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Sentinel Node Biopsy for Head and Neck Melanoma: A Systematic Review

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Abstract

Objective. This systematic review was conducted to examine the test performance of sentinel node biopsy in head and neck melanoma, including the identification rate and false-negative rate.

Data Sources. PubMed, EMBASE, ASCO, and SSO database searches were conducted to identify studies fulfilling the following inclusion criteria: sentinel node biopsy was performed, lesions were located on the head and neck, and recurrence data for both metastatic and nonmetastatic patients were reported.

Review Methods. Dual-blind data extraction was conducted. Primary outcomes included identification rate and test performance based on completion neck dissection or nodal recurrence.

Results. A total of 3442 patients from 32 studies published between 1990 and 2009 were reviewed. Seventy-eight percent of studies were retrospective and 22% were prospective. Trials varied from 9 to 755 patients (median 55). Mean Breslow depth was 2.53 mm. Median sentinel node biopsy identification rate was 95.2%. More than 1 basin was reported in 33.1% of patients. A median of 2.56 sentinel nodes per patient were excised. Sentinel node biopsy was positive in 15% of patients. Subsequent completion neck dissection was performed in almost all of these patients and revealed additional positive nodes in 13.67%. Median follow-up was 31 months. Across all studies, predictive value positive for nodal recurrence was 13.1% and posttest probability negative was 5%. Median false-negative rate for nodal recurrence was 20.4%.

Conclusion. Sentinel node biopsy of head and neck melanoma is associated with an increased false-negative rate compared with studies of non–head and neck lesions. Positive sentinel node status is highly predictive of recurrence.

Keywords

head and neck melanoma, sentinel lymph node biopsy, false-negative rate, systematic review

An estimated 68,130 new cases of malignant melanoma were predicted to be diagnosed in 2010, resulting in 8700 deaths.[1] Approximately 20% of primary lesions are located on the head and neck. Mortality rates among head and neck melanomas differ by site; lesions of the scalp and neck have the highest mortality, with a 10-year survival of 60%. Tumors located on the ear, face, and eyelid have 10-year survival rates of 70%, 80%, and 90%, respectively.[2]

Occult lymph node metastasis is present in 15% to 20% of patients with melanoma of the head and neck and clinically negative nodes.[3,4] Elective lymph node dissection (ELND) has been used to stage melanoma of the head and neck in these patients; however, morbidity associated with ELND includes cranial nerve XI transection, marginal nerve injury, and chyle leak.[5-8] Furthermore, no clear survival benefit has been shown with ELND.[9] The Intergroup Melanoma Trial, a randomized controlled trial by Balch et al,[9] included patients with head and neck melanoma in combination with truncal melanomas and analyzed the survival difference between ELND and a "watch and wait" algorithm. This study showed no survival difference between these 2 groups. In a cohort study by Kane et al,[10] analysis of 424 patients with stage I head and neck melanoma did not show a survival benefit for ELND by either univariate or multivariate analysis. One theory for the lack of

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survival benefit is that lymphatic dissemination in head and neck melanoma is unpredictable. In fact, up to 84% of lymphatic drainage patterns are different than clinically predicted,[11,12] and bilateral drainage patterns have been reported in 10% of patients.[13]

Given that the presence of lymph node metastasis carries a major prognostic implication, detection of these occult metastases is crucial for accurate staging.[14,15] However, because lymphatic metastases are found in a small percentage of patients with clinically negative nodes and because ELND offers no survival benefit, a technique that allows for accurate staging with minimal morbidity would be ideal. Sentinel lymph node biopsy (SNB) was first described by Morton in the early 1990s and has become a powerful technique in melanoma staging.[16] SNB has decreased the morbidity once associated with ELND by its minimally invasive technique and by limiting neck dissection to patients with positive sentinel nodes. Furthermore, sentinel lymph node status has been shown to be the most important predictor of survival.[17] Although there are no data to support an overall survival benefit conferred by the use of this procedure, a recent review by Tanis et al[18] examined the survival implications of patients with clinically node-negative head and neck melanomas being managed with either a "watch and wait" strategy, ELND, or SNB. This study concluded that no overall survival benefit was seen for patients undergoing SNB or ELND.[18]

Although technically feasible, using SNB in head and neck melanoma is met with several specific challenges. Preoperative lymphoscintigraphy to locate the sentinel node can be limited because the lymph node basins within the head and neck are often located close to the primary lesion. This makes it difficult to distinguish discrete nodes from the primary site because of background signal from the highly radioactive injection site. Also, because the distance between the melanoma and lymph node basin is often small, the tracer may quickly diffuse from sentinel nodes to nonsentinel nodes, making specific identification difficult. Finally, sentinel nodes that are not amenable to biopsy are more common in head and neck melanoma because of the presence of parotid lymph nodes.

Although institutions often standardize their sentinel lymph node procedures based on both anecdotal and published data, most of these studies include a majority of patients with melanoma outside of the head and neck region. Given the unique set of challenges associated with head and neck melanoma, optimization for these specific sites may be required. This systematic review of the literature sought to determine the test performance of SNB in head and neck melanoma, as measured by the identification rate and false-negative rate (FNR).

Methods

Eligibility Criteria

Studies (retrospective, prospective, randomized controlled trials) were considered eligible if they met the following criteria: (1) the malignant melanoma was diagnosed in the head and neck region, (2) sentinel lymph node biopsy was performed, (3) outcomes were reported for both metastatic and nonmetastatic patients, and (4) recurrence data were reported. Exclusion criteria included articles that could not be translated into English and studies reporting exclusively on positive SLN biopsies.

Information Sources and Search Strategy

A systematic review of the studies meeting the above criteria was performed by searching MEDLINE, through PubMed, and EMBASE and was supplemented with a recent 5-year abstract search from American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO) annual meetings. The Medical Subject Heading (MESH) keywords initially included *melanoma* and *sentinel lymph node*. Further limitation for head and neck specific studies was undertaken using various combinations of the following keywords: *sentinel*, *sentinel lymph node*, *melanoma*, *head*, and *neck*. Reference lists of original articles and review articles served as an additional resource in the search strategy. Additionally, expert consultation by the ASCO panel on melanoma was used to determine whether major studies had been overlooked by our search strategy.

Data Extraction

For each study, the following data were extracted: author, institution, year of study publication, journal citation, purpose of study, completion neck dissection (CND) irrespective of SNB result, start date, end date, type of study (prospective, retrospective, randomized controlled trial), inclusion criteria, exclusion criteria, number of patients, demographic data (female, male, mean age, median age, age range), pathologic information (location of lesion, mean Breslow, Breslow range, lowest Clark level, percentage ulceration, percentage partial regression), and prior interventions (biopsy, wide local excision, shave biopsy). Technical information including tracer type, volume, filtration, injection location, manual massage, time between injection and SNB, and pathology of the surgical specimen including type of immunohistochemistry performed was included. The number of patients successfully mapped, number of basins successfully mapped, number of sentinel nodes and total lymph nodes extracted, number of positive nodes, number of patients who underwent CND after SNB, and number of positive CND were recorded. Follow-up data, recurrence data, FNR, survival data, and complications were also documented when available. Data were independently extracted by 2 investigators (M.E.V. and N.d.R. or D.S.) to ensure homogeneity of data collection and to remove any subjective influence of the investigators on data collection and entry. Disagreements between the investigators were resolved by discussion and review of individual articles until a consensus was obtained.

Quality Assessment

Two reviewers independently assessed the quality of the studies selected. The Methodological Index for Non-Randomized Studies (MINORS) criterion was used.[6] This score quantifies the study quality based on 8 items—0, 1, or 2 points were assigned per item—up to a maximum score of 16 points. We

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considered 30 or more months of mean follow-up as adequate (2 points) and less than 30 months as suboptimal (1 point); zero points were given if no follow-up time was mentioned. No article was excluded based on the quality assessment, but sensitivity analysis was performed to estimate the effects of quality on the estimates.

Statistical Analysis

Primary outcomes for this analysis defined a priori included the proportion of patients successfully mapped, the FNR for nodal recurrence, and the predictive value positive (PPV) and negative (PVN) for nodal recurrence. Secondary outcomes included the predictive value for total recurrences. In nearly all studies identified, a CND was performed in patients with a positive SNB, whereas few studies performed CND in patients with negative SNB. The FNR was defined as the proportion of patients with a nodal recurrence after a negative SNB compared with the total positive SNB. The PVP was defined as the proportion of patients with positive SNB who recurred, and PVN was defined as the proportion of patients with a negative SNB who remained recurrence free. The complement of the latter (1 – PVN) is defined as the posttest probability negative (PTPN) and represents the proportion of patients with negative SNB who recur.

The distributions of all covariates were evaluated, and appropriate summary measures of central tendency and variability were estimated. Heterogeneity was based on Cochran's *Q* statistic, representing the weighted sum of squared differences between individual study effects and the pooled effect across studies, with the weights being those used in the pooling method. Summary measures of all outcomes across studies were estimated by the method of Mantel and Haenszel as the weighted sum of the individual estimates, where the weights are the reciprocal of the variance or the interstudy-adjusted variance of the estimates. A fixed-effects model assuming one true treatment effect was used when no significant heterogeneity was observed; otherwise a random effects model was used. Effect measures are presented for all studies combined as well as a priori defined subgroups in sensitivity analyses. Several covariates were regressed on the natural logarithm of the primary outcome measures. Hypothesis testing on summary effect estimates was based on the z statistic with estimates of standard error and 95% confidence intervals (95% CI) provided for all individual studies, as well as the summary overall effect estimate. All subgroup analyses, although planned a priori, should be considered exploratory and hypothesis-generating.

Results

Eligible Trials

The original search strategy returned 1435 references published between 1990 and 2009. Direct review of each reference immediately excluded 1199 articles that were found to be unrelated to this research. Subsequently, each abstract was reviewed using our inclusion and exclusion criteria, resulting in 26 articles that reported the use of SNB in patients with malignant melanoma of the head and neck. One additional study was excluded because of the use of a duplicate patient population. An extended search targeting only head and neck melanoma and using references from previously published articles returned an additional 7 studies that have been included in this analysis. Review of abstracts from the most recent 5 years of ASCO and SSO annual meetings did not yield additional relevant studies, nor did consultation with national experts in the field. A PRISMA flow chart for the study search and selection process is shown in **Figure 1**.

A total of 32 studies spanning the period from 1997 to 2009 were eligible for analysis (**Table 1**). Seventy-eight percent of studies were retrospective (n = 25) and 22% were prospective (n = 7). A total of 3442 patients were included, with study variations from 9 to 755 patients (median 55). Fifteen studies consisted of fewer than 50 patients (median 30), whereas 17 included 50 or more patients (median 106). All patients underwent SNB as a staging procedure for primary cutaneous malignant melanoma of the head or neck region. Three studies included only patients with successfully identified sentinel nodes, and 1 study did not report the number of patients with successfully identified sentinel nodes; these studies were excluded from the estimation of the identification rate. Mean Breslow was 2.53 mm (range, 0.02-20 mm).

Sentinel Node Identification Rate

Among the 28 evaluable studies, the median SNB identification rate was 94.0% (range, 64.8%-100%). Among 14 evaluable studies, more than 1 basin was reported in 33.1% of patients. A median of 2.56 sentinel nodes per patient were excised.

An increasing sentinel node identification rate was observed in more recent studies (**Figure 2**; $P < .0001$), larger studies ($P < .0001$), studies with greater mean Breslow depth ($P < .0001$), and studies with a greater proportion of ulcerated tumors ($P < .0001$). The identification rate was 91% (95% CI, 87.5%-93.6%) in studies with fewer than 50 patients and 95.0% (95% CI, 90.5%-97.9%) in studies with 50 or more patients ($P = .114$).

Sentinel Lymph Node Biopsy Results

In 15.08% of patients, SNB results were positive. Nearly all of these patients (median 100%) underwent CND. Based on 12 eligible studies, 13.67% of SNB positive patients who underwent CND were found to have additional positive nodes.

False-Negative Rate

A false-negative was defined as recurrence in patients with negative SNB. The FNR was independently calculated for each study because it was often cited inaccurately within the articles. Among 23 evaluable studies, the estimated FNR for nodal recurrence was 20.4%, with a range of 3.3% to 44%. Increasing FNR was observed in studies reporting longer mean follow-up (**Figure 3**; $P = .0372$). The FNR for nodal recurrence was 14.9% (95% CI, 7.2%-28.4%) in studies with

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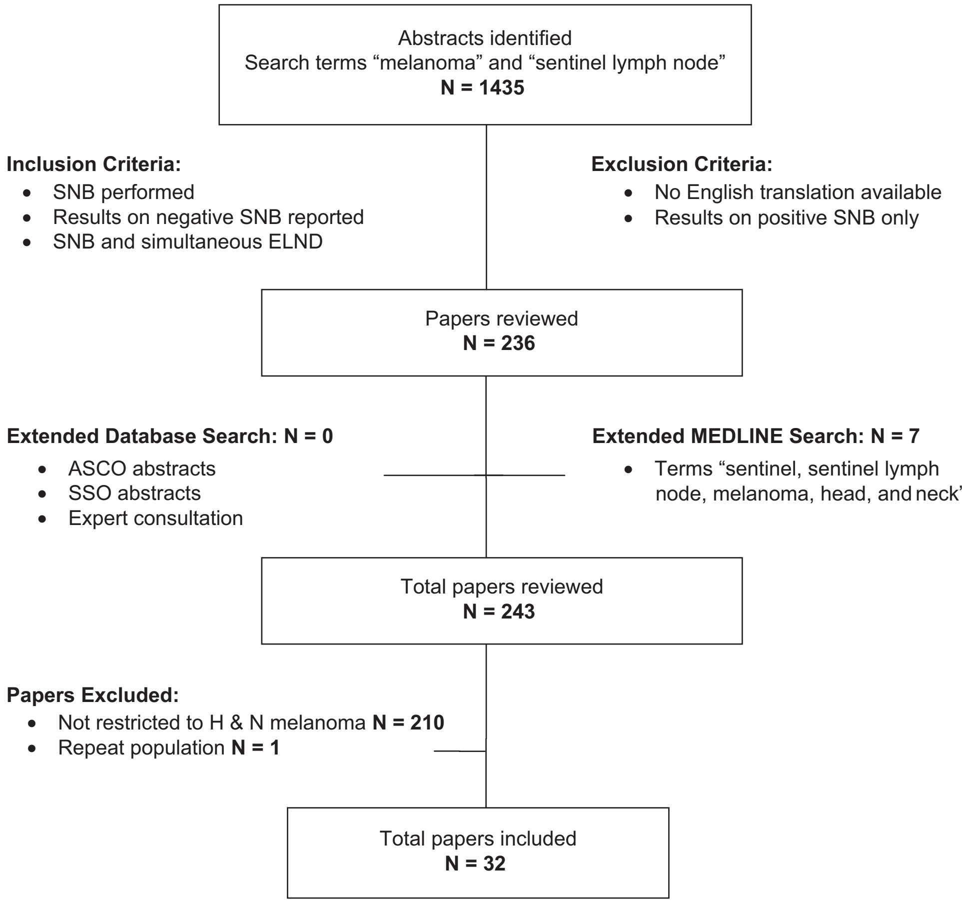

Figure 1. Systematic literature review strategy. ASCO, American Society of Clinical Oncology; ELND, elective lymph node dissection; SNB, sentinel lymph node biopsy; SSO, Society of Surgical Oncology.

fewer than 50 patients and 21.0% (95% CI, 17.1%-25.6%) in studies with 50 or more patients (P = .494).

Predictive Value Positive

Among 12 evaluable studies, the probability of recurrence in patients with a positive SNB (PVP) was estimated to be 13.1% for nodal recurrence, ranging from 3.3% to 42.9%. The PVP for nodal recurrence was 19.7% (95% CI, 9.4%-36.7%) in studies with fewer than 50 patients and 11.5% (95% CI, 7.5%-17.2%) in studies with 50 or more patients (P = .205). Among 14 evaluable studies, the estimated PVP for total recurrence was 40.4%, ranging from 16.7% to 57.1%. This is despite the fact that the majority of patients with a positive SNB underwent a complete lymph node dissection of the involved basin. The PVP for total recurrence was 39.7% (95% CI, 24.3%-57.5%) in studies with fewer than 50 patients and 40.5% (95% CI, 34.6%-46.6%) in studies with 50 or more patients (P = .934).

Posttest Probability Negative

The probability of nodal recurrence in patients with negative SNB (PTPN) was calculated from 23 evaluable studies. The estimated PTPN across studies was 5.0%, ranging from 0.7% to 10.5%. Increasing probability of nodal recurrence in SNB negative patients was associated with increasing FNR (**Figure 4**; P < .0001) and increasing median duration of follow-up (**Figure 5**; P = .0041). The PTPN for nodal recurrence was 4.3% (95% CI, 2.0%-8.7%) in studies with fewer than 50 patients and 5.1% (95% CI, 4.1%-6.4%) in studies with 50 or more patients (P = .786). Among 20 evaluable studies, the estimated PTPN for total recurrence was 14.1%, ranging from 2.0% to 30.8%. Increasing PTPN was associated with increasing proportion of patients with ulceration (P = .0210) and increasing median duration of follow-up (P = .0450). The PTPN for total recurrence was 16.0% (95% CI, 10.0%-24.6%) in studies with fewer than 50 patients and 13.5% (95% CI, 10.9%-16.7%) in studies with 50 or more patients (P = .513).

Details of the evaluated studies are available in the online appendix.

Discussion

This systematic review represents, to our knowledge, the largest study of test performance for SNB in patients with head and neck melanoma. A total of 3442 patients from 32 studies published between 1990 and 2009 were analyzed, with a median follow-up of 31 months. Our data show that identification of the sentinel node in head and neck melanoma is

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Table 1. Systematic Literature Search from 1990 to 2009 Resulted in 32 Studies Used in Analysis of Test Performance for SNB in Head and Neck Melanoma

Primary Author	Year of Publication	No. of Patients
Koskivuo[20]	2009	25
Gomez-Rivera[21]	2008	113
Agnese[22]	2007	755
Kilpatrick[23]	2007	87
Rigual[24]	2007	22
Shpitzer[25]	2007	15
Teltzrow[26]	2007	106
Berdahl[27]	2006	43
Doting[28]	2006	36
Leong[17]	2006	629
Lin[29]	2006	114
Carlson[30]	2005	132
Maccauro[31]	2005	61
Macneill[32]	2005	48
Alex[33]	2004	43
de Wilt[34]	2004	136
Fincher[35]	2004	51
Shpitzer[36]	2004	30
Chao[37]	2003	321
Cole[38]	2003	9
Pockaj[39]	2003	84
Schmalbach[40]	2003	87
Eicher[41]	2002	43
Patel[42]	2002	56
Medina-Franco[43]	2001	54
Rasgon[44]	2001	27
Jansen[45]	2000	30
Maffioli[46]	2000	17
Wagner[47]	2000	70
Alex[48]	1998	23
Bostick[49]	1997	117
Wells[50]	1997	58

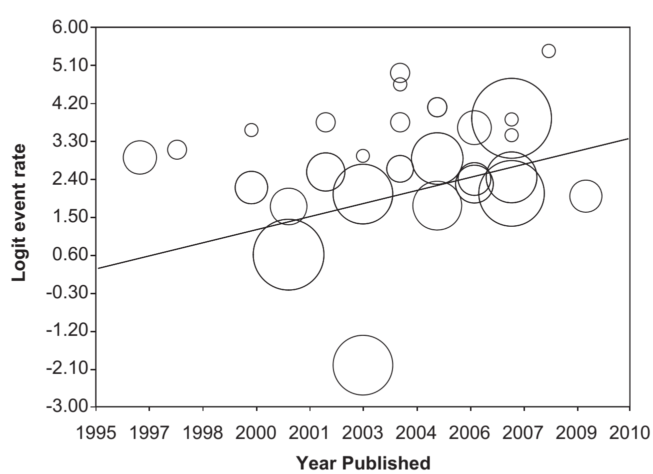

Figure 2. Increasing identification rate is associated with more recent publications.

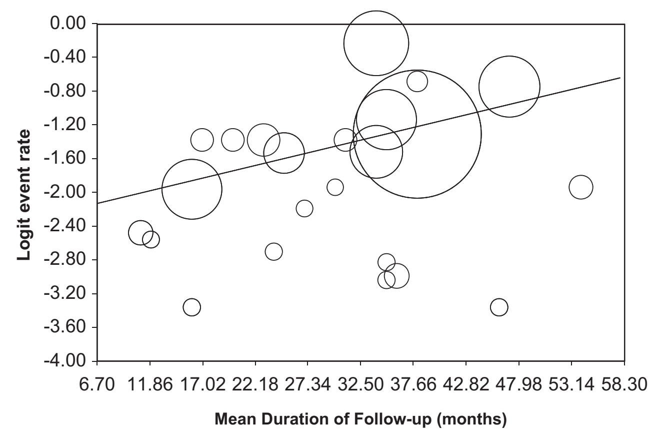

Figure 3. Increasing false-negative rate is associated with increasing mean duration of follow-up.

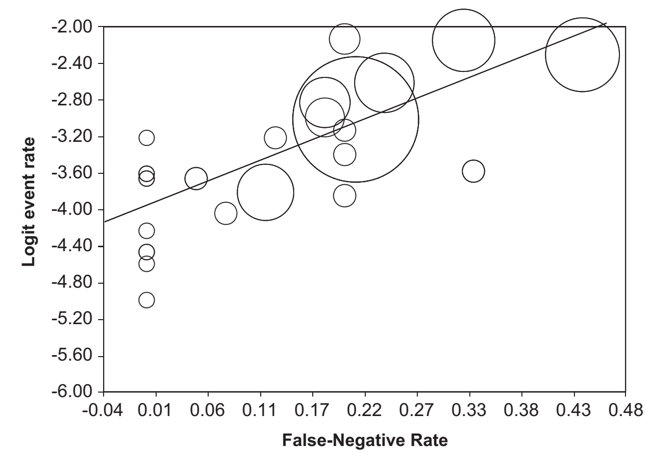

Figure 4. Increasing posttest probability negative for nodal recurrence is associated with increasing false-negative rate.

highly successful (93.4%). Increasing sentinel node identification rate was observed in more recent studies, larger studies, studies with greater mean Breslow depth, and those with a greater proportion of ulcerated tumors (all $P < .0001$). However, despite the technical success in the operating theater, this procedure results in an elevated FNR (20.4%) compared with non–head and neck lesions. Additionally, the likelihood of recurrence in patients with negative SNB and the FNR increased as length of follow-up increased. This suggests that the 20.4% FNR may be an underestimate of the true test performance for SNB in head and neck melanoma.

Previous systematic reviews have attempted to quantify SNB test performance in the population of patients with head and neck melanoma; however, to our knowledge, the most recent article was published in 2001 by Davison et al[3] and was limited in both patient numbers (N = 437) and length of follow-up, which ranged between 10 and 46 months (mean 24 months). This study reported

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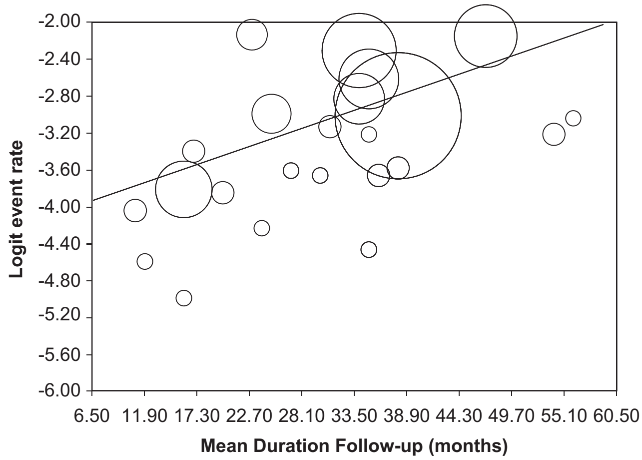

Figure 5. Increasing posttest probability negative for nodal recurrence is associated with increasing mean duration of follow-up.

an identification rate between 95% and 100% and an FNR ranging from 7.7% to 10.4%.[3] Our results diverge from these previously reported data, showing an FNR double that reported by Davison. This increased FNR is likely attributable to a combination of increased study size and increased length of follow-up in which to detect recurrences in negative SNB patients. Also, it is unclear whether the outcomes reported in this analysis were based on weighted statistics to account for the differences in the size of study populations, whereas our estimates account for this heterogeneity.

The discordance between a high identification rate and a high FNR is a curious one. One possible explanation is that in the head and neck region, the concentration of lymph nodes is high and it is not uncommon for the sentinel node to be located in close proximity to the tumor. The high radioactivity present at the tumor injection site often makes these nodes difficult, if not impossible, to identify.

A regression analysis of this data showed several statistically significant relationships. An increasing sentinel node identification rate was observed in more recent studies and larger studies ($P < .0001$). This suggests that there is an association between volume and the technical expertise of the surgeon as well as the outcomes of an institution. For this reason, it may be useful to compare the FNRs of tertiary care hospitals to those of lower volume centers to determine whether SNB should be restricted to high-volume referral institutions. Interestingly, studies including patients with greater mean Breslow depth ($P < .0001$) and a greater proportion of ulcerated tumors ($P < .0001$) were also associated with an increased identification rate. The cause for this association is unknown; however, we hypothesize that these pathologic factors may be associated with greater inflammation at the site of the primary tumor and may lead to local lymph node reactivity. These reactive enlarged nodes may be more easily identifiable than smaller normal nodes. One method of analyzing this may be to collect institutional data on the size of sentinel nodes associated with ulcerated melanomas and compare these with sentinel nodes from nonulcerated lesions. This review not only is important to determine the test performance of SNB as a staging procedure but also casts a critical eye on the management of patients with positive SNB. Given that the likelihood of recurrence in SNB positive patients is high despite CND (13.1% nodal recurrence and 40.4% total recurrence), it is reasonable to deduce that a positive SNB is a sign of systemic disease. Therefore, in this setting, the use of CND may be less important than the use of adjuvant systemic therapies. Only a small subgroup of studies (n = 12) had the data needed for this analysis, and thus the accuracy of this estimate may be limited. Furthermore, the high recurrence rate demonstrated by this study may be a major determinant of the lack of survival benefit associated with this procedure. Therefore, the true benefit of CND for patients with positive SNB remains unclear.

Several limitations of this systematic review need to be addressed. First, there is the issue of publication bias in that studies identifying certain outcomes may be more likely to be published in peer-reviewed literature than other studies. For instance, if articles with only high identification rates of SNB and low false-positive rates were published, then this would result in an overestimated test performance. Likewise, if a large study had not yet published recurrence data indicating a high likelihood of nodal recurrence, this too would bias our results toward a lower false-negative recurrence rate. However, after our comprehensive search of the literature, we used expert consultation through the ASCO panel on melanoma and it is thus unlikely that we have missed any substantial studies. Despite this comprehensive search, the number of studies included within this analysis is small (N = 32), encompassing 3442 patients, which may decrease the statistical power. This is largely because we chose to decrease the heterogeneity of the studies by limiting the review to patients with melanoma located only in the head and neck. It is furthermore important to note that not all studies reported each of our secondary outcomes. For instance, only 20 studies could be evaluated for mean Breslow depth, 16 for ulceration, and 22 for mean follow-up. However, because our goal was to be as inclusive as possible, we accepted this limitation. Although each secondary outcome may not include data from all of the studies within this systematic review, they do include, to our knowledge, all current data available in the peer-reviewed literature.

The 32 studies are clinically heterogeneous and largely retrospective. The techniques used for SNB were not standardized over these studies and indeed may not have been standardized at a given institution. The study sizes ranged widely, from 9 to 755 patients, which not only may bias results toward the larger studies but also may serve as a surrogate for variance in institutional expertise in performing SNB. The prognostic information supplied by SNB has become crucial in staging patients with malignant melanoma and selecting patients for adjuvant systemic therapy trials. Technical advances in SNB such as the use of computed tomography and single-photon emission computed tomography have been reported to improve sentinel node identification in head and neck melanoma, and their increased use may improve overall accuracy of SNB.[19]

In conclusion, SNB in head and neck melanoma presents specific technical challenges including the small distance between primary tumor and lymph node basins, the presence

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of multiple draining lymph node basins, and the involvement of parotid lymph nodes that are not amenable to biopsy. A standardized procedure for optimizing test performance in head and neck melanoma has yet to be determined, and advances are being investigated to increase SNB accuracy.

We have used pooled analyses from diverse sources and derived from more than 20 years of experience to summarize important characteristics of this technique. We hope that our work clarifies some important questions about SNB for head and neck melanoma and encourages further studies to validate its use on this important cohort of patients.

Author Contributions

Nicole de Rosa, contributed to conception and design, acquisition of data, analysis and interpretation of data, drafted the article, and approved final version; **Gary H. Lyman**, contributed to conception and design, acquisition of data, statistical analysis and interpretation of data, revised manuscript, and approved final version; **Damian Silbermins**, conception and design, acquisition analysis and interpretation of data, revised manuscript, and approved final version; **Matias E. Valsecchi**, conception and design, acquisition of data, analysis and interpretation of data, drafted and revised manuscript, and approved final version; **Scott K. Pruitt**, interpretation of data, revising manuscript critically for important intellectual content, and approved final version; **Douglas M. Tyler**, analysis and interpretation of data, revising manuscript critically for important intellectual content, and approved final version; **Walter T. Lee**, concept, analysis and interpretation of data, drafting and revising manuscript, and approved final version.

Disclosures

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Supplemental Material

Additional supporting information may be found at http://oto.sagepub.com/content/by/supplemental-data

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