JAMA Otolaryngology–Head & Neck Surgery | Original Investigation | FROM THE AMERICAN HEAD AND NECK SOCIETY

Sentinel Lymph Node Biopsy for Cutaneous Squamous Cell Carcinoma on the Head and Neck

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IMPORTANCE Metastasis of cutaneous squamous cell carcinoma (SCC) to the nodal basin is associated with a poor prognosis. The role of sentinel lymph node biopsy (SLNB) for regional staging in patients diagnosed with SCC is unclear.

OBJECTIVE To evaluate a single institution's experience with use of SLNB for regional staging of SCC on the head and neck.

DESIGN, SETTING, AND PARTICIPANTS A retrospective review of 53 patients who were diagnosed with SCC on the head and neck, at high risk for nodal metastasis based on National Comprehensive Cancer Network (NCCN) risk factors, and treated with wide local excision (WLE) and SLNB from December 1, 2010, through January 30, 2015, in a single academic referral center was performed. The follow-up period ended November 5, 2015. Sentinel lymph node biopsy paraffin blocks were retrieved and processed retrospectively with serial sectioning and immunohistochemical analysis (IHC) in cases with nodal recurrence following a negative SLNB.

MAIN OUTCOMES AND MEASURES Sentinel node (SN) identification rate, SLNB positivity rate, local recurrence, regional nodal recurrence, and distant recurrence.

RESULTS In 53 patients with 54 tumors, the SN identification rate was 94%. The SLNB positivity rate was 11.3%. On more thorough tissue processing and IHC, metastatic SCC was identified in 2 of 5 (40%) cases previously deemed negative. After reclassification of these cases, the adjusted SLNB positivity rate was 15.1%. The adjusted rate of false omission was 7.1% (95% CI, 2%-19%). Nodal disease developed in 20.8% overall. Angiolymphatic invasion (Cohen d, 3.52; 95% CI, 1.83-5.21), perineural invasion (Cohen d, 0.81; 95% CI, 0.09-1.52), and clinical size (Cohen d, 0.83; 95% CI, 0.05-1.63) were associated with the presence of nodal disease.

CONCLUSIONS AND RELEVANCE Rigorous study of SLNB for cutaneous SCC incorporating prospectively-collected comprehensive data sets based on standardized treatment algorithms is justified with potential to modify clinical practice. Our study demonstrates the critical importance of serial sectioning and IHC of the SLNB specimen for accurate diagnosis. Use of the NCCN guidelines may facilitate identification of patients with SCC at high risk for nodal metastasis.

JAMA Otolaryngol Head Neck Surg. 2016;142(12):1171-1176. doi:10.1001/jamaoto.2016.1927
Published online July 20, 2016.

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Squamous cell carcinoma (SCC) is the second most common skin cancer type with a continually increasing incidence and a predilection for chronically sun exposed sites including the head and neck.[1] Although the majority of cutaneous SCC is diagnosed early and treatment is curative, metastasis and death occurs. The regional lymph node basin is the site of first metastasis in roughly 85% of cases. The 5-year survival rate decreases from more than 90% for local disease to roughly 30% when regional node metastasis occurs.[2] The estimated number of annual nodal metastases ranges from 5604 to 12 572; annual deaths from 3932 to 8791.[3] Sentinel lymph node biopsy (SLNB) is standard care for staging the regional nodal basin for melanoma and Merkel cell carcinoma in appropriate patients.[4,5] Accurate staging drives treatment and treatment options. For melanoma, microscopic detection with SLNB and early completion lymph node dissection (CLND) results in improved regional control, fewer adverse effects, fewer overall number of positive nodes, and potential for small but improved survival in node-positive patients.[6] For Merkel cell carcinoma, microscopic detection with SLNB drives primary and adjuvant surgery and radiation decision making.[5] In contrast, it is unclear if SLNB has any benefit for high-risk cutaneous SCC. Our purpose was to report our series utilizing SLNB in the management of cutaneous SCC on the head and neck, and add unique data to contemporary reports for optimal design of future studies.

Key Points

Question Should patients with cutaneous squamous cell carcinoma (SCC) on the head and neck be considered for staging with sentinel lymph node biopsy (SLNB)?

Findings In this retrospective review of 53 patients, nodal metastasis was identified in 15.1% by SLNB and the rate of false omission was 7.1%. The importance of histologic processing of SLNB specimens was demonstrated.

Meaning Our findings indicate that there may be a role for SLNB in the treatment of SCC on the head and neck for patients at high risk of nodal metastasis as defined by the National Comprehensive Cancer Network guidelines.

Methods

Following University of Michigan institutional review board approval, a database was created to identify patients with head and neck cutaneous SCC treated at our institution with wide local excision (WLE) and SLNB for potential retrospective analysis. Written consent for inclusion in the database was obtained from patients at their consultation visit, and participants were not compensated. Patients treated from December 2010 to January 2015 were identified. Demographic, clinical, and histopathological data were obtained via the electronic medical record and by telephone contact with the patient if data was missing. The follow-up period ended November 5, 2015. Patients with multiple or prominent National Comprehensive Cancer Network (NCCN) risk factors for regional lymph node metastasis were considered for SLNB. Risk factors included: Breslow depth of 2 mm or more or Clark level of IV or V; rapid growth; locally recurrent; occurrence in a prior radiation or chronic inflammation and/or ulcer site; perineural invasion (PNI), angiolymphatic invasion (ALI); immunosuppression; size of 1 cm or more on the cheek, forehead, scalp, neck, or 0.6 cm or more on the face mask area; and poorly differentiated histologic pattern.[7]

Patients underwent preoperative lymphoscintigraphy using a mean dose of 2.3 μCi technetium Tc 99m sulfur colloid (CIS-US Inc) injected intradermally at the primary lesion site. Single photon emission computed tomography (SPECT-CT) imaging was performed 15 to 30 minutes following injection. Approximately 1 mL of vital blue dye (methylene blue or indigo carmine) was subsequently injected intradermally at the lesion site. Wide local excision was performed first to minimize shine-through from radiocolloid. Following WLE, a handheld gamma probe (Navigator GPS; RMD Instruments) was used to interrogate the nodal basins transcutaneously, using SPECT-CT as a guide. Each SN was dissected through small incisions from surrounding tissue using blunt dissection, taking care to identify and preserve nearby neurovascular structures. Tissue (WLE and SLNB) was processed using formalin-fixed permanent sections. Depending on size, SNs were bivalved or serially sectioned and stained with hematoxylin-eosin (H&E). Cytokeratin immunohistochemical (IHC) staining was variably performed per pathologist preference. Patients with a positive SLNB were counseled to undergo CLND. Adjuvant radiation or chemoradiation was individually considered under the auspices of the Multidisciplinary Head and Neck Tumor Board.

Demographic and clinical variables abstracted included: age, gender, primary vs recurrent, SCC arising within an area of prior radiation or chronic ulcer, immunosuppression, rapid growth, location, and clinical size. Treatment data included: excision margin size (cm) and adjuvant therapy if performed. Histopathologic factors from the initial biopsy and WLE included: histologic pattern, PNI, and ALI. Sentinel lymph node biopsy factors included: number of SNs, positive or negative, extracapsular extension (ECE), and IHC staining. Completion lymph node dissection factors included: number of nodes, positive or negative, and ECE. Outcome measures included: SN identification rate, SLNB positivity rate, local recurrence, regional nodal recurrence, and distant recurrence.

Sentinel lymph node biopsy paraffin blocks were retrieved for retrospective processing in cases with nodal recurrence in the basin following a negative SLNB. Slides were processed with 3 levels deeper in the tissue block separated by 50 to 80 μm. Four consecutive slides were stained at each level as: (1) H&E, (2) pancytokeratin (Cam 5.2 BD Biosciences, clone 5.2, dilution 1:40 and AE1/AE3 EMD Millipore, clone AE1/AE3, dilution 1:200;), (3) cytokeratin MNF-116 (DAKO, clone MNF 116, dilution 1:100), and (4) unstained. Initial and newly processed slides were reviewed independently by 2 pathologists (L.L. and J.B.M.).

All clinical and laboratory assessments were summarized with standard descriptive statistics. Continuous variables were

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summarized using mean, standard error, and range. Categorical variables were summarized by frequency and percentage for each response category (N, %). Standard strategies for assessing diagnostic test accuracy were employed. A t test was used to determine if continuous assessments were significantly different between the groups based on nodal disease status. A Wilcoxon-Mann-Whitney test with exact *P* values was used for ordinal assessments or when normality was violated. Fisher exact or χ^2 tests assessed group differences for categorical data. The standardized mean difference effect size, Cohen d, and corresponding 95% CIs were computed using means, standard deviations, and χ^2 φ coefficients. All data was analyzed using SAS statistical software (SAS Institute, Inc; version 9.3) and the Practical Meta-Analysis Effect Size Calculator.[8]

Results

Fifty-three patients with 54 tumors treated with WLE and SLNB were identified. Mean age was 73 years (range, 47-90 years). Nine (17%) were women; 44 (83%) were men. Twenty-four (44.4%) tumors were located on the cheek, temple, or forehead; 14 (25.9%) on the scalp; 9 (16.7%) on the ear; 4 (7.4%) on the lip; 2 (3.7%) on the neck; and 1 (1.9%) on the nose. Six (11.1%) were recurrent. One (1.9%) developed within an area of radiation and 1 (1.9%) within a chronic ulcer. Fourteen tumors (25.9%) exhibited rapid growth. Mean lesion clinical diameter was 2.56 cm. Ten (18.5%) initial biopsies showed a well differentiated histologic pattern, 23 (42.6%) were moderately differentiated, 15 (27.8%) were poorly differentiated, 2 (3.7%) were sarcomatoid, and 4 (7.4%) did not have a histologic pattern reported. Fourteen (26.4%) patients were immunosuppressed; 9 had an organ transplant, 2 had chronic lymphocytic leukemia, 1 had non-Hodgkin lymphoma, and 2 patients were on immunosuppressive medication for ulcerative colitis and rheumatoid arthritis, respectively. A WLE was performed and SLNB attempted for all 54 lesions. The mean WLE margin was 1.3 cm. The tumor in the WLE specimen exhibited higher grade tumor differentiation compared with the diagnostic biopsy in 9 (17%) lesions: 6 graded initially as well differentiated were changed to moderate and 3 went from moderate to poor.

Although PNI and ALI were inconsistently reported, PNI was noted in 19 (35.2%) tumors and ALI in 5 (9.3%). Eleven (57.9%) tumors with PNI were poorly differentiated, 7 (36.8%) were moderately differentiated, and 1 (5.3%) was well differentiated. Three (60%) of the tumors with ALI were poorly differentiated, 2 (40%) were moderately differentiated. Four tumors with ALI also had PNI.

The SN was identified in 50 (94%) of 53 patients. Tracers failed to migrate in 1 failed SLNB, low radioactivity counts minimally elevated over background with no identifiable blue node were noted in 1, and no nodal tissue was identified by histological examination in the third failed SLNB. The average number of SNs identified per case was 3 (range 1-8). Six (11.3%) of the 53 patients had a positive SLNB, prior to retrospective reanalysis with more thorough tissue processing as below. Five had 1 positive node and 1 had 2 positive nodes, with ECE noted in 2 (33%) of the 6 positive SLNB cases. Immunohistochemical analysis was performed in 29 (58%) of 50 patients where SNs were identified. Of the 6 patients who had a positive SN, 3 had IHC performed. In 1 case, the SN was noted to be positive only on IHC. Five of the 6 patients with a positive SLNB underwent CLND. One patient was diagnosed with multiple comorbidities following SLNB, obviating CLND. Two (40%) of the 5 who underwent CLND had additional positive nodes (1/21 and 13/26 nodes, respectively).

Mean follow up time for the entire group was 25.5 months (range, 2-57 months). Local recurrence occurred in 5, with an average time of 11 months (range, 3-24 months). In 3, SCC invaded the central nervous system, causing death. Regional nodal recurrence occurred in 6 patients; 5 following a negative SLNB and 1 following a positive SLNB treated with CLND. Two of these patients first developed a local recurrence (2 and 4 months prior to nodal recurrence, respectively). On retrospective review of the SLNB specimens (as detailed below), 1 of these patients was found to have a positive SLNB. Because of this finding and because we did not want to underestimate the development of nodal disease in this high-risk population, we did not exclude patients from the study analysis if they had a clinical local recurrence prior to clinical nodal recurrence. Average time to nodal recurrence was 7.5 months (range, 2-22 months). Two patients developed distant metastasis. One had a failed SLNB with bone metastasis 17 months later. The other developed lung metastases 4 years after WLE and negative SLNB, however, in the interim had developed many other primary cutaneous SCCs.

Thus, in this patient cohort, there were 5 false-negative SLNB results. The false-negative rate was 45.5% (5 false negatives/[5 false negatives +6 true positives]), 95% CI, 21% to 72%. The false-omission rate (patients with a negative SLNB that failed in the nodal basin) was 11.4% (5 false negatives/[5 false negatives +39 true negatives]), 95% CI, 5% to 24%.

Overall, 11 (20.8%) patients had nodal disease identified by SLNB or palpable recurrence. Angiolymphatic invasion (Cohen d, 3.52; 95% CI, 1.83-5.21), perineural invasion (Cohen d, 0.81; 95% CI, 0.09-1.52), and clinical size (Cohen d, 0.83; 95% CI, 0.05-1.63) were associated with the presence of nodal disease. All patients with nodal disease were referred for adjuvant therapy; 1 declined. Two completed radiation to the nodal basin. Eight had radiation to the primary site and nodal basin, 2 of these 8 had concurrent chemotherapy, with carboplatin in 1 and cisplatin in the other.

The 5 original SLNB tissue blocks from patients with a negative SLNB and nodal recurrence in the negative basin were retrieved and processed with more thorough serial sectioning and IHC. On independent review by 2 pathologists, metastatic SCC was identified in deeper sections by both pathologists in 2 of 5 cases (40%). In 1, deeper sections revealed SCC evident on both H&E and IHC (**Figure 1** and **Figure 2**). In the other, SCC was only identified by IHC. The original H&E and IHC (performed in 4 cases) slides were confirmed negative by both pathologists. After reclassification of these 2 cases as positive, our adjusted false-negative rate was 27.3% (3 false negatives/[3 false negatives +8 true positives]), 95% CI, 10% to 57%. The adjusted false omission rate was 7.1% (3 false negatives/[3 false negatives +39 true negatives]), 95% CI, 2% to 19%.

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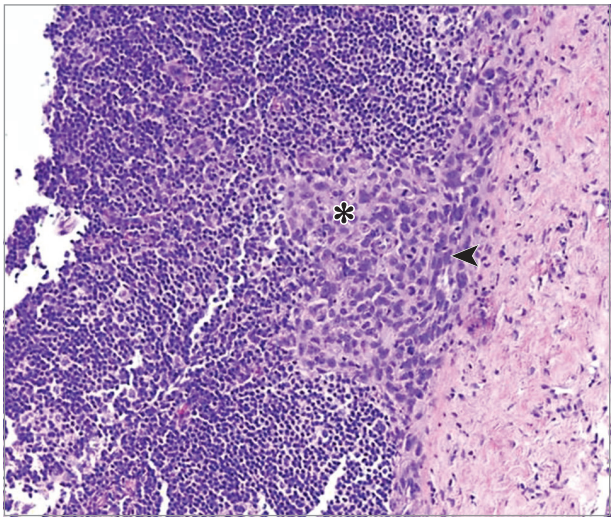
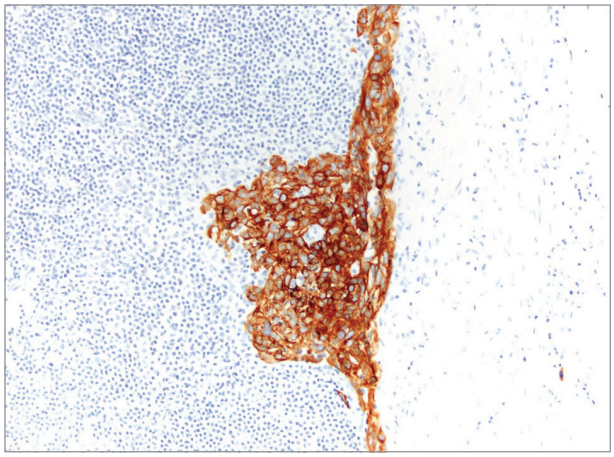
Figure 1. Histopathologic Image



Deeper section into the block demonstrates a focus of metastatic squamous cell carcinoma involving the subcapsular sinus (black arrowhead) and parenchyma (asterisk) of sentinel lymph node. Hematoxylin-eosin stain (original magification ×200).

Figure 2. Immunostain



Focus of metastatic squamous cell carcinoma in sentinel lymph node staining with pancytokeratin immunostain (original magnification ×100).

Sentinel lymph node biopsy after prior wide local excision, at least theoretically, may be less accurate owing to prior surgery at the primary site. In this cohort, 1 patient with recurrent SCC as an indication for mapping was found to have a positive SLNB. After reclassification of the SLNB status in 2 cases, as above, no patients with recurrent SCC as an indication for staging with SLNB had a nodal recurrence following negative SLNB.

Discussion

We present data on 53 patients with cutaneous SCC on the head and neck treated with WLE and SLNB, the largest single-institution cohort reported to date. Our results and previous data form a foundation and validate the need for rigorous prospective study of SLNB for cutaneous SCC, with potential to modify clinical practice. Our results confirm feasibility of SLNB for head and neck cutaneous SCC identifying a SN in 94% of cases with the combined use of radiocolloid, vital blue dye, and SPECT-CT. We uniquely demonstrate the critical importance of serial sectioning and IHC of the SLNB specimen for accurate diagnosis.

The data, including our own, pertaining to SLNB for cutaneous head and neck SCC is globally limited by heterogeneous risk factor reporting; inconsistent data, surgical details, and study design; relatively small numbers, limited follow-up, and most of the data are retrospective in nature.[9-22]

Several factors may lead to higher rates of nodal recurrence after a negative SLNB including: surgeon, pathologist, and nuclear medicine experience and/or technique; prior surgery in the area with scar tissue affecting migration of the tracers; accuracy of tracer injection sites; and specimen processing. The increased accuracy of SLNB on the head and neck for melanoma with the use of SPECT-CT is documented.[23] Our work underscores the importance of standardizing SLNB technique and histopathological tissue processing protocols for cutaneous SCC. Numerous studies document enhanced detection of small tumor deposits by use of comprehensive serial sectioning and IHC for melanoma.[24-30] Sentinel lymph node biopsy processing for SCC is limited by a paucity of data. One study[9] of SLNB for mucosal SCC utilizing IHC staining reported an approximately 10% higher detection rate of metastatic deposits in the SN with IHC compared with use of H&E alone. While the use of frozen sections for analysis of the SLNB for SCC guides proceeding to an immediate CLND, reliability data are absent with clinically significant consequences for false-positive and false-negative results, which both occur. Based on our experience, optimal histopathological evaluation of the SLNB for cutaneous SCC includes formalin-fixed, permanent section processing with serial sectioning with H&E and IHC staining.

A systematic literature review analyzing SLNB for cutaneous SCC on the head and neck was published in 2014. Eleven publications with 73 total patients met the authors' inclusion criteria (range 1-15 patients/report, median 5). The overall rate of SLNB positivity was 13.5%. The rate of regional nodal recurrence in the same basin following a negative SLNB was 4.76% (range 0%-33%).[31] A more rigorous multi-center prospective study of SLNB for high-risk cutaneous SCC on the head and neck involving 57 patients was published in 2015. Patients had at least 1 high-risk factor defined as tumor size larger than 2 cm, poorly differentiated histology, perineural invasion, lymphovascular invasion, invasion into the subcutaneous fat or thickness of more than 5mm, local recurrence, location on the ear or lip, immunosuppression, and SCC arising in a scar. Seven (12.3%) of 57 had a positive SLNB. The SLNB specimens were processed with formalin-fixed permanent sections stained with H&E and IHC in 55, with 2 processed with frozen sections because the SN was deemed suspicious for metastatic SCC intraoperatively. No nodal recurrences were reported following a negative SLNB; mean follow-up was 19.4

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months. One nodal recurrence occurred after a positive SLNB, another after a failed SLNB. The overall rate of nodal disease was 14% (7 positive SLNB, 1 nodal recurrence). Predictors of nodal disease were multiple high-risk factors (P = .008), PNI (P = .05), and ALI (P = .05).[32]

The lack of a cutaneous SCC National Tumor Registry impedes large retrospective multi institutional analysis of prognostic factors. Risk factors associated with a higher rate of local recurrence and metastases are currently defined based on low-moderate evidence and expert consensus.[7,33,34] We evaluated our data using effect size to aid in comparison of the relative size of effect of each NCCN high-risk feature with regard to the presence of nodal disease and found that presence of ALI, presence of PNI, and a large clinical size had a large effect on the development of nodal disease. The large width of the CIs around the estimates of the false-negative and false-omission rates, however, exposes the small sample size and demonstrates the variability of these estimates. Until higher level evidence is produced, our results, which are relatively consistent with the literature, suggest that utilization of the NCCN guidelines may facilitate appropriate patient selection for future study design and current consideration for SLNB.[7]

Limitations

Limitations of our study include a retrospective design associated with missing data of some variables of interest, relatively short follow-up including some patients lost to follow-up after the immediate postoperative period, and overall small numbers despite being the largest single institution report. The purpose of our study was to review our institutional experience utilizing SLNB for cutaneous SCC on the head and neck to provide a basis to optimize future prospective analyses over a long period of time with long-term follow-up. We included outcomes data, although not complete, for all patients to add to the current body of literature on the subject, acknowledging that, owing to the limited follow-up for some of our patients, the rates of recurrence and false-omission may be underestimates. Despite these limitations, our study provides unique data, particularly with regard to histologic processing of the SLNB specimens, and additional evidence to justify future investigation incorporating prospectively-collected, homogeneous, comprehensive data sets based on standardized treatment algorithms.

Conclusions

Rigorous study with optimal methodology is necessary to improve surgical and histopathologic protocols for SLNB for cutaneous SCC and to advance our understanding of what role SLNB may play with respect to improved staging for patients at high risk of nodal metastasis. Further work will be necessary to determine if early identification and intervention leads to improved outcomes for these patients.

ARTICLE INFORMATION

Accepted for Publication: June 3, 2016.

Published Online: July 20, 2016. doi:10.1001/jamaoto.2016.1927.

Author Contributions: Alison B. Durham had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Durham, Lowe, Malloy, Bradford, Johnson, McLean.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Durham, Lowe, Malloy, Chubb.
Critical revision of the manuscript for important intellectual content: Durham, Lowe, Malloy, McHugh, Bradford, Johnson, McLean.
Statistical analysis: Chubb.
Administrative, technical, or material support: Durham, McLean.
Study supervision: Lowe, Malloy, Bradford, Johnson, McLean.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Previous Presentation: This study was presented at the American Head & Neck Society Ninth International Conference on Head and Neck Cancer; July 20, 2016; Seattle, Washington.

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