 (80.2)			

Abbreviations: CI, confidence interval; RR, risk ratio; SLN, sentinel lymph node.

[a]The number of patients may not equal the total number of the cohort because of missing data.

is controversial, SLN biopsy is widely accepted as an accurate means of providing important prognostic information for patients with intermediate-thickness melanoma.[5]

This analysis was limited to patients with thick melanoma. In fact, the median tumor thickness (5.6 mm) was quite thick and, as such, most of the patients had many of the tumor-related factors that one usually attributes to high-risk melanoma. These patients have advanced local tumors and a very high risk of systemic disease at the time of presentation.[19] As evidence mounts, it appears that melanoma is a biologically heterogeneous disease. Even for patients with thick primary tumors, there are some patients who might have better survival than others. Methods of stratifying those patients are beneficial from a prognostic and (potentially) therapeutic standpoint. Despite the accuracy of SLN biopsy findings, up to 15% of patients overall will develop metastatic disease without histologic evidence of nodal metastasis; this risk is greater among patients with thick primary tumors.[20-22] This, combined with the high risk of distant metastatic disease in patients with thick melanoma, has led to controversy regarding the utility of SLN biopsy in these patients.

We found that nearly 42% of patients with thick melanoma had tumor-positive SLNs at biopsy, which is similar to previously published results.[10,12,13,23] This is critically important because the status of the SLN predicts patient survival independent of tumor thickness. This holds true for patients with thick melanoma. Our data show that patients with a tumor-negative SLN survive longer than those with nodal metastasis at the time of diagnosis. Others have found this to be true as well.[13,23]

The DFS and OS rates in the present study are similar to those seen in other studies of patients with thick melanoma.[10-12] On multivariate analysis, factors that were found to affect DFS were increasing tumor thickness and SLN positivity. Others have also reported the impact of increasing tumor thickness on DFS in the setting of thick melanoma.[11] Primary tumor ulceration was not associated with DFS in our study. This is different from previously published data,[10,24] although ulceration was a significant predictor of OS.

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The most common site of recurrent melanoma was distant metastasis. This is not surprising given the tumor thickness of the study cohort. Similar to previously published reports,[13,23] most of the recurrences are distant. We did not find any difference in the rate of distant or local/in-transit recurrence between the patients with tumor-positive SLNs and those with tumor-negative SLNs. We did, however, find that patients with tumor-negative SLNs had a greater risk of regional nodal basin recurrence. This too is not surprising given that patients with tumor-negative SLNs did not undergo CLND. Slightly more than 13% of patients with tumor-negative SLNs developed recurrent disease within the mapped nodal basin. Although this percentage is quite high, this pattern of recurrence was not isolated. In fact, most of these nodal recurrences occurred in conjunction with other recurrences, especially distant metastases. This indicates that SLN biopsy with CLND for patients with thick melanoma is an excellent procedure for achieving regional disease control. The ability to provide durable regional control for patients with nodal metastasis is an important goal of treatment. Furthermore, we found that 6 of the patients with positive SLNs who did not undergo CLND (20%) ultimately had recurrences within the previously mapped nodal basin. This rate is what one would expect for a tumor-positive non-SLN. This is interesting, and is being further addressed by the current Multicenter Selective Lymphadenectomy Trial II.

The OS seen in the present study is similar to that reported in other series of SLN biopsies for patients with thick melanoma.[13,23] In fact, for patients in our study who had tumor-positive SLNs, there was a 5-year OS similar to those of patients with tumor-positive SLNs from studies by Thompson and Shaw,[25] Ferrone et al,[24] and Gajdos et al.[13] The 2 factors found to influence OS in the series from M. D. Anderson Cancer Center[10] were tumor ulceration and SLN status. In addition to these factors, we also found that increasing tumor thickness and sex influenced OS. The median tumor thickness in our study was greater than that of Gershenwald et al,[10] and perhaps this had some influence on the results. Gajdos et al[13] also found tumor thickness to be associated with OS for patients with T4 melanoma; however, tumor ulceration did not affect survival for their patients with a tumor-positive SLN.

In conclusion, SLN biopsy provides useful prognostic information for patients with thick melanoma; those with tumor-negative SLNs have improved DFS and OS compared with those with tumor-positive SLNs. Sentinel lymph node biopsy and CLND for patients with tumor-positive SLNs is an excellent strategy for achieving regional nodal disease control. Therefore, SLN biopsy for patients with thick primary melanoma has important prognostic and therapeutic implications. For these reasons, SLN biopsy need not be applied only to patients with intermediate-thickness melanoma but should be used for patients with thick primary tumors as well.

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REFERENCES

1. Balch CM, Soong SJ, Murad TM, Ingalls AL, Maddox WA. A multifactorial analysis of melanoma, II: prognostic factors in patients with stage I (localized) melanoma. *Surgery*. 1979;86(2):343-351.
2. Balch CM, Soong SJ, Gershenwald JE, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. *J Clin Oncol*. 2001;19(16):3622-3634.
3. McMasters KM, Noyes RD, Reintgen DS, et al; Sunbelt Melanoma Trial. Lessons learned from the Sunbelt Melanoma Trial. *J Surg Oncol*. 2004;86(4):212-223.
4. Scoggins CR, Ross MI, Reintgen DS, et al; Sunbelt Melanoma Trial. Gender-related differences in outcome for melanoma patients. *Ann Surg*. 2006;243(5):693-700.
5. Gershenwald JE, Thompson W, Mansfield PF, et al. Multi-institutional melanoma lymphatic mapping experience: the prognostic value of sentinel lymph node status in 612 stage I or II melanoma patients. *J Clin Oncol*. 1999;17(3):976-983.
6. Morton DL, Wanek L, Nizze JA, Elashoff RM, Wong JH. Improved long-term survival after lymphadenectomy of melanoma metastatic to regional nodes: analysis of prognostic factors in 1134 patients from the John Wayne Cancer Clinic. *Ann Surg*. 1991;214(4):491-501.
7. Clary BM, Brady MS, Lewis JJ, Coit DG. Sentinel lymph node biopsy in the management of patients with primary cutaneous melanoma: review of a large single-institutional experience with an emphasis on recurrence. *Ann Surg*. 2001;233(2):250-258.
8. Thompson JF, Shaw HM. Should tumor mitotic rate and patient age, as well as tumor thickness, be used to select melanoma patients for sentinel node biopsy? *Ann Surg Oncol*. 2004;11(3):233-235.
9. Morton DL, Cochran AJ, Thompson JF, et al; Multicenter Selective Lymphadenectomy Trial Group. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg*. 2005;242(3):302-313.
10. Gershenwald JE, Mansfield PF, Lee JE, Ross MI. Role for lymphatic mapping and sentinel lymph node biopsy in patients with thick (≥4 mm) primary melanoma. *Ann Surg Oncol*. 2000;7(2):160-165.
11. Jacobs IA, Chang CK, Salti GI. Role of sentinel lymph node biopsy in patients with thick (>4 mm) primary melanoma. *Am Surg*. 2004;70(1):59-62.
12. Carlson GW, Murray DR, Hestley A, Staley CA, Lyles RH, Cohen C. Sentinel lymph node mapping for thick (≥4 mm) melanoma: should we be doing it? *Ann Surg Oncol*. 2003;10(4):408-415.

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13. Gajdos C, Griffith KA, Wong SL, et al. Is there a benefit to sentinel lymph node biopsy in patients with T4 melanoma? *Cancer*. 2009;115(24):5752-5760.
14. McMasters KM. The Sunbelt Melanoma Trial. *Ann Surg Oncol*. 2001;8(9)(suppl): 41S-43S.
15. Ross MI, Reintgen D, Balch CM. Selective lymphadenectomy: emerging role for lymphatic mapping and sentinel node biopsy in the management of early stage melanoma. *Semin Surg Oncol*. 1993;9(3):219-223.
16. Uren RF, Howman-Giles RB, Shaw HM, Thompson JF, McCarthy WH. Lymphoscintigraphy in high-risk melanoma of the trunk: predicting draining node groups, defining lymphatic channels and locating the sentinel node. *J Nucl Med*. 1993; 34(9):1435-1440.
17. Reintgen D, Cruse CW, Wells K, et al. The orderly progression of melanoma nodal metastases. *Ann Surg*. 1994;220(6):759-767.
18. Roaten JB, Pearlman N, Gonzalez R, Gonzalez R, McCarter MD. Identifying risk factors for complications following sentinel lymph node biopsy for melanoma. *Arch Surg*. 2005;140(1):85-89.
19. Reintgen DS, Cox EB, McCarty KS Jr, Vollmer RT, Seigler HF. Efficacy of elective lymph node dissection in patients with intermediate thickness primary melanoma. *Ann Surg*. 1983;198(3):379-385.
20. Gershenwald JE, Colome MI, Lee JE, et al. Patterns of recurrence following a negative sentinel lymph node biopsy in 243 patients with stage I or II melanoma. *J Clin Oncol*. 1998;16(6):2253-2260.
21. Gadd MA, Cosimi AB, Yu J, et al. Outcome of patients with melanoma and histologically negative sentinel lymph nodes. *Arch Surg*. 1999;134(4):381-387.
22. Essner R, Conforti A, Kelley MC, et al. Efficacy of lymphatic mapping, sentinel lymphadenectomy, and selective complete lymph node dissection as a therapeutic procedure for early-stage melanoma. *Ann Surg Oncol*. 1999;6(5):442-449.
23. Essner R, Chung MH, Bleicher R, Hsueh E, Wanek L, Morton DL. Prognostic implications of thick (≥4-mm) melanoma in the era of intraoperative lymphatic mapping and sentinel lymphadenectomy. *Ann Surg Oncol*. 2002;9(8):754-761.
24. Ferrone CR, Panageas KS, Busam K, Brady MS, Coit DG. Multivariate prognostic model for patients with thick cutaneous melanoma: importance of sentinel lymph node status. *Ann Surg Oncol*. 2002;9(7):637-645.
25. Thompson JF, Shaw HM. The prognosis of patients with thick primary melanomas: is regional lymph node status relevant, and does removing positive regional nodes influence outcome? *Ann Surg Oncol*. 2002;9(8):719-722.

DISCUSSION

Mark Faries, MD, Santa Monica, California: This large prospective multicenter trial from the Sunbelt Melanoma Group has helped establish SLN biopsy as standard in melanoma and has elucidated many critically important parameters in the care of clinically localized disease. Among other advances, the trial has confirmed the accuracy of this surgical technique in a multiinstitutional setting; helped to establish a technical, intraoperative definition of an SLN; and identified predictors of nodal metastasis.

Currently, the authors take on the utility of SLN biopsy in the setting of thick melanoma. Traditional thinking has been that the propensity of these patients to suffer early development of distant metastases precludes the possibility of benefit from early treatment of regional lymph nodes. Such patients were disqualified from prior elective lymph node dissection trials for this reason. However, the advent of SLN biopsy has allowed a low-morbidity technique to assess regional nodes and thereby select patients for nodal surgery.

Previous retrospective series have shown the prognostic significance of the sentinel node even with thick primary lesions, and this report provides vital validation of those findings in a multicenter setting and a prospective trial. It should help put to rest questions regarding the appropriateness of sentinel node biopsy in patients with thick primary melanoma.

Despite this significant report, several important questions remain.

First, patients with these high-risk melanomas are sometimes radiographically evaluated preoperatively for distant or large nodal metastases. Were many of your patients studied by PET [positron emission tomography], CT [computed tomography], or brain MRI [magnetic resonance imaging]? Did any have preoperative nodal assessment by ultrasound? If such assessments were common in trial subjects, it might impact the population that was analyzed and have implications for patient selection in clinical practice.

Second, while sentinel node biopsy followed by complete dissection was highly successful in preventing regional recurrence, it appears there was a substantial risk for regional recurrence in the sentinel node *negative* group. Since this rate was higher than would be expected for a false-negative rate, do you think intransit disease, which is more common with these thick primaries, was responsible for many of these regional recurrences?

Finally, the decision to perform a minimally invasive lymph node biopsy is relatively easy. Clearly, the prognostic value, proven here, is substantial. The harder decision is whether to perform a CLND when the sentinel node is positive. Although this larger operation is the current standard of care, it clearly has greater morbidity, and its therapeutic impact is still not defined. Among your patients with sentinel node metastasis, only 18% had disease in nonsentinel nodes found during the completion dissection. Was the prognosis of those with nonsentinel node metastasis poor enough to suggest that their ship had sailed and that early removal of those nodes would not be beneficial? Were there any predictors of nonsentinel node metastasis such as Breslow thickness, age, or ulceration?

Overall, this report demonstrates the tremendous value of prospective clinical trials in guiding treatment and establishing standards of care.

Dr Scoggins: With regard to the first question, patients who were found to be tumor-positive on SLN biopsy underwent radiographic evaluation at the discretion of the treating institution. Computed tomography and CT/PET were commonly used for patients to be staged, and, if patients were found to have widely metastatic disease, they were more likely not to undergo CLND. You will notice that we only had 71 patients who underwent CLND, although we had 100 patients who had a tumor-positive SLN. Ultrasound evaluation of the nodal basin was not a routine component of the Sunbelt Melanoma Trial. When the Sunbelt study was written in 1996, the role of ultrasound in assessing the nodal basin was not appreciated, and it simply was not included as part of the trial protocol.

Your second question touched on the false-negative rate and recurrence in the mapped nodal basin. The false-negative rate for the Sunbelt Melanoma Trial was 10.2%, and those data were presented at the Society of Surgical Oncology [meeting] this year and hopefully will be in print soon. Thirteen percent of our patients with a thick melanoma who underwent a tumor-negative SLN biopsy recurred in the nodal basin, and 13% certainly is higher than the overall 2.4% risk of recurrence in a previously mapped nodal basin as seen in overall results from Sunbelt. You are absolutely correct that the adverse tumor-specific features seen in this group of thick melanoma patients, such as a higher incidence of lymphovascular invasion, very thick tumor, and high percentage of ulceration, place a patient at a higher risk for local-regional recurrence. These adverse factors drive a higher risk for recurrence in the previously mapped nodal basin.

Your third question relates to the ability to predict tumor-positive non-SLNs. Although we have not formally analyzed this, you are absolutely correct in that factors associated with "bad" melanoma—tumor thickness, ulceration, advanced age, and male gender—certainly will go on and almost assuredly play a role in the ability to predict which non-SLNs contain tumor cells.

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