Original Article

Sentinel Lymph Node Biopsy Is Accurate and Prognostic in Head and Neck Melanoma

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BACKGROUND: Sentinel lymph node biopsy (SLNB) has emerged as a widely used staging procedure for cutaneous melanoma. However, debate remains around the accuracy and prognostic implications of SLNB for cutaneous melanoma arising in the head and neck, as previous reports have demonstrated inferior results to those in nonhead and neck regions. Through the largest single-institution series of head and neck melanoma patients, the authors set out to demonstrate that SLNB accuracy and prognostic value in the head and neck region are comparable to other sites. **METHODS:** A prospectively collected database was queried for cutaneous head and neck melanoma patients who underwent SLNB at the University of Michigan between 1997 and 2007. Primary endpoints included SLNB result, time to recurrence, site of recurrence, and date and cause of death. Multivariate models were constructed for analyses. **RESULTS:** Three hundred fifty-three patients were identified. A sentinel lymph node was identified in 352 of 353 patients (99.7%). Sixty-nine of the 353 (19.6%) patients had a positive SLNB. Seventeen of 68 patients (25%) undergoing completion lymphadenectomy after a positive SLNB result had at least 1 additional positive nonsentinel lymph node. Patients with local control and a negative SLNB failed regionally in 4.2% of cases. Multivariate analysis revealed positive SLNB status to be the most prognostic clinicopathologic predictor of poor outcome; hazard ratio was 4.23 for SLNB status and recurrence-free survival ($P < .0001$) and 3.33 for overall survival ($P < .0001$). **CONCLUSIONS:** SLNB is accurate and its results are of prognostic importance for head and neck melanoma patients. ***Cancer* 2012;118:1040-7.** © *2011 American Cancer Society.*

KEYWORDS: cutaneous, melanoma, head and neck, sentinel lymph node biopsy, accuracy, prognosis.

INTRODUCTION

First described by Morton et al in 1992, sentinel lymph node biopsy (SLNB) has become a common staging procedure for cutaneous melanoma.[1,2] Accurately predicting the status of the regional lymph node basin, a positive SLNB identifies a subset of patients who may benefit from completion lymphadenectomy and are candidates for adjuvant therapy and/or clinical trials.

Proximity of cranial nerves and ambiguous lymphatic drainage pose unique challenges to performing the SLNB procedure in the head and neck region.[3-5] Two large series (n = 3897) have demonstrated higher recurrence rates in previously mapped negative nodal basins in the head and neck region relative to other anatomic regions, suggesting inferior SLNB accuracy.[6,7] Furthermore, consistent correlation between SLNB status and overall survival (OS) is lacking in head and neck melanoma series.[8-10] Hence, despite the general adoption of SLNB for extremity and truncal cutaneous melanoma, there remains debate around SLNB accuracy and prognostic value in the head and neck region.

Through the largest single-institution series of head and neck melanoma patients, we set out to demonstrate that SLNB accuracy and prognostic value in the head and neck region are comparable to other sites.

MATERIALS AND METHODS

Patients

This study was approved by the University of Michigan Institutional Review Board. A prospectively collected melanoma database was queried for cutaneous head and neck melanoma patients who underwent SLNB at the University of

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Michigan between 1997 and 2007. All patients were initially evaluated at the University of Michigan Multidisciplinary Melanoma Clinic. All primary melanomas and sentinel lymph node (SLN) histology slides were reviewed by a dermatopathologist(s) in the melanoma program, with a standard 14-point melanoma profile generated for the primary lesion. Patients with melanoma >1.0 mm Breslow depth or between 0.75 and 0.99 mm Breslow depth with other adverse pathologic or clinical findings were counseled for consideration of SLNB as previously described.[11] Patients with a positive SLNB received recommendation for completion lymphadenectomy followed by referral to medical oncology for consideration of adjuvant therapy, including high-dose interferon alfa-2b or clinical trials. Patients with a negative SLNB were followed clinically for recurrence.

SLNB

Patients underwent preoperative lymphoscintigraphy using techniques previously described 2 to 4 hours before surgery.[12,13] All SLNB procedures were performed by surgeons specializing exclusively in the head and neck region (C.R.B. and R.S.R.). After resection of the primary melanoma site with margins dictated by the National Comprehensive Cancer Network guidelines, nodal basin radioactivity was measured with handheld gamma probes (Navigator GPS; RMD Instruments, Waterton, Mass).[14] One- to 3-cm incisions were made directly over sites of highest radioactivity and parallel to relaxed skin tension lines. In the majority of cases, facial nerve monitoring or handheld nerve monitors were used to minimize neural injury risk during dissection. In addition to radioactivity level, 1 author (C.R.B.) also routinely used intradermal blue dye (isosulfan or methylene blue) to locate the SLN. Another author (R.S.R.) used intradermal blue dye in cases where *shine through* limited lymph node identification, particularly in the parotid basin. Shine through occurs when gamma emission from the injected primary site artificially elevates the measured radioactivity of nearby nodal basins, rendering those gamma counts inaccurate. Lymph node removal continued until the operative bed emitted <10% of the ex vivo count of the highest emitting lymph node and until any blue dyed or suspicious appearing nodes were removed. All lymph nodes were serially sectioned and evaluated histologically with hematoxylin and eosin stained sections and immunostains (S-100, Melan-A, and/or HMB-45) as previously described.[15]

Statistical Analysis

Primary endpoints included SLNB result, time to recurrence, site of recurrence, and date and cause of death. Secondary endpoints included failure to identify a SLN at surgery and cranial nerve injuries. A false-negative SLNB was defined as a negative SLNB in a patient who developed regional recurrence during follow-up without previously or simultaneously diagnosed local or in-transit recurrence. Data was collected by database query, chart review, telephone interviews, and the Social Security Death Index.

All time to event endpoints were calculated from the date of SLNB. OS was calculated from SLNB date until death or last follow-up. Recurrence-free survival (RFS) was calculated from SLNB date until recurrence, death, or last follow-up. Recurrence was defined as local (in or adjacent to the primary scar), satellite or in-transit (within or >2 cm of the primary melanoma and the first echelon nodal basin, respectively), regional (regional nodal basin), or distant (visceral or distant nodal basin). For all endpoints, patients not experiencing the events were censored at their date of last follow-up. The term *median follow-up* was defined as the median of follow-up time for all patients calculated from the date of SLNB until death or last known follow-up date.

The product-limit method of Kaplan and Meier was used to estimate the survival probabilities. Cox proportional hazards regression was used to assess the possible association between patient, tumor, and SLNB characteristics and the time to event endpoints. Because death was a component for endpoints, age of the patient at biopsy was expected to be significantly associated. Hence, the associations of the other characteristics were adjusted for the patient's age. Best multivariate models were constructed by first modeling all covariates simultaneously, and then iteratively removing only the most nonsignificantly associated covariate, re-estimating the mode, and repeating, until only significant covariates remained. Patient age, year SLNB was performed (as categorized in Table 1), histologic features of the primary tumor including Breslow depth, mitotic rate (mitosis/mm^2), presence or absence of regression and ulceration, and SLNB status were included in the multivariate analysis. P values <.05 were considered significant for all statistical tests.

RESULTS

Three hundred fifty-three patients with cutaneous melanoma of the head and neck underwent SLNB at the

Table 1. Patient and Tumor Characteristics by Positivity of Sentinel Lymph Nodes

Characteristic	PSLN		P[a]
	Yes	No	
Age at SLNB			
Mean [SD]	50.2 [21.6]	54.3 [18.4]	.1479
Minimum-maximum	6-86	1-87	
Age quartiles, No. (%)			
1st: ≤44 years	23 (25.6)	67 (74.4)	.0724
2nd: 45-58 years	10 (11.4)	78 (88.6)	
3rd: 59-69 years	21 (23.6)	68 (76.4)	
4th: 70+ years	15 (17.4)	71 (82.6)	
Body site, No. (%)			
Posterior scalp	8 (25.8)	23 (74.2)	.0831
Anterior scalp	15 (35.7)	27 (64.3)	
Parietal/postauricular	6 (17.1)	29 (82.9)	
Forehead/temple/eyebrow	6 (15.8)	32 (84.2)	
Preauricular/cheek	9 (16.1)	47 (83.9)	
Nose	0	9 (100)	
Lip/chin/jawline/submentum	3 (14.3)	18 (85.7)	
Anterior/supraclavicular neck	2 (5.7)	33 (94.3)	
SCM/posterior neck	5 (25.0)	15 (75.0)	
Eye	1 (14.3)	6 (85.7)	
Ear	14 (23.7)	45 (76.3)	
Year of SLNB			
1997-1999	12 (14.5)	71 (85.5)	.3087
2000-2004	32 (22.9)	108 (77.1)	
2005-2007	25 (19.2)	105 (80.8)	
Breslow depth, mm			
Mean [SD]	3.0 [1.8]	2.4 [1.8]	.0116
Minimum-maximum	0.8-9.0	0.6-15.0	
Mitotic rate, per hpf			
Mean [SD]	4.4 (5.0)	3.6 (6.3)	.2599
Minimum-maximum	0-22.0	0-50.0	
Regression			
Present	4 (21.1)	15 (78.9)	.8629[b]
Absent	62 (19.4)	257 (80.6)	
Unknown	3 (20.0)	12 (80.0)	
Ulceration			
Present	19 (30.7)	43 (69.3)	.0132[b]
Absent	46 (16.9)	227 (83.1)	
Unknown	4 (22.2)	14 (77.8)	

Abbreviations: hpf, high-power field; PSLN, positive sentinel lymph node; SCM, scalene muscle; SD, standard deviation; SLNB, sentinel lymph node biopsy.

[a] Chi-square test for categorical covariates and the *t* test for continuous covariates.

[b] Unknown category was omitted from statistical test.

University of Michigan between 1997 and 2007. The median patient age was 53 years (range, 1-87 years). The median follow-up time was 35 months (range, 3 months to 10.6 years). The mean Breslow depth was 2.5 mm (range, 0.6-15.0mm). Ulceration was present in 17.5% of patients. Detailed patient and tumor data are found in Table 1. The majority of lesions were located on the scalp

Table 2. Head and Neck Melanoma Sites

Body Site	Patients, No. (%)
Scalp	108 (30.6)
Face	101 (28.6)
Nose	9 (2.5)
Neck	76 (21.5)
Ear	59 (16.7)

Table 3. Site of First Recurrence in Sentinel Lymph Node-Negative Patients

Site	Patients, No. (%)
Local/in-transit/satellite	7 (15.9)
Regional	12 (27.3)
Distant	14 (31.8)
Local + regional	4 (9.1)
Local + distant	4 (9.1)
Local + regional + distant	3 (6.8)

(108 patients, 31%) followed by the face (101 patients, 29%) and neck (76 patients, 22%). A complete list of head and neck sites involved by melanoma in our data set is found in Table 2.

At least 1 SLN was identified in 352 patients (99.7%). There were no patients who sustained permanent cranial nerve injuries during the SLNB procedure. A small unmeasured subset experienced neuropraxia of a facial nerve branch that promptly resolved postoperatively. Of the 353 patients, 69 (19.6%) had at least 1 positive SLN. Patients with a positive SLN had thicker primary tumors ($P = .0116$) and were more likely to have ulceration of the primary lesion ($P = .0132$) (Table 1). Sixty-eight of 69 patients with a positive SLNB underwent completion lymphadenectomy. Seventeen patients (25%) in the completion lymphadenectomy group had at least 1 positive non-SLN.

Of the 283 patients with a negative SLNB, 44 (15.5%) had disease recurrence (Table 3). Overall, there were 19 regional recurrences, 7 of which were in conjunction with simultaneous local, in-transit, or distant recurrences. Of the 12 patients who recurred first in the regional basin alone, 9 recurred in the same basin from which the SLN was originally taken, whereas 3 recurred in a basin that was not identified as a primary draining basin during the original SLNB procedure. There were thus 12 false-negative SLNB results. The false-negative rate (FNR) of our data set was 14.8% (12 false negatives/12 false negatives + 69 true positives). The negative predictive value of a negative SLNB was 95.8%. Alternatively

Table 4. Univariate Associations[a] of the Patient/Tumor Characteristics and Sentinel Node-Positive Status With Recurrence-Free Survival

Characteristic	*P*
Breslow depth	.0002
Mitotic rate	.0372
Regression	.6354
Ulceration	.0002
PSLNB	<.0001

Abbreviation: PSLNB, positive sentinel lymph node biopsy.
[a] Each association is adjusted for patient age at surgery.

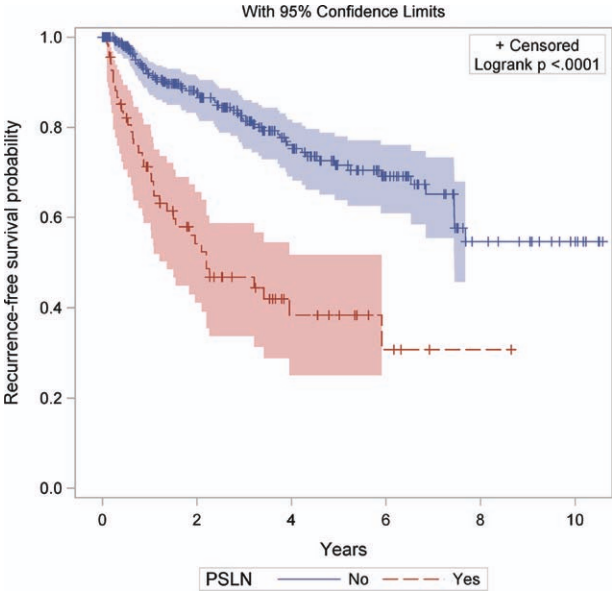

Figure 1. Recurrence-free survival estimates by sentinel lymph node biopsy status with 95% confidence limits are shown. PSLN, positive sentinel lymph node.

stated, patients with local control and a negative SLNB failed regionally in 4.2% of cases, which is the false-omission rate (12 false negatives/12 false negatives + 271 true negatives).

Positive SLNB status was the factor most strongly associated with decreased RFS and decreased OS on univariate analysis (Table 4). The Kaplan-Meier curves for SLNB status and RFS and OS are presented in Figures 1 and 2, respectively. A life table for SLNB status and OS is presented in Table 5. Independent comparison of patients with a positive non-SLN on completion lymphadenectomy with those with a negative completion lymphadenectomy did not demonstrate statistically different OS or RFS (Figs. 3, 4).

On multivariate analysis (Tables 6 and 7), positive SLNB status was the single strongest prognostic factor for decreased RFS (hazard ratio, 4.23) and decreased OS (hazard ratio, 3.33). Breslow depth of the primary tumor significantly decreased RFS (hazard ratio, 1.15), and the presence of ulceration significantly decreased OS (hazard ratio, 2.05).

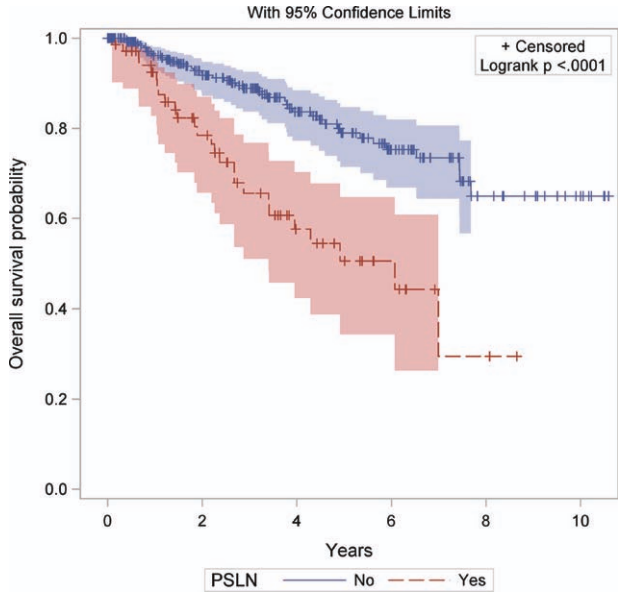

Figure 2. Overall survival estimates by sentinel lymph node biopsy status with 95% confidence limits are shown. PSLN, positive sentinel lymph node.

DISCUSSION

Our series represents the largest single-institution series of SLNB for head and neck melanoma to date. Despite concerns about the procedure for this population compared with truncal or extremity melanomas, SLNB is accurate, and its results are of prognostic importance for head and neck melanoma patients. Several important discussion points, questions, and conclusions result from examination and interpretation of our data.

In only 1 of 353 consecutive SLNB procedures was an SLN not identified. This SLNB identification rate of 99.7% and other very high rates in the literature (Table 8) support the concept that this procedure is feasible in the head and neck region despite ambiguous lymphatic drainage and small lymph node size.[5] Our 99.7% SLNB identification rate in the head and neck region compares favorably to the nonhead and neck SLNB identification rate in the Multicenter Selective Lymphadenectomy Trial 1 (97.5%),[5] the overall rate in the Sunbelt Melanoma Trial (99.7%),[16] and the European Organization of Research and Treatment of Cancer data set (100%).[17]

Previous reports, however, have suggested inferior SLNB accuracy in the head and neck region relative to nonhead and neck sites by reporting lower SLNB

Table 5. Life Table for SLN Status

Time Interval, y	SLN Positive				SLN Negative			
	P	SE	D	N	P	SE	D	N
0-2	78.5	5.3	13	69	91.7	1.9	18	283
2-4	57.7	7.2	9	41	83.7	2.8	12	176
4-6	50.6	7.9	2	18	75.3	3.8	8	102
6-8	29.5	13.5	2	8	65.0	5.9	6	51

Abbreviations: D, number that died within the interval; N, number at risk at the beginning of the interval; P, product-limit estimate of survival until the end of the interval; SE, standard error of the survival estimate; SLN, sentinel lymph node.

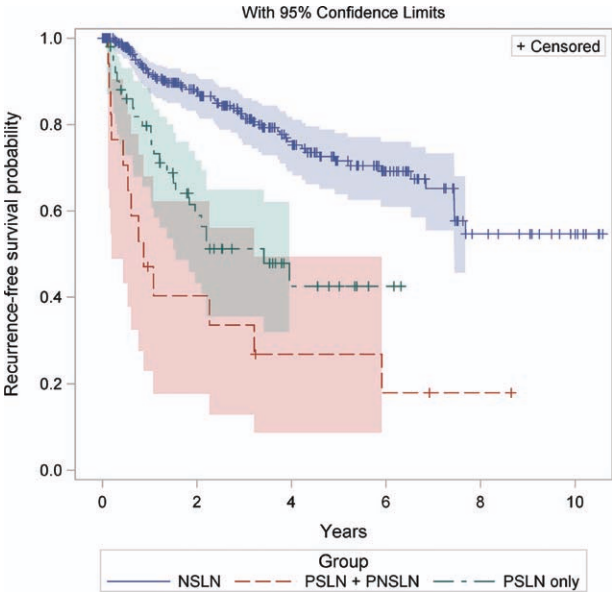

Figure 3. Recurrence-free survival estimates by sentinel and nonsentinel lymph node biopsy status with 95% confidence limits are shown. NSLN, nonsentinel lymph node; PNSLN, positive nonsentinel lymph node; PSLN, positive sentinel lymph node.

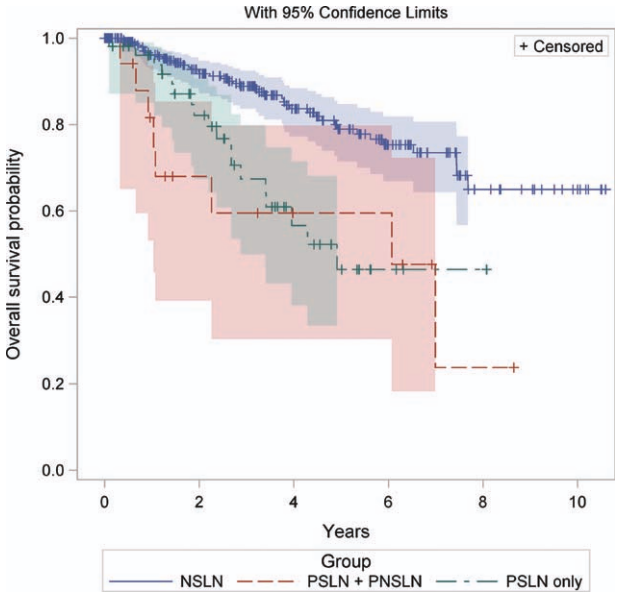

Figure 4. Overall survival estimates by sentinel and nonsentinel lymph node biopsy status with 95% confidence limits are shown. NSLN, nonsentinel lymph node; PNSLN, positive nonsentinel lymph node; PSLN, positive sentinel lymph node.

positivity rate for the head and neck. For instance, Chao et al for the Sunbelt Melanoma Trial showed a 20.7% positive SLNB rate that varied based on the targeted nodal basin: 23% and 20% for trunk and extremity, respectively, versus 15% for the head and neck ($P < .001$).[6] Other large series also have reported similar SLNB positivity rates for head and neck melanomas.[7,18] Our review of the literature specifically addressing head and neck melanoma reveals inconsistent SLNB positivity rates across mainly smaller series. These series showed a low compiled positivity rate of 13.4% that might suggest decreased accuracy in the head and neck area (Table 8). One may speculate that lower SLNB positivity rates in the head and neck region are related to discordant, ambiguous lymphatic channels that decrease the chance of identifying the true SLN. In contrast to previous findings, however, our large series confirmed a high SLNB positivity rate of 19.7% in the head and neck region, suggesting acceptable accuracy in the context of the overall rate of positivity for nonhead and neck melanomas in the Sunbelt Melanoma Trial (21.4%),[6] as well as other reports.[7,18]

A superior indicator of SLNB accuracy may be the failure rate of a negative SLNB in predicting regional control. Comparing failure rates of SLNB across different series is problematic, as definitions of *false negative* are often inconsistent from series to series. Because a local recurrence could result in a regional recurrence, we define a false-negative result as a regional recurrence in the absence of a local or in-transit recurrence. This is in keeping with other large series specifically addressing regional recurrence after negative SLNB results.[7,19] Although most series report the FNR to describe SLNB failure, some calculate it correctly (false negative/false negative + true positive), whereas others do not (false negative/false negative + true negative).

Table 6. Best Multivariate Model for Recurrence-Free Survival

Characteristic	Hazard Ratio (95% CI)	*P*
Breslow depth, 1-mm increase	1.15 (1.04-1.27)	.0049
Age at diagnosis, 1-year increase	1.03 (1.02-1.04)	<.0001
PSLNB	4.23 (2.73-6.54)	<.0001

Abbreviations: CI, confidence interval; PSLNB, positive sentinel lymph node biopsy.

Table 7. Best Multivariate Model for Overall Survival

Characteristic	Hazard Ratio (95% CI)	*P*
Ulceration, present vs absent	2.05 (1.22-3.45)	.0069
Age at diagnosis, 1-year increase	1.03 (1.02-1.05)	<.0001
PSLNB	3.33 (1.99-5.58)	<.0001

Abbreviations: CI, confidence interval; PSLNB, positive sentinel lymph node biopsy.

Table 8. Published Head and Neck-Specific SLNB Data Sets

Study	Follow-up, mo	Total Patients	Failed SLNB	SLNB Identification Rate, %	Positive SLNB, No. of Patients	Positive SLNB Rate, %
Bostick 1997[32]	46	117	7	94.0	14	12.7
Wells 1997[33]	11.6	58	3	94.8	6	10.9
Carlson 2000[34]	15.9	58	1	98.3	10	17.5
Jansen 2000[35]	21.5	30	3	90.0	8	29.6
Wagner 2000[36]	10.7	70	0	100.0	12	17.1
Medina-Franco 2001[37]	15	38	3	92.1	4	11.4
Patel 2002[28]	20	56	4	92.9	4	7.7
Schmalbach 2003[38]	25	80	1	98.9	14	17.7
Chao 2003[a,6]	15.5	321			43	
de Wilt 2004[22]	34	136	3	97.8	14	10.5
Shpitzer 2004[25]	31	30	2	93.3	4	14.3
Carlson 2005[20]	34.7	132	7	94.7	22	
MacNeil 2005[39]	22.4	44	3	93.2	7	17.6
Leong 2006[a,9]	39.6	614			62	
Doting 2006[23]	54	36			7	
Lin 2006[40]	7	114	3	97.4	14	12.6
Telztrow 2007[21]	47	106	12	88.7	17	18.1
Kilpatrick 2007[41]	16	87	7	92.0	14	17.5
Agnese 2007[42]	38.4	131			12	
Gomez-Rivera 2008[10]	34	113	0	100.0	23	20.4
Koskivuo 2009[43]		25	0	100.0	4	16.0
Kelly 2009[24]	39.6	40	13	67.5	6	22.2
Total		2776	100		366	
Saltman 2010[8]	37	234	16	93.2	28	12.8
Compiled				94.0		13.2

Abbreviation: SLNB, sentinel lymph node biopsy.
[a] Multi-institutional series.

The latter is more accurately termed the false-omission rate. We consider the false-omission rate to be more clinically relevant, as it represents the proportion of patients who recur in the nodal basin after a negative SLNB result, and we will thus use it as our basis for discussion.

Previous data suggest a higher false-omission rate in the head and neck region relative to nonhead and neck regions. After recalculations were made where necessary, the compiled false-omission rate across head and neck melanoma series with a minimum 30-month follow-up is 9.3%.[8,10,20-25] The literature predicts a lower false-omission rate when considering nonhead and neck melanomas, including the European Organization for Research and Treatment of Cancer Melanoma Group data set (4.7%),[17] John Wayne Cancer Center data set (4.8%),[26] Multicenter Selective Lymphadenectomy Trial 1 (3.4%),[18] and others.[7,19] Contrary to previous head and neck melanoma results, our false-omission rate of 4.2% demonstrates comparable and acceptable accuracy with respect to the procedure's ability to predict regional control in the head and neck. Stated differently, our data suggest that only 4.2% of patients will recur in any regional basin (mapped or unmapped) after a negative SLNB when local control has been achieved.

Examined together, our SLNB positivity rate and false-omission rate suggest that the accuracy of SLNB is equivalent between the head and neck region and other anatomic sites. We attribute the accuracy within our data set to surgical familiarity with head and neck anatomy by surgeons specializing exclusively in the head and neck.

Our accuracy may also be secondary to our collective expertise in nuclear medicine and histopathology.

This data set also substantiates the prognostic implications of SLNB in patients with head and neck melanoma. In general, for all cutaneous melanomas, the prognostic value of SLNB is well known. The analysis of the American Joint Committee on Cancer's melanoma database of >16,000 patients led to the inclusion of nodal micrometastasis in the classification of melanoma TNM stage.[27] In addition, Morton et al showed SLN status to be the most significant predictor of survival in multivariate analysis in the biopsy arm of the prospective randomized Multicenter Selective Lymphadenectomy Trial 1.[18]

However, head and neck melanoma series have not consistently put forth convincing evidence to verify the prognostic significance of SLNB in this region. Smaller series, such as those of Doting et al, Patel et al, and Gomez-Rivera et al, failed to elucidate a correlation between SLN status and survival on multivariate analysis.[10,23,28] Through pooled data from >600 patients, Leong et al for the Sentinel Lymph Node Working Group established a correlation between SLN status and RFS on multivariate analysis (hazard ratio, 2.8), but the data was nonsignificant with regard to OS.[9] Saltman et al had similar findings in their single-institution series of 234 patients.[8] On the basis of our review of the literature, the Winship Cancer Institute at Emory University is the only group to have previously put forth evidence through multivariate analysis that SLN status is correlated with OS in head and neck melanoma through a smaller series of 132 patients.[20]

This current data set of 353 patients puts forward powerful data indicating that SLN status is highly prognostic in the head and neck region. Far more predictive than Breslow depth or ulceration, SLN status was the single most prognostic clinicopathologic factor in our series. We report a hazard ratio for positive SLN status and decreased RFS at 4.23 ($P < .0001$) on multivariate analysis (Table 5). The hazard ratio for positive SLN status and decreased OS was 3.33 ($P < .0001$) on multivariate analysis (Table 6). These findings are likely a result of both the previously documented reliability and accuracy of the SLNB procedure at our institution and our large series size capable of detecting such correlations.

A question that remains is whether SLNB is safe when performed in the head and neck region. Some argue the intricate cranial nerve anatomy and presence of major blood vessels make SLNB in the head and neck an unsafe practice relative to other nodal basins. However, the literature does little to support this premise. Chao et al report 2 permanent accessory nerve injuries, but no cases of permanent facial nerve paresis in >300 head and neck SLNB procedures included in the Sunbelt Melanoma Trial.[6] Other large head and neck melanoma SLNB series do not comment on procedure-related morbidity.[8,9] Picon et al, Loree et al, and Ollila et al reviewed a combined 134 parotid mapping cases with a compiled 6% rate of temporary facial nerve paresis, but no cases of permanent facial paresis.[29-31] PubMed searches using the keywords "sentinel," "melanoma," and "facial nerve" failed to identify a reported case of permanent facial nerve paresis. A similar search yielded no cases of clinically relevant carotid artery injuries. Our series further supports the safety of the SLNB procedure in the head and neck. We experienced no reported permanent facial nerve injuries, damage to other cranial nerves, or clinically significant vascular injuries in 353 consecutive cases.

Overall, our findings support that SLNB should be performed in patients with head and neck melanoma for the same indications as patients with truncal or extremity melanoma with comparable feasibility, safety, accuracy, and prognostic value.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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