

Original Investigation

Clinical Significance of Microscopic Melanoma Metastases in the Nonhottest Sentinel Lymph Nodes

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IMPORTANCE A practice gap exists in the surgical removal of sentinel lymph nodes, from removal of only the most radioactive (hottest) lymph node to removal of all lymph nodes with radioactivity greater than 10% of the hottest lymph node.

OBJECTIVE To determine the clinical significance of melanoma in sentinel lymph nodes that are not the hottest sentinel node and to determine the risk for disease progression based on sentinel lymph node status and primary tumor characteristics.

DESIGN, SETTING, AND PARTICIPANTS Consecutive patients with cutaneous melanoma with sentinel lymph nodes resected from January 5, 2004, to June 30, 2008, with a mean follow-up of 59 months, at Massachusetts General Hospital were included in this retrospective review. The last year of follow-up was 2012. The operative protocol led to resection of all sentinel lymph nodes with radioactivity greater than 10% of the hottest lymph node. The number of lymph nodes removed, technetium-99m counts for each sentinel lymph node, presence or absence of sentinel lymph node metastases, primary tumor characteristics, disease progression, and melanoma-specific survival were recorded.

MAIN OUTCOMES AND MEASURES Microscopic melanoma metastases in the hottest and nonhottest sentinel lymph nodes and factors that correlate with disease progression and mortality.

RESULTS A total of 1575 sentinel lymph nodes were analyzed in 475 patients. Ninety-one patients (19%) had positive sentinel lymph nodes. Of these, 72 (79%) had metastases in the hottest sentinel lymph node. Of 19 cases with tumor present, but not in the hottest sentinel lymph node, counts ranged from 26% to 97% of the hottest node. Progression occurred in 43% of patients with sentinel node metastasis, regardless of whether the hottest lymph node was positive. In patients with negative sentinel lymph nodes, 11% developed metastases beyond the sentinel lymph node basin and 3.4% recurred in the basin. Mitogenicity of the primary tumor was associated with mortality (odds ratio, 2.435; 95% CI, 1.351-4.391; $P < .001$). Removing only the hottest sentinel lymph node would have led to false-negative results in 19 of 475 (4%) of all patients and 19 of 91 patients (21%) with positive sentinel lymph nodes. The 8-year survival in patients with at least 1 positive sentinel lymph node was less than 55%. The presence of more than 1 mitosis per square millimeter in the primary cutaneous melanoma was associated with decreased survival.

CONCLUSIONS AND RELEVANCE Microscopic melanoma metastases was associated with disease progression and mortality, whether present in the hottest sentinel lymph node or not. These observations emphasize the importance of removing the less hot nodes, addressing a practice gap in the surgical approach to patients with melanoma.

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Staging cutaneous melanoma with sentinel lymph node (SLN) mapping is the most important surgical advance in melanoma management in the past quarter century.¹ Unlike carcinoma of the breast, isolated melanoma cells in the SLNs have prognostic significance.^{2,3} Patients with negative SLNs have an estimated 3-year disease-free survival of 90% compared with 60% for patients with positive SLNs.⁴ This procedure is offered to patients with clinically localized American Joint Committee on Cancer stage I and II cutaneous melanoma with primary tumors more than 1 mm thick, tumors less than 1 mm with mitotic activity and/or ulceration, or other risk factors such as lymphovascular invasion.⁵⁻⁷ When metastatic melanoma is identified in a SLN, including even a solitary tumor cell, patients are upstaged to American Joint Committee on Cancer stage III.⁸ The identification of melanoma in a SLN has significant clinical effect. More than 90% of patients with positive SLNs undergo completion lymphadenectomy (CLND) and most also receive adjuvant therapy^{9,10} or targeted therapy.¹¹ On the other hand, patients with negative SLNs undergo no further surgery or adjuvant therapy.

At Massachusetts General Hospital, SLN biopsy is performed using preoperative lymphoscintigraphy, with technetium-99m-labeled sulfur colloid and sometimes isosulfan blue dye injected at the site of the primary cutaneous melanoma.⁹ A scintillation camera documents static and dynamic images demonstrating pathways of lymphatic drainage to the sentinel nodes.¹² The blue dye enables visualization of the sentinel node (s), while a handheld gamma probe identifies areas of tracer uptake in situ.¹³ After removal of the first SLN, the ex vivo radioactive counts accumulated during a 10-second interval are recorded. The remaining lymph nodes are excised if they are estimated to have more than 10% of the counts of the hottest lymph node in situ and then, based on ex vivo counts, the SLNs are determined to be SLNs (>10%) or non-SLNs (\leq 10% counts of the hottest SLN as measured ex vivo). Laboratory protocols for histological SLN analysis vary widely.¹⁴⁻¹⁷ In this study, a 9-slide protocol that included 3 levels, 3 hematoxylin and eosin stains, and 6 immunohistochemical stains was used.^{18,19} The clinical significance of microscopic melanoma metastases in patients who did not have tumor in the hottest SLNs was examined in relationship to disease progression and primary tumor characteristics. The number and location of mapped basins in relationship to the rate of node positivity and regional recurrence were also evaluated.

Methods

A search of the Massachusetts General Hospital Pathology Service electronic files identified 475 patients with cutaneous melanoma with SLNs removed from January 5, 2004, to June 30, 2008. Clinical and pathological data retrieved from the medical record included date of birth, sex, diagnosis date, primary tumor prognostic factors, location of SLN basins, number of SLNs, and radioactive counts recorded for each SLN. Follow-up information included the status of lymph nodes from CLND, melanoma recurrence, distant metastasis, and status at the last clinical encounter or date of melanoma-specific

death. This study was approved by the Partners HealthCare institutional review board (2008P001469). Patient consent was waived because this was a retrospective study involving discarded tissue and medical records.

In histopathological analysis, SLNs were bivalved or sectioned longitudinally, submitted entirely, and processed following a protocol that yielded 9 tissue sections obtained at 3 levels 80 μ m apart.¹⁹ The 3 slides in each set of serial sections were stained for Mart-1 (mouse melanoma antigen recognized by T cells; clone: M2-7C10, Signet Laboratories), hematoxylin and eosin, and S-100 (Dako).

Tumor burden was measured in 68 cases in which at least 1 slide was available for re-review (missing cases included those that had been sent to outside institutions and not returned), using methods described previously.¹⁹ Two of the authors (L.M.D. and A.Z.C.L.) assessed the central expansion diameter of the metastasis and also quantified total tumor volume as rare individual cells (1-3 cells), individual cells or small cluster (4-10 cells), individual cells or aggregates (11-30 cells), small nodule (31 cells- \leq 2 mm), or large nodule (>2 mm). This reflected the total number of tumor cells that appeared in all stained sections, whereas the size categories, such as greater than 2 mm, and the central expansion diameter reflected the size of the largest single deposit.

Statistical analysis was performed using Fisher exact tests and Mann-Whitney *U* rank sum tests to compare the differences between patients with positive and negative SLNs. Fisher exact tests were used to compare pathologic features of the positive SLNs and outcome. Survival curves were constructed using Kaplan-Meier estimates and the log-rank test was used in the comparison of survival curves between groups. Disease-free survival was defined as the time from SLN mapping date to the first evidence of recurrence or metastases beyond the SLN basin. Patients with no evidence of such metastases were censored at their last follow-up or death. Overall melanoma-specific survival was defined as the time from SLN mapping to the date of melanoma-specific death. Covariates were evaluated using a multivariate Cox proportional hazards model with an outcome of progression-free survival using the covariates of SLN status, primary tumor mitoses per square millimeter, ulceration, neurotropism, microscopic satellites, regression, vascular invasion, and Clark level.

Results

The clinical and pathological features of 475 patients are shown in **Table 1**. Microscopic SLN metastases were identified in 91 patients (19%) and benign capsular nevi were observed in 38 (8%) (**Table 2**). There were no significant differences in sex or age between patients without melanoma in the SLNs and patients with SLNs positive for microscopic melanoma metastasis. Primary tumors located in special sites ($n = 15$, including 11 acral, 3 vulvar, and 1 anal melanoma) were more frequent in the SLN-positive group ($P = .01$). On the other hand, lentigo maligna melanomas were more frequent in the SLN-negative group ($P < .02$). The mean primary tumor thickness was greater for patients with

Table 1. Clinical Features and Pathologic Characteristics of the Primary Melanoma According to SLN Status

Characteristic	SLN (N = 475)		Frequency of Positive SLNs, %	P Value
	Negative (n = 384)	Positive (n = 91)		
Sex, No. (%)				
Male	200 (52)	56 (61)	22	.13
Female	184 (48)	35 (38)	16	.13
Age at diagnosis, y				
Median (range)	53 (10-92)	52 (7-84)		.56
Mean	52	49		.08
Site of primary tumor, No. (%)				
Scalp	24 (6)	5 (5)	17	>.99
Face	43 (11)	6 (7)	13	.25
Neck	14 (4)	1 (1)	7	.32
Trunk	152 (40)	38 (42)	20	.72
Upper extremity	62 (16)	10 (11)	14	.26
Lower extremity	81 (21)	24 (26)	23	.33
Special site ^a	8 (2)	7 (8)	47	.01
Type, No. (%)				
Superficial spreading	166 (43)	37 (41)	18	.72
Nodular	101 (26)	29 (32)	22	.30
Lentigo maligna	22 (6)	0 (0)	0	<.02
Acral/mucosal lentiginous	6 (2)	2 (2)	25	.65
Desmoplastic/nevrotropic	10 (3)	2 (2)	17	>.99
Unknown/unclassified	46 (12)	17 (19)	27	.12
Nevoid	12 (3)	0 (0)	0	.13
Spitzoid	12 (3)	2 (2)	14	>.99
MELTUMP	9 (2)	2 (2)	18	>.99
Thickness, mean (range), mm ^b	2.19 (0.45-6.0)	3.40 (1-14)		<.001
Ulceration, No./Total No. (%)				
Present	68/340 (20)	21/81 (26)	24	.29
Absent	272/340 (80)	60/81 (74)	18	
Mitoses per mm ² , median (range)				
0, No./Total No. (%)	53/323 (16)	7/80 (9)	12	.16
1, No./Total No. (%)	70/323 (22)	7/80 (9)	9	<.01
>1, No./Total No. (%)	200/323 (62)	66/80 (82)	25	<.001
Tumor-infiltrating lymphocytes, No./Total No. (%)				
Absent	110/317 (35)	34/78 (44)	24	.13
Present, nonbrisk	190/317 (60)	41/78 (53)	18	.48
Present, brisk	17/317 (5)	3/78 (4)	15	.78
Neural invasion, No./Total No. (%)				
Absent	276/301 (92)	62/73 (85)	18	.12
Present	25/301 (8)	11/73 (15)	31	
Vascular invasion, No./Total No. (%)				
Absent	292/305 (96)	67/75 (89)	19	.04
Present	13/305 (4)	8/75 (11)	38	
Regression, No./Total No. (%)				
Absent	291/302 (96)	70/73 (96)	27	.74
Present	11/302 (4)	3/73 (4)	21	
Microscopic satellites, No./Total No. (%)				
Absent	254/261 (97)	58/62 (93)	19	.23
Present	7/261 (3)	4/62 (6)	36	

Abbreviations:
MELTUMP, melanocytic tumor of undetermined malignant potential; SLN, sentinel lymph node.

^a Vulvar, acral, and anal melanomas. The negative-SLN group included 3 vulvar and 5 acral melanomas, while the positive-SLN group included 1 anal and 6 acral melanomas.

^b The mean primary tumor thickness for the entire cohort was 2.4 mm; median, 1.5 mm.

positive SLNs ($P < .01$), and mitotic activity and vascular invasion were more commonly observed in this group ($P < .001$ and $P < .05$, respectively).

In a multivariate Cox proportional hazards model with an outcome of progression-free survival, using the covariates of SLN status, mitoses per square millimeter, ulcer-

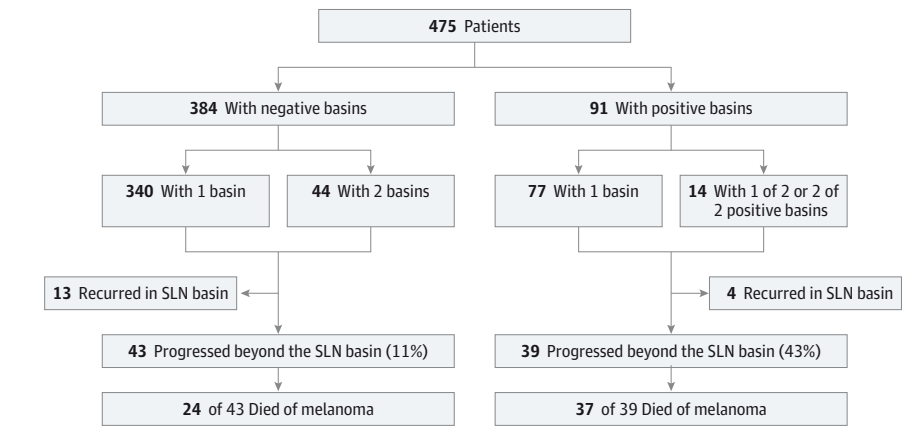
Table 2. SLN Characteristics

Characteristic	SLN (N = 475)		
	Negative (n = 384)	Hottest Positive (n = 72, 79%)	Positive But Not Hottest (n = 19, 21%)
Total No. of SLNs harvested	1238	234	93
SLNs harvested per patient, median (range)	3 (1-20)	3 (1-20)	5 (3-8)
Mean	3.2	3.25	4.89
Capsular nevus present, No. (%)	37 (10)	1 (13)	0 (0)
Average No. of SLNs harvested	3.22	3.3 ^a	4.9
No. of positive SLNs, mean (range)	NA	1.4 (1-6)	1.2 (1-3)
No. of SLNs harvested			
1	83	21	NA
2	97	12	1
3	79	18	5
4	46	9	2
5	39	4	4
≥6	40	9	6
Size of melanoma metastasis in SLNs, %			
1-3 Cells	NA	9	0
4-10 Cells	NA	13	10
11-30 Cells	NA	28	40
>30 Cells-2 mm	NA	33	40
>2 mm	NA	20	10
Central expansion diameter, median (mean)	NA	0.75 (1.6)	0.65 (0.5)

Abbreviations: NA, not applicable; SLN, sentinel lymph node.

^a Mean number of SLNs removed is 4.15 in cases where more than 1 node was removed and the hottest SLN was positive.

Figure 1. Flow Diagram for Sentinel Lymph Node (SLN) Basin Mapping in 475 Patients, Microscopic Lymph Node Status, and Patient Outcomes



The number of basins did not correlate with SLN positivity or negativity.

ation, neurotropism, microsatellites, regression, vascular invasion, and Clark level, significant association with disease progression was observed for SLN status ($P < .001$), mitoses per square millimeter ($P < .001$), vascular invasion ($P = .02$), and Clark level ($P = .02$). Mitoses and tumor thickness were entered into the model as continuous variables; the others were entered as class variables. Ulceration, tumor-infiltrating lymphocytes, neural invasion, regression, and microscopic satellites were not significantly different between the 2 groups. Mean and median follow-up from time of SLN mapping to last encounter or date of death were 60 and 64 months, respectively.

While SLNs are usually mapped to a single lymph node basin, occasionally lymphoscintigraphy showed more than 1 basin draining the cutaneous tumor. A single SLN basin was mapped in 417 patients and 2 basins in 58 patients (Figure 1). Of 384 patients with negative SLNs, 340 had 1 negative basin and 44 patients had 2 negative basins. Of the 91 patients with positive SLNs, 77 had SLNs removed from 1 basin and 14 patients had SLNs removed from 2 basins (8 patients with positive SLNs in 1 of 2 basins and 6 with positive SLNs in both mapped basins).

A total of 533 lymph node basins were mapped including 267 axillary, 138 groin (superficial inguinal and external iliac/

pelvic), 113 neck (supraclavicular/jugular/parotid/periauricular/submental), 10 occipital, 2 popliteal, and 3 epitrochlear (Table 3). Metastases were identified in 18% of axillary basins (47 of 267), 25% of groin basins (34 of 138), and 11% of neck basins (12 of 113); there were no statistically significant differences in the rate of node positivity between sites of mapped basins.

More than 3 SLNs were removed on average. In the 91 patients with positive SLNs, 327 nodes were removed, and in the 384 patients with negative SLNs, 1238 nodes were removed (mean, 3.6 and 3.2 SLNs, respectively). On average, 4 or more SLNs were removed in patients without the hottest positive SLNs (mean, 4.9; 19 patients) compared with fewer than 4 in those with the hottest positive SLNs (mean, 3.3; 72 patients) ($P = .02$; Table 2). There was no correlation between the number of SLNs taken and disease progression or survival. In patients with positive SLNs, most commonly only 1 lymph node contained tumor (64 of 91 patients; range, 1-6; median, 1). A survival advantage was not associated with the number of positive SLNs, although our cohort contained only 27 patients with more than 1 positive SLN.

The hottest SLNs contained metastatic melanoma in 72 of 91 cases (79%). Of the 19 patients without tumor in the hottest lymph node, 13 (14%) had melanoma in the second hottest lymph node. Four patients (4%) had no tumor detected in the first or second hottest SLNs but had metastases in the third hottest node. Two patients (2%) had no tumor identified until the fourth hottest lymph node. The hottest lymph node with melanoma metastasis ranged from 26% to 100% of the hottest lymph node removed. There was no significant difference in tumor burden between the hottest and nonhottest positive SLNs (Table 2). While the presence of a SLN metastasis was associated with a reduced recurrence-free and overall melanoma-specific survival ($P < .001$), prognosis was no different if the metastasis was present in the hottest node or not (Figure 2).

Of the 91 patients with positive SLNs, 84 (92%) underwent CLND. Six of 84 patients (7%) had additional positive lymph nodes in the CLND. Two of these patients had tumors in the hottest SLNs; 4 did not but they had tumors in other SLNs. All 6 patients with positive CLND had a melanoma-associated death. Of 78 patients with negative CLND, 29 had a melanoma-specific death. Two of seven patients who did not have CLND died of melanoma-associated causes. Overall, of 91 patients with positive SLNs, 39 (43%) progressed and 37 of these died of melanoma (ie, 41% disease-specific death rate in patients with positive SLNs).

Of the 384 patients with negative SLNs, 43 (11%) progressed to develop metastases; of these, 24 died (mean follow-up, 61 months). Recurrence in the mapped basin occurred in 13 (3.4%). Recurrences occurred a mean of 36 months after the SLN procedure (range, 8-69 months). When patients with negative SLNs were evaluated, tumor thickness did not show an association with tumor progression or survival. On the other hand, mitogenicity showed a powerful correlation with disease progression and survival ($P = .002$) (Figure 2).

In this cohort, 80 patients had stage IB tumors. No SLN metastases were observed in the 59 patients with primary tumor

Table 3. Lymph Node Basins, Status, and Recurrence in 475 Patients With Cutaneous Melanoma^a

Lymph Node Basin Site	Total No. of Basins With Sentinel Lymph Nodes Removed	No. (%)	
		Basins With Melanoma	Basins With Melanoma Recurrence
Axillary	267	47 (18)	6 (2.2)
Groin ^b	138	34 (25)	1 (0.7)
Neck ^c	113	12 (11)	6 (5.3)
Occipital	10	3 (30)	0
Epitrochlear	3	1 (30)	0
Popliteal	2	0	0

^a There were no statistically significant differences in the rate of node positivity between sites of mapped basins.

^b Groin includes superficial inguinal and external iliac/pelvic basins.

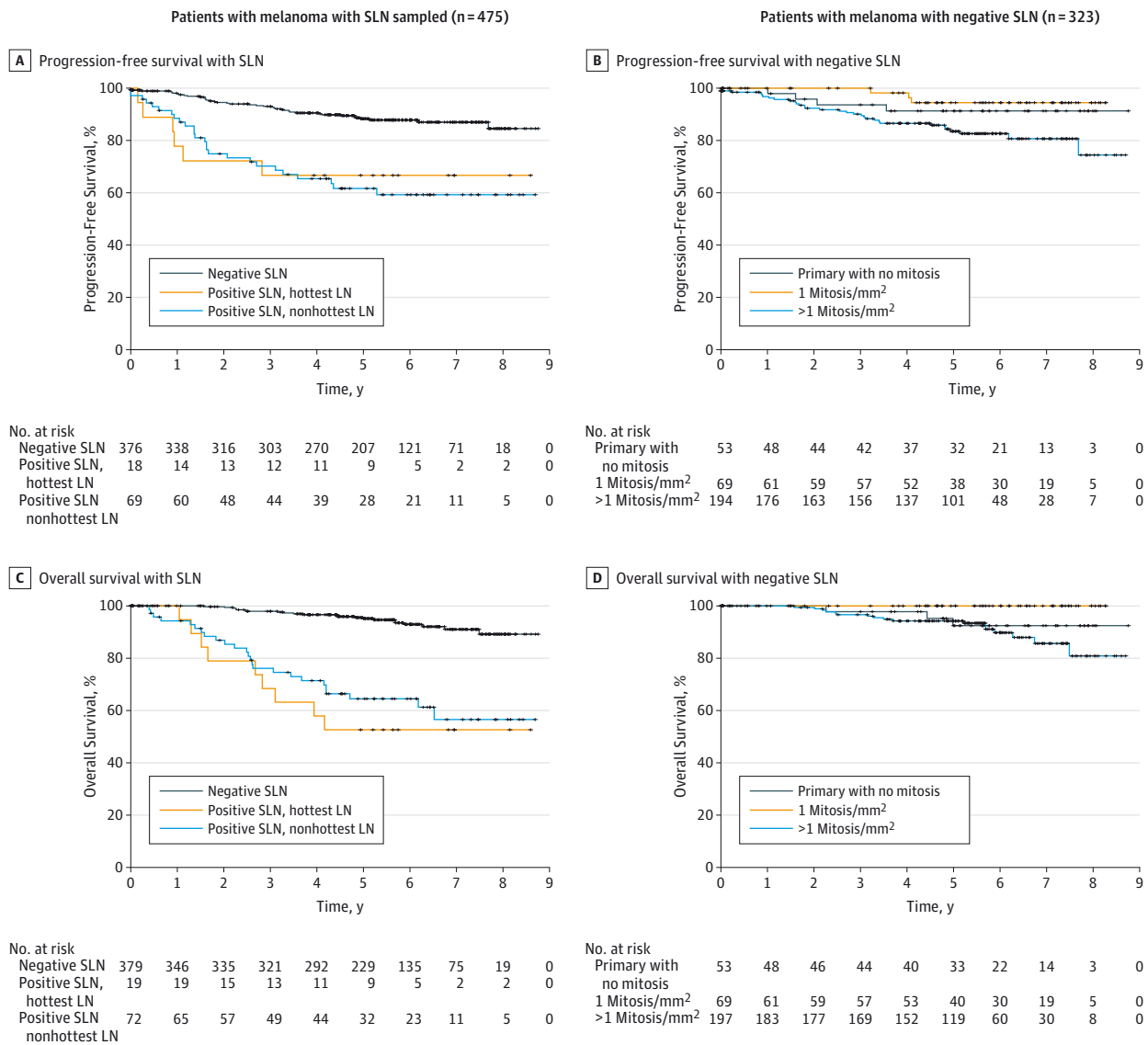
^c Neck includes supraclavicular, jugular, parotid, periauricular, and submental basins.

less than 1 mm (mean, 0.79 mm; range, 0.45-0.98 mm). The mean number of SLNs taken in patients with tumors less than 1 mm was 2.8. Four patients with tumor thickness less than 1 mm progressed: 2 developed metastases beyond the SLNs (0.7 mm and 3 mitoses per square millimeter; and 0.82 mm and 4 mitoses per square millimeter) and 2 patients died of metastatic melanoma (0.9 mm and 10 mitoses per square millimeter; and 0.96 mm and 0 mitoses per square millimeter). Sentinel lymph node mapping was performed in 21 patients with 1-mm-thick primary tumors and metastatic melanoma was detected in 4 (19%). Of these 4 patients, 1 died of melanoma, 1 died of other causes, and 2 have remained without recurrence or metastasis at 78 and 74 months after SLN mapping. Additionally, relapse was observed in 2 patients with 1-mm-thick primary tumors and negative SLNs; 1 developed local recurrence and 1 died of metastatic melanoma (one had a mitogenic primary tumor and the other did not). Sentinel lymph node mapping in patients with very thin melanoma remains controversial; nevertheless, in our cohort, 9% of patients with primary tumors 1 mm or less progressed to develop metastases beyond the SLN basin.

Discussion

Lymphatic mapping and SLN biopsy, first described in 1992, is a well-established technique for identifying micrometastatic disease in regional nodal basins, with relatively minimal morbidity.²⁰⁻²² The tumor status of regional lymph nodes is known to be the most important prognostic factor for patients with early-stage melanoma as evidenced by the 90% vs 60% 3-year disease-free survival of patients without and with positive SLNs, respectively.^{4,23-25} The 2009 American Joint Committee on Cancer Melanoma Staging Committee recommended SLN biopsy as a staging procedure in patients with primary melanomas thicker than 1 mm or with tumors 1 mm or less in thickness but with ulceration or 1 mitosis per square millimeter and clinically or radiographically uninvolved regional lymph nodes.⁸ The prognostic significance of SLN mapping for thin melanomas was reaffirmed by the development

Figure 2. Survival Analyses in Patients With Cutaneous Melanoma



Time from sentinel lymph node (SLN) removal to metastasis beyond the SLN basin (progression, A and B) and death from melanoma-associated cause (overall survival, C and D). Sentinel lymph node status and survival in 475 patients with melanoma (A and C). Patients with microscopic melanoma in the hottest SLNs (orange, n = 72), microscopic melanoma not in the hottest SLN

(blue, n = 19), and without SLN metastases (black, n = 384) ($P < .001$). Primary tumor mitogenicity and survival in 323 patients with melanoma and negative SLNs (B and D). Patients with primary tumor with more than 1 mitosis per square millimeter (blue, n = 200), 1 mitosis per square millimeter (orange, n = 73), and no mitosis (black, n = 50) ($P < .001$).

of a joint clinical practice guideline after expert panel review by the American Society of Clinical Oncology and the Society of Surgical Oncology.²⁶

In this study of 475 patients, 19% had microscopic metastases in SLNs and 8% had capsular nodal nevi.^{18,27} Primary tumor site and sex did not influence the likelihood of SLN metastases.²⁸ Patients with primary tumors in special sites were more frequent in the positive-SLN group ($P = .01$); however, these tumors were thicker (median, 3.0 mm) than the tumors from other sites (median, 1.5 mm), perhaps explaining the increased rate of metastasis. Sentinel lymph node metastasis correlated with tumor thickness, mitoses per square millimeter,

and vascular invasion. Mitotic rate (odds ratio, 2.435; 95% CI, 1.351-4.391; $P < .001$) and vascular invasion ($P = .02$) also showed association with progression beyond the SLN in multivariate analysis. While tumor type is usually not prognostically significant when tumor thickness is accounted for, no patient with lentigo maligna melanoma had a positive SLN. This could not be explained by tumor thickness alone given that the patients with lentigo maligna melanoma did not have significantly thinner tumors than patients with other types of melanoma (median, 1.4 vs 1.6 mm).

Similar to prior reports, the most frequently mapped SLN basins were the axilla, groin, and neck, in that order.²⁹ The rate

of SLN positivity (11%-25%) and rate of basin recurrence (1%-5%) were not significantly different between mapped sites. Some basins are more difficult to map accurately, particularly for head and neck primaries; multidirectional drainage, with smaller and more numerous lymph nodes, may serve as confounding factors.³⁰ While some studies reported higher rates of recurrence after negative SLN mapping in these basins, others did not.^{22,31}

Overall, 1565 SLNs were removed from 533 lymph node basins in 475 patients. The mean number of SLNs removed per basin was 3 and did not differ between patients with positive and negative SLNs. The range of 1 to 3 nodes is similar to that reported in other cohorts.^{27,32} In 72% of patients with positive SLNs, the hottest SLNs contained metastatic melanoma. In 4% of patients, or 28% with positive SLNs, metastases were present but not found in the hottest SLNs. The radioactive counts of the SLNs with metastatic melanoma ranged from 26% to 100% of the hottest SLNs. The progression-free survival and overall survival were no different for patients without the hottest positive SLNs and those with the hottest positive SLNs. This finding underscores the importance of removing more than 1 SLN.

While the SLN has been described as the first encountered node in a lymphatic chain that drains a specific primary skin site, the intricacies of lymphatic organization are occasionally complicated.^{22,33} Confirmation of SLN status was historically based on the presence of blue dye²¹ but now also relies on nodal radioactivity. While the node that is the most radioactive, or hottest, may be considered the sentinel one, current practice considers SLNs to be those with more than 10% of the counts of the hottest node. Overall, some would champion the concept that SLN status is best determined by the concomitant presence of blue dye and high radioactivity.^{21,34} We demonstrate that the current practice of removing nodes with more than 10% radioactivity of the hottest SLNs is not too exhaustive. Our study demonstrates that, at times, it is not even the second or third, but sometimes it is the fourth, hottest node that contains metastasis. Furthermore, the distribution of tumor size in these nonhottest nodes was comparable with the distribution in the hottest, demonstrating that these nodes were equally significant in tumor burden.

Patients with positive SLNs had a high rate of tumor progression (43%); 41% died of metastatic melanoma. Completion lymphadenectomy was performed in 92% of patients with positive SLNs; of these, 7% had additional metastases identified with this procedure. At Massachusetts General Hospital,

CLND is offered to all patients with positive SLNs regardless of SLN tumor size because CLND provides staging information and is associated with improved regional node control.^{27,35} In our study, all patients with metastases in the CLND died of metastatic melanoma, in contrast to one-third of the patients with negative CLND, findings supporting the prognostic significance of positive non-SLNs.³⁶ No patients with negative SLNs underwent CLND.

Patients with negative SLNs have longer progression-free survival and overall survival than those with positive SLNs. Nevertheless, 4% of node-negative patients recurred in the SLN basin and 11% progressed to develop metastases beyond the SLN basin. This is comparable with the 4% basin recurrence rate and 9% overall recurrence rate in tumor-negative SLN basins previously reported.^{31,37} The mean follow-up for patients with negative SLNs in this cohort was 5 years; 6% had died of metastatic melanoma. Notably, negative-SLN patients who progressed were more likely to have mitogenic primary tumors. These findings may provide support for increased surveillance of these patients with mitogenic primary melanoma and negative SLNs.

Sentinel lymph node mapping may be offered to patients with primary melanoma 1 mm or less if they have additional risk factors including mitoses, ulceration, and lymphovascular invasion. In this cohort, 9% of patients with primary tumors 1 mm or less progressed with melanoma metastases beyond the SLN basin. In patients with primary melanoma 1 mm or less, the melanoma-specific death rate was 25% (1 of 4) for those with positive SLNs and 4% (3 of 76) for those with negative SLNs. This observation is congruent with previous reports that SLN status has prognostic value for patients with high-risk thin melanomas.^{38,39}

Conclusions

Overall, SLN serves as a robust staging parameter for patients with localized cutaneous melanoma. Removing more than 1 SLN provides increased detection of clinically significant metastases. More than 4% of patients had metastases present in SLNs that was not the most radioactive; disease progression was identical to patients with tumors in the hottest SLNs. Closing the practice gap and removing more than just the hottest SLN allows the identification of patients at risk for developing melanoma progression that may benefit from additional surgery and adjuvant therapy.

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Luo, Tsao, Duncan.

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