Original Article

Is There a Benefit to Sentinel Lymph Node Biopsy in Patients With T4 Melanoma?

Csaba Gajdos, MD[1]; Kent A. Griffith, MPH, MS[2]; Sandra L. Wong, MD[1]; Timothy M. Johnson, MD[1,3];
Alfred E. Chang, MD[1]; Vincent M. Cimmino, MD[1]; Lori Lowe, MD[4]; Carol R. Bradford, MD[5];
Riley S. Rees, MD[1]; and Michael S. Sabel, MD[1]

BACKGROUND: Controversy exists as to whether patients with thick (Breslow depth >4 mm), clinically lymph node-negative melanoma require sentinel lymph node (SLN) biopsy. The authors examined the impact of SLN biopsy on prognosis and outcome in this patient population. **METHODS:** A review of the authors' institutional review board-approved melanoma database identified 293 patients with T4 melanoma who underwent surgical excision between 1998 and 2007. Patient demographics, histologic features, and outcome were recorded and analyzed. **RESULTS:** Of 227 T4 patients who had an SLN biopsy, 107 (47%) were positive. The strongest predictors of a positive SLN included angiolymphatic invasion, satellitosis, or ulceration of the primary tumor. Patients with a T4 melanoma and a negative SLN had a significantly better 5-year distant disease-free survival (DDFS) (85.3% vs 47.8%; $P < .0001$) and overall survival (OS) (80% vs 47%; $P < .0001$) compared with those with metastases to the SLN. For SLN-positive patients, only angio-lymphatic invasion was a significant predictor of DDFS, with a hazard ratio of 2.29 ($P = .007$). Ulceration was not significant when examining SLN-positive patients but the most significant factor among SLN-negative patients, with a hazard ratio of 5.78 ($P = .02$). Increasing Breslow thickness and mitotic rate were also significantly associated with poorer outcome. Patients without ulceration or SLN metastases had an extremely good prognosis, with a 5-year OS >90% and a 5-year DDFS of 95%. **CONCLUSIONS:** Clinically lymph node-negative T4 melanoma cases should be strongly considered for SLN biopsy, regardless of Breslow depth. SLN lymph node status is the most significant prognostic sign among these patients. T4 patients with a negative SLN have an excellent prognosis in the absence of ulceration and should not be considered candidates for adjuvant high-dose interferon. *Cancer* 2009;115:5752–60. © 2009 American Cancer Society.

KEY WORDS: Breslow depth, interferon, melanoma, sentinel lymph node biopsy.

The preliminary results from the Multicenter Selective Lymphadenectomy Trial-I represent the first randomized prospective clinical trial to reveal a potential survival advantage to performing sentinel lymph node (SLN) biopsy in patients with malignant melanoma. However, these results were limited to patients

with intermediate-thickness melanoma.[1] Controversy continues to surround the use of SLN biopsy in patients with both thin (<1.0 mm in Breslow thickness) and thick melanoma (≥4.0 mm in Breslow thickness). For patients with thin melanoma, the discussion has centered around identifying a subset of these patients who may still benefit from SLN biopsy.[2-8] For patients with thick melanoma, there remains controversy as to whether SLN biopsy is beneficial.

The arguments for performing SLN biopsy at the time of wide local excision in any patient with melanoma include prognostic and staging information, implications of SLN status for adjuvant therapy decisions, and the potential therapeutic impact of completion lymph node dissection in patients with a positive SLN. However, many clinicians contend that SLN biopsy may not be necessary in patients with thick melanoma, because these patients have a high rate of both regional and systemic occult disease at the time of presentation.[9] Thus, SLN biopsy may not provide significant prognostic information beyond Breslow thickness, nor would completion lymph node dissection have any significant impact on outcome should the SLN biopsy be positive. In regard to adjuvant therapy, high-dose interferon alpha-2b was approved by the US Food and Drug Administration (FDA) in 1995 for adjuvant therapy of both lymph node-positive and T4 lymph node-negative disease,[10] so these patients are already candidates for treatment based on their tumor thickness. Thus, SLN biopsy may not be necessary for adjuvant therapy decisions. To shed additional light on this controversy, we examined the impact of SLN biopsy among patients with melanoma ≥4.0 mm in Breslow thickness.

MATERIALS AND METHODS

This study was approved by the University of Michigan Institutional Review Board. Our prospectively collected melanoma database was queried for patients with primary cutaneous melanoma ≥4.0 mm in Breslow thickness (American Joint Committee on Cancer [AJCC] stage T4) who underwent definitive surgical treatment at the University of Michigan between January of 1997 and December of 2007. After excluding patients with clinical or radiographic evidence of distant disease, 293 consecutive cases were identified. Our SLN biopsy technique and method of SLN evaluation has been described previously.[3] All primary lesions and SLN biopsy slides were reviewed by 1 of 4 dermatopathologists at the University of Michigan, who generated a 14-point melanoma profile for the primary lesion. Survival information was obtained from computerized medical records and from the Tumor Registry. The local and disease-free survival (DDFS) were calculated from the time of definitive surgery. Locoregional recurrence was defined as any local recurrence, in-transit recurrence, or regional recurrence within a primary draining lymph node basin.

Statistical Methods

Patient and tumor characteristics were tested for significant association with a positive SLN using the chi-square and t test for categorical and continuous characteristics, respectively. Overall survival (OS) and DDFS were calculated for each patient beginning at the date of surgery. For OS patients known to be alive were censored on their last contact date. For DDFS, patients were followed until date of documented distant disease or death. Patients known to be alive without intervening distant failure were also censored on their last contact date. The product limit method of Kaplan and Meier was used to estimate survival probabilities, with the population stratified by the positivity of the sentinel lymph node basin. Cox proportional hazard models were used to estimate the bivariate association between survival endpoints and the available patient and tumor characteristics. Those characteristics found to be significantly associated in bivariate models were simultaneously modeled, to create a best multivariate model for both endpoints separately. The best multivariate model was defined as the model that resulted from application of a backward elimination algorithm, whereby the multivariate model was pared down iteratively, removing sequentially the characteristic with the highest Wald-type P value, until only significant characteristics remained. This model schema was also applied to those cases with negative sentinel lymph nodes and those with at least 1 positive sentinel lymph node, separately. Significance for all statistical tests was defined as a P value <5%.

RESULTS

Patient Characteristics

The patient characteristics of the study population are listed in Table 1. The mean age of patients was 58 years, with a range of 4 to 94 years, including 7 patients under the age of 16 years. The median Breslow thickness was 5.6 mm, with a range of 4 to 24 mm. Primary tumor distribution was relatively well distributed between the trunk, head and neck, and extremities. Six patients had subungual melanomas. The most common melanoma histologic pattern subtype was nodular (38%), followed by superficial spreading (20%), desmoplastic (9%), acral lentigo (6%), and lentigo maligna (5%). Ulceration was present in over half of the cases (53%), and angiolymphatic invasion was present in nearly 1 quarter (24%).

SLN Status

Of the 293 patients, 18 (6%) presented with clinically evident regional metastases. Of the remaining 275 patients, SLN biopsy was performed in 227 (83%). Of the 48 clinically lymph node-negative patients who did not have a SLN biopsy, 21 did not undergo the procedure based on the patient's elderly age and comorbidities. In 17 cases, the patient and physician opted not to perform SLN biopsy for undocumented reasons. In 8 patients, a SLN biopsy was attempted but failed. Two patients had an elective lymph node dissection (ELND). For patients who had a successful SLN biopsy, the melanoma mapped to a single basin in 161 patients, 2 basins in 65, and 3 basins in 2. The median number of harvested SLNs per basin was 2 (range, 1-10).

The SLN was positive in 107 (47%) patients. Factors associated with a positive SLN are presented in Table 2. There was no association between the year of surgery and the presence of a positive SLN. Histologic pattern subtype was significant primarily because patients with a desmoplastic melanoma had a significantly lower risk of SLN metastases (11%), an observation we have previously reported.[11,12] Location of the primary melanoma did impact the likelihood of a positive SLN, with a lower likelihood in melanoma on the head and neck, although this too may be driven by the high percentage of desmoplastic melanoma in this region. Among 57 head and neck melanomas undergoing SLN biopsy, 13 (23%) were desmo-

Table 1. Characteristics of 293 Patients With Thick Primary Melanoma

Characteristics	No. (%)
Age, y	
Median	58
Range	4-94
Sex	
Male	193 (66)
Female	100 (34)
Primary site	
Trunk	95 (33)
Head and neck	76 (26)
Upper extremity	64 (22)
Lower extremity	52 (18)
Subungual	6 (2)
Breslow thickness, mm	
Median	5.6
Mean	6.6
Range	4-24
Ulceration	
Present	155 (53)
Absent	136 (46)
Unknown	2 (1)
Angiolymphatic invasion	
Present	67 (23)
Absent	220 (75)
Equivocal	2 (1)
Unknown	4 (1)
Mitotic rate, mitoses/mm^2	
Median	4
Range	0-50
Clinical nodal involvement	
Yes	18 (6)
No	275 (94)

plastic, with a SLN positivity rate of 15% compared with 35% for nondesmoplastic melanoma. Satellitosis ($P = .009$), angiolymphatic invasion ($P = .001$), and ulceration ($P = .007$) were all significantly more likely to be associated with a positive SLN, whereas sex, mitotic rate, regression, and neurotropism were not predictive. Although Breslow thickness is strongly predictive of SLN positivity, among patients with thick (≥ 4.0 mm) melanomas, the incidence of a positive SLN did not continue to rise significantly with increasing thickness.

Sixty-eight patients received high-dose adjuvant interferon therapy (46 lymph node positive, 18 lymph node negative, and 2 with an unknown nodal status). Four recurred while receiving treatment, and therapy was discontinued secondary to severe side effects in 12. Five

Table 2. Association of Patient Characteristics With a Positive SLN Among Patients With T4 Melanoma

Characteristic	With SLN Biopsies		Chi-Square Test *P*
	Negative SLN	Positive SLN	
Sex, No. (%)			
Female	40 (39.0)	38 (38.0)	.73
Male	80 (40.4)	69 (35.8)	
Patient age at surgery, mean y (SD)	54.5 (18.0)	53.9 (16.6)	.78
Histologic subtype			
Nodular	41 (36.6)	37 (33.0)	.03
Superficial spreading	19 (32.2)	28 (47.5)	
Other	15 (39.5)	14 (36.8)	
Desmoplastic	19 (70.4)	3 (11.1)	
Acral lentigo	8 (42.1)	8 (42.1)	
Lentigo maligna	7 (43.8)	5 (31.3)	
Polypoid	3 (25.0)	7 (58.3)	
Spitz-like melanoma	5 (50.0)	5 (50.0)	
Location			
Head and neck	39 (51.3)	17 (22.4)	.02
Lower extremity	20 (38.5)	25 (48.1)	
Upper extremity	24 (34.3)	21 (30.0)	
Trunk	34 (35.8)	44 (46.3)	
Breslow depth, mean mm (SD)	6.5 (2.6)	6.4 (3.2)	.84
Mitotic rate, mean mitoses/mm^2 (SD)	6.4 (7.5)	9.3 (7.0)	.14
Regression, No. (%)			
No	102 (39.5)	98 (38.0)	.23*
Yes	13 (43.3)	7 (23.3)	
Unknown	2 (40.0)	2 (40.0)	
Satellitosis, No. (%)			
No	109 (43.4)	87 (34.7)	.01
Yes	7 (18.4)	18 (47.4)	
Unknown	1 (25.0)	2 (50.0)	
Angiolymphatic invasion, No. (%)			
No	100 (45.7)	71 (32.4)	.001
Yes	16 (22.9)	34 (48.6)	
Unknown	1 (25.0)	2 (50.0)	
Ulceration, No. (%)			
No	64 (47.1)	39 (28.7)	.007
Yes	53 (34.2)	67 (43.2)	
Unknown	0	1 (50.0)	
Neurotropism, No. (%)			
No	100 (39.5)	94 (37.2)	.45
Yes	16 (44.4)	11 (30.6)	
Unknown	1 (25.0)	2 (50.0)	

SLN indicates sentinel lymph node; SD, standard deviation.
*Unknown/missing group is excluded from the statistical test.

Table 3. Univariate Associations With Overall Survival, SLN Biopsy Population

Characteristic	*P*		
	All Cases	PSLN	NSLN
Patient's age at surgery	.0046	.0864	.0142
Histologic subtype	.4016	.9134	.4290
Location	.5000	.1347	.3742
Breslow depth	.0060	.0472	.0348
Mitotic rate	.0004	.1711	.0005
Regression	.2849	.5108	.6805
Satellitosis	.0219	.1495	.2678
Angiolymphatic invasion	.0002	.0131	.1210
Ulceration	.0022	.4344	.0062
Neurotropism	.8357	.5654	.7706
Two nodal drainage basins	.7105	.2745	.9847
PSLN	<.0001		
Adjuvant biologic therapy (interferon)	.1594	.1024	.0976

SLN indicates sentinel lymph node; PSLN, positive SLN; NSLN, negative SLN.

patients received an experimental vaccine, and 2 underwent biochemotherapy. One hundred eighty-three patients received no interferon treatment. Adjuvant therapy data was not available for 37 patients.

Survival

The median follow-up was 43 months. The locoregional recurrence rate was 22%. For patients with a negative SLN, the locoregional recurrence rate was 11%, compared with 34% with a positive SLN. Among the clinically lymph node-negative patients who did not have an SLN biopsy, the locoregional recurrence rate was 21%. Among the 17 cases where the patient and/or physician opted not to perform SLN biopsy not based on age or comorbidities, the locoregional recurrence rate was slightly higher (29%).

The majority of patients were alive without known melanoma recurrence at the time of last follow-up (174 patients, 59%). Eighty-two (28%) patients developed distant recurrence. No data regarding DDFS was available for 10 patients. Seventy-one (24%) patients died of melanoma, 33 (11%) died without disease, 11 (4%) were alive with known recurrence, and died of unknown cause 4 (1%).

The associations between prognostic factors and both OS and DDFS were studied among patients with thick melanomas who underwent successful SLN biopsy. Several factors were associated with OS on univariate analysis, noted in Table 3, including increasing patient age

Table 4. Multivariate Cox Proportional Hazards Models for Overall Survival, SLN Biopsy Population

Characteristic	Hazard Ratio	95% Confidence Interval	P
All cases			
Patient's age at surgery	1.02[*]	1.002-1.03	.0313
Breslow depth	1.10[*]	1.03-1.18	.0032
Mitotic rate	1.03[*]	1.00-1.06	.0577
Positive sentinel lymph nodes, yes vs no	2.28	1.37-3.77	.0014
Angiolymphatic invasion	2.07	1.23-3.49	.0063
Positive SLN cases only			
Breslow depth	1.10[*]	1.005-1.21	.0396
Angiolymphatic invasion	2.27	1.22-4.21	.0094
Negative SLN cases only			
Patient's age at surgery	1.04[*]	1.01-1.06	.0074
Breslow depth	1.15[*]	1.05-1.26	.0022
Mitotic rate	1.07[*]	1.03-1.10	.0003

SLN indicates sentinel lymph node.
[*] Hazard ratio for a 1-unit change in the covariate.

FIGURE 1. Kaplan-Meier overall survival analysis for sentinel lymph node-positive and -negative patients with thick (T4) primary melanoma is shown.

($P = .004$), increasing Breslow thickness ($P = .006$), increasing mitotic rate ($P = .004$), and the presence of satellitosis ($P = .02$), angiolymphatic invasion ($P > .001$), ulceration ($P = .002$), and at least 1 positive SLN ($P < .001$). On multivariate analysis, the most significant predictors of OS in patients with thick primary melanomas were increasing patient age ($P = .03$), increasing Breslow thickness ($P = .003$), the presence of at least 1 positive SLN ($P < .001$), and the presence of angiolymphatic invasion ($P = .006$) (Table 4). Figure 1 demonstrates the Kaplan-Meier OS analysis for patients with thick primary melanoma stratified by the SLN status. The 5-year OS for SLN-positive patients was 47% (95% confidence interval [CI], 35.2-57.8) compared with 80% (95% CI, 70.1-87; $P < .0001$) in SLN-negative patients.

We next stratified patients by their SLN status and examined separately which factors were most prognostic for SLN-negative patients and SLN-positive patients (Table 4). On multivariate analysis for SLN-positive patients, both increasing Breslow thickness and the presence of angiolymphatic invasion were significant. In contrast, the most significant predictors of outcome for SLN-negative patients with thick melanoma were increasing patient age, increasing Breslow thickness, and the mitotic rate.

We also examined the impact of these prognostic factors on DDFS. As shown in Table 5, DDFS was signif-

icantly associated with location of the primary melanoma ($P = .003$), increasing mitotic rate ($P = .001$), increasing Breslow thickness ($P = .004$), presence of angiolymphatic invasion ($P < .0001$), presence of ulceration ($P = .0002$), and SLN positivity ($P < .0001$). Although patient age was a significant predictor of OS, it was not significant when looking at DDFS. On multivariate analysis, both angiolymphatic invasion ($P = .005$) and ulceration ($P = .009$) maintain significance; the most significant predictor of DDFS is SLN positivity, with a hazard ratio of 3.95 for at least 1 positive SLN. Figure 2 demonstrates the Kaplan-Meier DDFS analysis for patients with thick primary melanoma stratified by SLN status. The 5-year DDFS for SLN-positive patients was 47.8% (95% CI, 35.9-58.8), compared with 85.3% in SLN-negative patients (95% CI, 75.1-91.6; $P < .0001$).

Again, we performed separate analyses for lymph node-negative and lymph node-positive disease DDFS (Table 6). For SLN-positive patients, only angiolymphatic invasion was a significant predictor of DDFS, with a hazard ratio of 2.29 ($P = .007$). Ulceration, which was significant when looking at the entire group, was not significant when examining SLN-positive patients. When analyzing only the thick, SLN-negative patients, ulceration was the most significant factor, with a hazard ratio of

Table 5. Univariate Associations With Distant Failure-Free Survival, SLN Biopsy Population

Characteristic	*P*		
	All Cases	PSLN	NSLN
Patient's age at surgery	.3062	.2174	.8907
Histologic subtype	.2508	.8091	.7871
Location	.0033	.0269	.2075
Breslow depth	.0038	.2074	.0008
Mitotic rate	.0010	.1368	.0061
Regression	.1561	.9166	.9912
Satellitosis	.1332	.2347	.9926
Angiolymphatic invasion	<.0001	.0075	.2118
Ulceration	.0002	.1169	.0063
Neurotropism	.3003	.7276	.7048
Two nodal drainage basins	.1883	.8416	.2863
PSLN	<.0001		
Adjuvant biologic therapy (interferon)	.8859	.2132	.9914

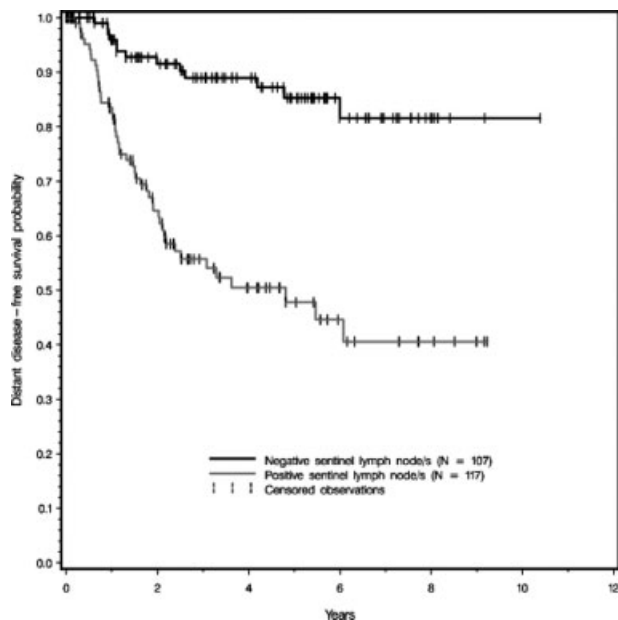SLN indicates sentinel lymph node; PSLN, positive SLN; NSLN, negative SLN.

FIGURE 2. Kaplan-Meier distant disease-free survival analysis for sentinel lymph node-positive and -negative patients with thick (T4) primary melanoma is shown.

Table 6. Multivariate Cox Proportional Hazards Model for Distant Failure-Free Survival, SLN Biopsy Population

Characteristic	Hazard Ratio	95% Confidence Interval	*P*
All cases			
Angiolymphatic invasion	2.18	1.26-3.76	.0052
Ulceration	2.17	1.21-3.87	.0092
Positive sentinel lymph nodes, yes vs no	3.95	2.11-7.41	<.0001
Positive SLN cases only			
Angiolymphatic invasion	2.29	1.25-4.20	.0075
Negative SLN cases only			
Breslow depth	1.16[*]	1.06-1.26	.0007
Mitotic rate	1.05[*]	1.004-1.09	.0307
Ulceration	5.78	1.24-26.90	.0255

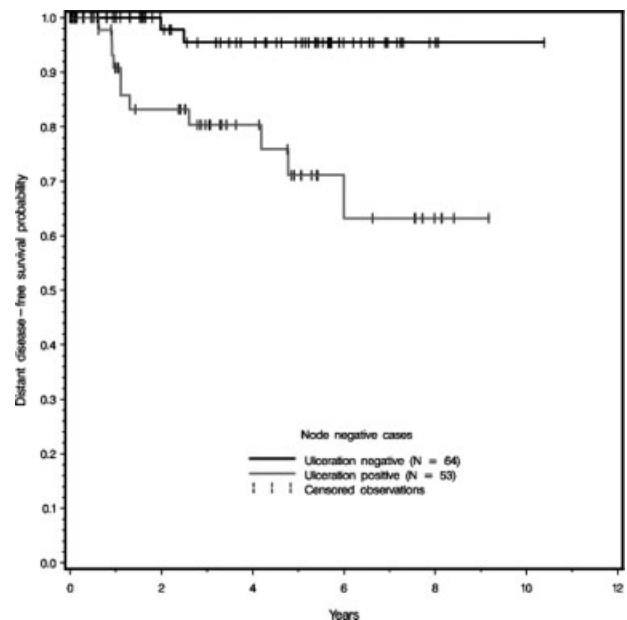[*] Hazard ratio for a 1-unit change in the covariate.

FIGURE 3. Kaplan-Meier distant disease-free survival analysis for ulcerated and nonulcerated sentinel lymph node-negative patients with thick (T4) primary melanoma is shown.

5.78 ($P = .02$). Increasing Breslow thickness and mitotic rate were also significantly associated with poorer outcome. Figure 3 shows the Kaplan-Meier DDFS for SLN-negative patients with thick melanoma stratified by the presence of ulceration, showing the significant impact of ulceration on outcome (log-rank *P* value of .0034). Figure 4 represents DDFS for SLN-positive patients with thick melanoma, demonstrating the poor survival regardless of ulceration ($P = .4$).

DISCUSSION

These results represent a large single-institution experience with thick melanoma. SLN biopsy was offered to the majority of clinically lymph node-negative patients and was positive in almost half (47%). In this population,
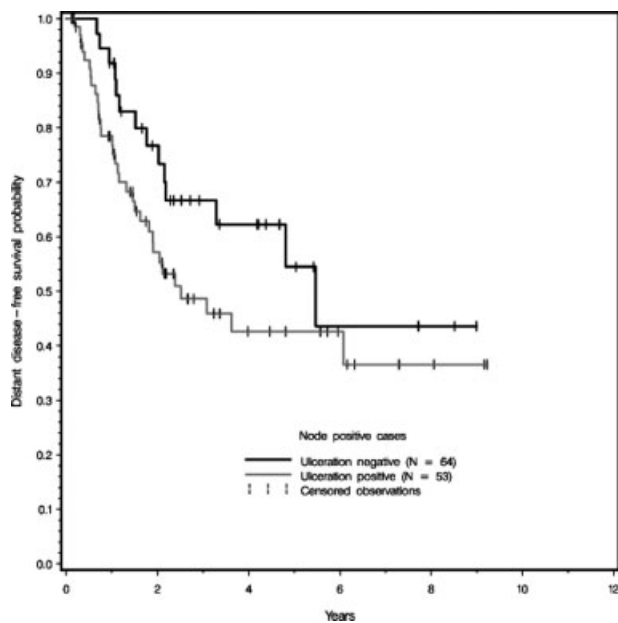
FIGURE 4. Kaplan-Meier distant disease-free survival analysis for ulcerated and nonulcerated SLN-positive patients with thick (T4) primary melanoma is shown.

angiolymphatic invasion, satellitosis, and ulceration were predictive of SLN positivity. With a median follow-up of 43 months, patients with a T4 melanoma and a negative SLN had a significantly better 5-year DDFS (85.3% vs 47.8%; $P < .0001$) and OS (80% vs 47%; $P < .0001$) compared with those with metastases to the SLN. The SLN status was the most prognostic of outcome on multivariate analysis. In addition to a positive SLN, angiolymphatic invasion and ulceration were also predictive of DDFS, whereas increasing age, Breslow thickness, and angiolymphatic invasion were associated with OS. However, when SLN-positive and SLN-negative patients were analyzed separately, a slightly different picture emerges. Patient age is only a significant predictor of OS in SLN-negative patients, and had no impact on DDFS. Among patients with thick melanomas, angiolymphatic invasion was a significant predictor of both OS and DDFS among SLN-positive patients, whereas mitotic rate was a significant predictor of both OS and DDFS among SLN-negative patients. Among SLN-negative patients with T4 melanoma, ulceration was the most significant predictor of outcome. Despite the Breslow thickness, patients without ulceration or SLN metastases had an extremely good prognosis, with a 5-year OS >90% and a 5-year DDFS of 95%.

The introduction of the SLN biopsy in 1992 by Morton et al has substantially changed the surgical management of cutaneous melanoma.[13] Although the potential benefits of SLN biopsy have been demonstrated in the interim results from the Multicenter Selective Lymphadenectomy Trial-I, this was limited to patients with melanoma of between 1.2 mm and 3.5 mm Breslow thickness.[1] Controversy remains regarding the appropriate selection of patients with thin melanoma for SLN biopsy and the need for SLN biopsy in patients with thick melanoma. Several authors have examined this latter topic with mixed results.

Before the onset of the SLN biopsy, surgeons debated but generally felt that ELND played little role in patients with clinically lymph node-negative melanoma ≥4 mm in Breslow thickness (T4N0), because these patients were at such high risk for distant disease. Whether SLN status has any prognostic or therapeutic value in this T4N0 subset is unknown. SLN status is often used to make decisions regarding adjuvant therapy, specifically the use of high-dose interferon alfa-2b, which is FDA-approved for high-risk melanoma. Although a positive SLN is the most common indication for adjuvant high-dose interferon alpha-2b, high-risk melanoma is also defined as AJCC stage IIB or C (T4a/bN0M0). Therefore, regardless of SLN status, patients with thick melanomas are already candidates for adjuvant therapy, further arguing against the need for SLN biopsy among these patients.

With regard to the prognostic information obtained from SLN biopsy, previous reports have been mixed (Table 7). Jacobs et al[14] found a difference in median survival between patients with a negative versus positive SLN, but this was not statistically significant. Cherpelis et al[15] also found a nonsignificant difference in survival. Essner et al[16] found SLN status to be a predictor of DFS but not OS. These reports raised concern about the prognostic value of SLN status in thick melanoma.

In contrast, several studies found that SLN status was 1 of the most significant predictors of outcome among patients with thick melanoma. Ferrone et al[17] described a risk stratification model for this group of patients using SLN status, age, the presence of ulceration, and primary tumor thickness to categorize patients into low-, moderate-, and high-risk groups, and recommended use of their nomogram rather than the current staging

Table 7. Studies Examining SLN Biopsy in Patients With Thick Melanoma

Author	Year	No.	F/U, mo	Mean Thickness, mm	SLN Positive	SLN− Survival	SLN+ Survival	P
Carlson[19]	2003	114	37.8 (mean)	6.3	32.5%	82% (3 y OS)	57% (3 y OS)	.006
Gershenwald[18]	2000	131	36 (median)	6.3	39%	82.4% (3 y OS)	58% (3 y OS)	.006
Jacobs[14]	2004	43	—	6.4	44%	Mean RFS, 53 mo	Mean RFS, 44 mos	NS
Essner[16]	2002	135	31 (median)	5.9	35%	60% (5 y OS)	50% (5 ys OS)	NS
Thompson & Shaw[20]	2002	172	24 (median)	5.0 (median)	30%	74% (5 y OS)	41% (5 y OS)	.0005
Ferrone[17]	2002	126	25 (mean)	6.7	30%	56% (5 y RFS)	32% (5 y RFS)	<.001
Cherpelis[15]	2001	201*	51 (mean)	5.2	37%	82% (3 y OS)	70% (3 y OS)	NS
Gutzmer[21]	2007	152	33 (median)	5.2 (median)	48.7%	67.6% (5 y OS)	53.2% (5 y OS)	.007
Gajdos	Current study	228	43 (median)	5.6 (median)	47%	80% (5 y OS)	46.9% (5 y OS)	<.0001

F/U indicates follow-up; SLN, sentinel lymph node; OS, overall survival; RFS, relapse-free survival; NS, nonsignificant.
* Melanoma >3.0 mm.

system based on the significant survival difference in a subgroup of patients with T4N0 melanoma previously thought to have a poor prognosis. The data substantiated the importance of SLN biopsy in this patient population, as did a study by Gershenwald et al[18] involving 131 patients with T4N0 primary melanomas. They reported SLN status and ulceration as being the most powerful indicator of DFS and OS and recommended routine performance of this procedure for patients with thick primary melanoma for risk stratification. Similarly, the Emory group also found ulceration and SLN status to be the most powerful predictor of DFS, with SLN status retaining its significance in predicting OS.[19]

Our study represents the largest single-institution study of SLN biopsy in patients with thick T4 melanoma and clearly demonstrates the accuracy of the prognostic information gained. The SLN status was the most significant predictor of both DDFS and OS in our population, and ulceration was highly significant among the SLN-negative patients. This information is not purely academic, but should help guide adjuvant therapy decisions. Although in this study the adjuvant use of high-dose interferon alpha-2b was not significantly associated with either an improved DDFS or OS, the retrospective nature of this analysis limits any conclusions regarding the impact of high-dose interferon alpha-2b. However, the 5-year DDFS and OS of T4 patients who are SLN negative and have no ulceration (95% and 90%, respectively), most of whom received no adjuvant therapy, suggests that there would be little benefit of adjuvant high-dose interferon alpha-2b in this population. If the SLN is negative but ulceration is present, the likelihood of distant recurrence is still significant, and high-dose interferon alpha-2b may play a role.

In conclusion, SLN biopsy should be the standard method not only of staging patients with thick melanoma but also of guiding adjuvant therapy decisions. Assuming adequate surgical therapy, patients with a negative SLN have a good prognosis despite the thick primary tumor, and in the absence of ulceration, they have an extremely low rate of distant recurrence and excellent OS. Adjuvant high-dose interferon is clearly not indicated.

Conflict of Interest Disclosures

The authors made no disclosures.

References

1. Morton DL. Interim results of the Multicenter Selective Lymphadenectomy Trial (MSLT-I) in clinical stage I melanoma. Paper presented at: 41st Annual Meeting of the American Society of Clinical Oncology; May 13-17, 2005; Orlando, Fla.

2. Paek SC, Griffith KA, Johnson TM, et al. The impact of factors beyond Breslow depth on predicting sentinel lymph node positivity in melanoma. *Cancer*. 2007;109:100-108.

3. Sondak VK, Taylor JMG, Sabel MS, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. *Ann Surg Oncol*. 2004;11:247-258.

4. Kesmodel SB, Karakousis CP, Botbyl JD, et al. Mitotic rate as a predictor of sentinel lymph node positivity in patients with thin melanomas. *Ann Surg Oncol*. 2005;12:449-458.

5. Puleo CA, Messina JL, Riker AI, et al. Sentinel node biopsy for thin melanomas: which patients should be considered? *Cancer Control*. 2005;12:230-235.

6. Bleicher RJ, Essner R, Foshag LJ, et al. Role of sentinel lymphadenectomy in thin invasive cutaneous melanomas. *J Clin Oncol*. 2003;21:1326-1331.

7. Agnese DM, Abdessalam SF, Burak WE, et al. Cost-effectiveness of sentinel lymph node biopsy in thin melanomas. *Surgery*. 2003;134:542-547.

8. Schwartz JL, Wang TS, Hamilton TA, et al. Thin primary cutaneous melanomas: associated detection patterns, lesion characteristics, and patient characteristics. *Cancer*. 2002; 95:1562-1568.

9. Perrott RE, Glass LF, Reintgen DS, Fenske NA. Reassessing the role of lymphatic mapping and sentinel lymphadenectomy in the management of cutaneous malignant melanoma. *J Am Acad Dermatol*. 2003;49:567-588.

10. Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol*. 1996;14:7-17.

11. Arora A, Lowe L, Su LD, et al. Wide excision without radiation for desmoplastic melanoma. *Cancer*. 2005;104:1462-1467.

12. Su LD, Fullen DR, Lowe L, et al. Desmoplastic and neurotropic melanoma. Analysis of 33 patients with lymphatic mapping and sentinel node biopsy. *Cancer*. 2004; 100:598-604.

13. Morton DL, Wen DR, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg*. 1992;127:392-399.

14. Jacobs IA, Chang CK, Salti G. Role of sentinel lymph node biopsy in patients with thick (>4 mm) primary melanoma. *Am Surg*. 2004;70:59-62.

15. Cherpelis BS, Haddad F, Messina J, et al. Sentinel lymph node micrometastasis and other histologic factors that predict outcome in patients with thicker melanomas. *J Am Acad Dermatol*. 2001;44:762-766.

16. Essner R, Chung MH, Bleicher R, et al. Prognostic implications of thick melanoma in the era of intraoperative lymphatic mapping and sentinel lymphadenectomy. *Ann Surg Oncol*. 2002;9:754-761.

17. Ferrone CR, Panageas KS, Busam KJ, et al. Multivariate prognostic model for patients with thick cutaneous melanoma: importance of sentinel lymph node status. *Ann Surg Oncol*. 2002;9:637-645.

18. Gershenwald JE, Mansfield PF, Lee JE, Ross MI. Role for lymphatic mapping and sentinel lymph node biopsy in patients with thick primary melanoma. *Ann Surg Oncol*. 2000;7:160-165.

19. Carlson GW, Murray DR, Hestley A, et al. Sentinel lymph node mapping for thick melanoma: should we be doing it? *Ann Surg Oncol*. 2003;10:408-415.

20. 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;9:719-722.

21. Gutzmer R, Satzger I, Thoms K-M, et al. Sentinel lymph node status is the most important prognostic factor for thick melanomas. *J Dtsch Dermatol Ges*. 2007;6:198-203.