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Utility of Head and Neck Cutaneous Squamous Cell Carcinoma Sentinel Node Biopsy: A Systematic Review

Mostafa M. Ahmed, MD¹, Brian A. Moore, MD², and Cecelia E. Schmalbach, MD³

Abstract

Objective. Sentinel lymph node biopsy (SLNB) is standard of care for melanoma, but its role in cutaneous squamous cell carcinoma (cSCC) has not been established. Study objectives include: (1) analyze the feasibility and reliability SLNB for head and neck (H&N) cSCC and (2) identify risk factors associated with a positive SLN.

Data Sources. MEDLINE, PubMed, Cochrane, and ASCO databases searches conducted (1946-2013).

Review Methods. Using the PRISM model, a comprehensive systematic review of H&N cSCC SLNB studies with associated recurrence rates was conducted. Dual-blinded data extraction identify primary outcomes (successful SLN harvest and false omission rate) and secondary outcomes (risk factors associated with a +SLN).

Results. Two hundred twenty-one articles were screened; 73 patients from 11 publications met inclusion criteria (3 case series; 8 prospective cohorts). Studies ranged from 1 to 15 patients (median 5). Median age was 74 years. Median follow-up was 21.5 months. Average tumor size was 3.09 cm. At least 1 SLN was identified in 100% of patients (median 2). Ten (13.5%) had a positive SLN; no additional metastatic nodes were identified in 9 patients receiving completion lymphadenectomy. Tumor diameter was not associated with SLN status (P = .09; 95% CI, –.27 to 3.02). Risk factors (tumor depth, perineural invasion, location, differentiation) were not consistently recorded. Three of 63 (4.76%) failed regionally following a negative SLNB.

Conclusion. H&N cSCC SLNB is feasible and reliable for staging, with a false omission rate of 4.7% mirroring melanoma. Prospective studies documenting high risk features are required to further define its role.

Keywords

sentinel node, cutaneous squamous cell carcinoma, skin cancer

Introduction

Cutaneous squamous cell carcinoma (cSCC) is the second most common skin cancer in the United States, accounting for approximately 700,000 new cases each year¹ and 25% of annual skin cancer deaths.²-⁴ While the majority of patients with cSCC have an overall favorable prognosis, a subset exhibit aggressive disease resulting in a dismal 25% 5-year and 16% 10-year survival rate.⁵ Ten percent of patients are recalcitrant to treatment and experience local recurrence, while an additional 5% develop metastatic disease. Ultimately, over 4000 patients die from cSCC each year.¹ The associated total direct cost of non-melanoma skin cancer treatment has surpassed $1.5 billion.⁶

Regional metastasis to cervical lymph nodes remains the most important prognostic factor dictating head and neck (H&N) cSCC recurrence rates and overall survival.⁵,⁷,⁸ Early and accurate identification of cervical lymph node metastasis is imperative because subsequent therapy, to include lymphadenectomy and adjuvant radiotherapy, is based upon this stage. Sentinel lymph node biopsy (SLNB) offers a minimally invasive, cost-effective means of accurately staging the neck while avoiding the morbidity associated with a formal neck dissection.⁹,¹⁰ Although it is considered standard of care for the work-up of high-risk
cutaneous melanoma patients, its role in the staging of cSCC has not been established.

To date, research into the application of cSCC SLNB is limited to small series. For this reason, we conducted a systematic review of the literature to determine the feasibility and reliability of SLNB for H&N cSCC. In an attempt to identify high-risk cSCC patients who may benefit from SLNB, the secondary objective of the study was to identify risk factors associated with a positive SLN.

Methods

Eligibility Criteria

The study protocol was developed a priori using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) process. All studies (retrospective, prospective, and randomized controlled trials) using SLNB for staging of H&N cSCC were considered eligible for inclusion if follow-up and recurrence rates were reported. Individuals who had undergone prior cSCC excision and/or radiation were included since this subset of patients are recognized as high risk and may potentially benefit from SLNB staging. There were no language restrictions.

Studies were excluded if they did not involve H&N primary sites; if the specific H&N outcomes could not be discerned from truncal and extremity outcomes; if the cSCC data could not be extrapolated from other cutaneous cancers such as Merkel cell carcinoma, adenocarcinoma, and melanoma; or if it was a repeat patient cohort. All cases of mucosal lip SCC were excluded since lesions in this area are considered an oral cavity subsite, warranting different staging and treatment; patients with lip SCC were only included if there was clear documentation of cutaneous as opposed to mucosal origin.

The primary study objective was to determine the reliability of SLNB for cSCC as demonstrated in the rate of false omission (rate of regional recurrence in a previously mapped nodal basin found to be negative for occult disease on SLNB). Therefore, cross-sectional studies without patient follow-up, investigations only reporting on positive sentinel lymph node patients, and patient cases with less than 5 months follow-up were excluded. In an effort to be inclusive, corresponding authors were contacted in an attempt to obtain missing data prior to excluding the article from study.

Information Sources and Search Strategies

With the assistance of an information specialist, a computerized Ovid/Medline database search was conducted from January 1, 1946, through November 19, 2012, using the subject headings of January 1, 1946, through November 19, 2012, using the targeted Ovid/Medline database search was conducted from with the assistance of an information specialist, a computerized database search was conducted from January 1, 1946, through November 19, 2012, using the subject headings of January 1, 1946, through November 19, 2012, using the targeted Ovid/Medline database search was conducted from

The aforementioned comprehensive searches were reviewed by 2 investigators (MA and CS). Abstracts meeting inclusion/exclusion criteria and abstracts in which more information was required were pulled for complete article review, which was conducted by both authors in a blinded fashion. Discrepancies in article inclusion were resolved in discussion between the authors.

Data Collection and Extraction

Prior to data extraction, a Microsoft Excel H&N cSCC data collection sheet was constructed. Study design information included: lead author, institution/country, study dates, study type (prospective, retrospective, randomized control trial), and inclusion/exclusion criteria. Patient demographics included: number of patients, age (mean, median, range), and gender. The following tumor characteristics were collected: high-risk histologic features, tumor location (ear, scalp, face, neck, nose, lip, temple/brow, occiput), tumor diameter in centimeters, tumor depth of invasion, and if it was a recurrent lesion. Details on the SLN technique were recorded to include: imaging (none, preoperative lymphoscintigraphy, or SPECT-CT), application of radioactive colloid (type and amount), use of blue dye (isosulfan, methylene blue, none), use of facial nerve monitoring, and use of frozen section for SLN analysis. SLNB complications were recorded to include: cranial nerve injury (7, 10, 11, 12), internal jugular vein or carotid artery (internal, external, common) injury, postoperative infection, seroma, hematoma, and wound dehiscence. The data collection sheet was piloted among the authors for the first 5 studies of review in order to ensure that the data collection sheet was comprehensive and that information was collected in a standardized fashion.

Outcome measures of interest included: number of patients successfully mapped (defined as harvesting at least 1 SLN), number of SLNs per patient, number of positive SLN per patient, and number of echelons mapped per patient. An echelon was defined as having at least 1 SLN harvested from the nodal basin (ie, level 1, 2, 3, 4, 5, 6, or parotid). The number of patients who underwent completion neck dissection following SLN procedure was collected, along with the number of additional positive nodes on final pathology. The length of follow-up was recorded in months. Disease-free survival rate, overall survival rate, and recurrence rate (local, regional, distant, locoregional, local and distant, regional and distant) were collected. Regional recurrence within a previously mapped negative SLNB echelon was noted and considered a SLN failure.
Validity Assessment

Reviewers independently assessed the quality of the selected studies using the revised and validated Methodological Items for Non-Randomized Studies (MINORS). For our noncomparison systematic review, 8 methodological items were assessed for a potential maximal score of 16. Table 1 summarizes the items that were scored as 0 (not reported), 1 (inadequately reported), and 2 (reported and adequate). Articles were not excluded based on the MINORS quality assessment. The information was utilized to estimate the study quality and to identify areas of improvement for future prospective SLNB studies.

Table 1. MINORS assessment of non-randomized studies.a

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aScoring: 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). Ideal score is 16 for noncomparative studies.

Statistical Analysis

Primary and secondary outcome measures were defined a priori. Feasibility included the proportion of patients successfully mapped. Comparing SLN failure rates across studies can be problematic due to inconsistencies in the definition of a false negative24,25 and warrants clarification. The False Negative Rate (FNR) = false negative/(false negative + true positives); it is the probability of obtaining a negative SLN when metastatic disease is present. Negative predictive value (NPV) = true positive/(true positive + false negative). The rate of false omission (RFO) represents the proportion of SLN negative patients with regional recurrence in the setting of local control. The false rate of omission = false negative rate/(false negative + true negative rates) and is equivalent to 1-NPV.

The small cohort size of each study precluded meaningful Cochrane Q calculation and formal meta-analysis. All studies meeting inclusion criteria for this review provided individual patient data, demonstrated similar inclusion/exclusion criteria, and were designed specifically to determine feasibility of SLNB in cSSC. Therefore, individual patient data were pooled and patients were divided into 2 groups based on SLN status: positive (+SLN) and negative (–SLN). Each cohort was defined using descriptive statistics.

Risk factors associated with a +SLN were calculated using a 2-tailed Student t-test for continuous variables and Fisher’s exact test for dichotomous variables (IBM SPSS Statistics 21.0, New York). P < .05 was deemed statistically significant and 95% confidence intervals (CI) were calculated. Continuous covariates included patient age and tumor size as measure in diameter. Implementing the recently developed AJCC cSSC staging guidelines,15 patients were also categorized by tumor size (≤ 2 cm and >2 cm). The RFO was recalculated for each individual study and for the entire 73 patient cohort.

Results

Study Selection and Characteristics

The initial computerized search strategy and associated hand search generated 221 articles (Figure 1). One hundred seventy abstracts were screened after removing duplicate articles; 132 abstracts did not meet inclusion/exclusion criteria. Thirty-eight articles underwent full manuscript review. Eighty-seven articles did not meet inclusion/exclusion criteria at the data extraction level for reasons summarized in Figure 1. Eleven studies from 5 countries met inclusion/exclusion criteria for analysis in this systematic review (Table 2).8,12-21

Three were identified as case series8,19,20 and 8 as prospective cohort studies12-18,21; there were no retrospective or randomized trials identified.

Study details for each article included in this systematic review are provided in Table 2. The majority of the studies offered SLNB to H&N cSSC patients with high-risk features based on tumor diameter, depth of invasion, perineural invasion, and poorly differentiated histology. Ten of the studies reported SLNB technique: all utilized lymphoscintigraphy with a radioactive nuclear colloid12-16,18,21 and 5 utilized blue dye intraoperatively as a complementary means for node identification.8,13,15,18,19 Specific technique details such as timing and volume of tracer were not routinely reported.

Studies ranged from 2 to 15 patients with an overall median of 5 patients. The median age was 74 years (range, 37-93 years). Gender was reported in 8 articles: overall 33 (84.6%) male and 6 (15.4%) female. The average tumor size was 3.09 cm in diameter (range, 0.5-12 cm). Median follow-up was 21.5 months (range, 5-59 months).
At least 1 SLN was identified in 100% of patients (median 2; range, 1-5). Six of the 11 studies (82%) identified +SLN patients. Overall, 10 of 73 (13.7%) of patients were found to have a +SLN. Individual patient data for the +SLN subset is summarized in Table 3. The most common primary tumor location in the setting of a +SLN was the face (n = 5), followed by cheek (n = 2), scalp (n = 1), and auricle.
The remaining 63 patients (86.3%) with a +SLNB were followed clinically for a median of 21.5 months (range, 5-69 months). Three of 63 (4.76%) developed regionally metastasis in a previously mapped nodal basin (Table 4). Therefore, the regional failure rate in the setting of a +SLNB (rate of false omission) was 4.76%. The 3 failures did not demonstrate perineural invasion; however, patient 1 presented with a recurrent lesion that had previously been excised and irradiated. Using the pooled patient data, cSCC SLNB carried a 77% sensitivity, 100% specificity, and 95.2% negative predictive value (NPV).

Discussion

The feasibility and reliability of H&N cSCC SLNB for accurate staging is imperative because regional lymph node metastasis is the most important prognostic factor for this patient population. It is also important to recognize that H&N cutaneous cancers drain first via the superficial lymphatic system to superficial nodes in the face and parotid bed, which are not included in a traditional neck dissection. The SLNB technique provides a means to identify these superficial nodes, yielding important prognostic information to guide both physician and patient in subsequent treatment options. It helps to identify the small subset of patients harboring occult nodal disease who may benefit from a completion neck dissection and/or adjuvant radiation. On a broader perspective, accurate staging allows for identification of a homogeneous population of patients who can then be enrolled and meaningfully stratified in clinical trials.

This systematic review encompasses a 73 patient cohort, which marks the largest study to date investigating the role of H&N SLNB for cSCC. This investigation differs from previous reviews in that it is H&N specific (excluding...
trunk, extremity, eyelid, and anogenital SCC), includes all languages, and augments the published literature with hand searches of the grey literature (ie, abstracts, posters). This comprehensive review ultimately included 11 different studies from 5 countries. Heterogeneity among the included articles did not compromise external validity as evident by the fact that the overall 10% rate of occult nodal metastasis, as well as individual study rates (range, 0%-40%) were all consistent with that reported in the literature.28

This review successfully demonstrated feasibility of the SLNB technique within the setting of H&N cSCC; 100% of patients had at least 1 SLN successfully harvested. No deaths, major complications, or minor complications related to the procedure were reported. However, it should be noted that only 1 study in the review specifically mentioned complications.16 Large, prospective melanoma studies have successfully demonstrated that in experienced hands, this technique can be applied with minimal morbidity, even in the parotid nodal basin.9,25,29,30 Though one can extrapolate minimal risk in the setting of cSCC histology, future prospective investigations warrant dedicated reporting of complications to include death, wound infection, hematoma, seroma, damage to cranial nerves, and damage to great vessels.

The 4.76% rate of false omission reported in this systematic review is promising because it mirrors that of trunk, extremity, and H&N melanoma9,25,30 where the procedure is already considered standard of care and incorporated into the National Comprehensive Network Guidelines.11 Given the associated 95.2% NPV, we conclude that SLNB is a reliable technique when applied in the setting of H&N cSCC. Though the impact on tumor recurrence and overall survival remains to be determined, we advocate SLNB for the staging of H&N cSCC patients deemed at risk for recurrence.

This review highlights the potential limitation of SLNB in the setting of previously treated cSCC. One of the 3 patients who failed regionally in the setting of a SLNB presented with a recurrent scalp tumor, which had previously been resected and irradiated.8 Both interventions potentially disrupt the lymphatic drainage and limit the ability for SLNB to identify the at risk nodal basin. Therefore, surgeons should proceed with caution when counseling patients on the use of SLNB in the setting of previously biopsied or treated disease. The current NCCN guidelines do not include SLNB in the treatment algorithm for cSCC. However, the melanoma working group has suggested that surgeons can still offer SLNB to previously treated patients, but they must do so with the clear understanding that the reliability of the technique remains to be determined in this setting.11

Unfortunately the small (n = 10) cohort of +SLN patients precluded the ability to identify high-risk features corresponding to a +SLN. In order to truly discern which cSCC patients would benefit from the procedure, a prospective, multi-institutional trial is required. The heterogeneity and inconsistent reporting of previous smaller studies (Table 1) serves to highlight areas of improvement. In order to successfully conduct a meaningful trial, investigators will need to consistently report patient risk factors such as tumor diameter, depth of invasion, Clark’s level of invasion, specific tumor location, perineural invasion, histologic differentiation, immunosuppression, and recurrent disease. It will also be imperative to exclude the mucosal lip because it is an oral cavity subsite and should not be included in dedicated cutaneous studies. Patient selection must be clearly outlined and should incorporate the high-risk factors recently defined in the new cSCC AJCC staging system specific to cSCC32; depth of invasion >2 mm, Clark level ≥ IV, perineural invasion, primary site involving the ear or non-mucosal lip, and poorly/undifferentiated histology. Information on adjuvant therapy to include radiation to the primary and/or draining nodal basins must be clearly documented for each patient given the potential impact on disease free and overall survival.

The SLNB technique warrants standardization. As demonstrated in Table 2, intraoperative technique varied from radionuclide colloid alone to combined colloid with intraoperative blue dye. However, the technique was often not disclosed. Given the improved rate of melanoma SLN identification from 87% with blue dye alone to 99% with combined dye and colloid (P < .0001),33 future H&N cSCC SLNB trials must incorporate both modalities. Similarly, Vermeer et al identified an additional 2.6 SLN per patient and a 55% rate of altered surgical approach when fused SPECT-CT was added to traditional lymphoscintigraphy.34 For this reason, preoperative work-up would ideally incorporate radionuclide scanning with SPECT-CT. Lastly, the surgical margins and associated adjuvant therapy for each patient would be informative as both can potentially impact recurrence rates.

<table>
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Abbreviations: NS, not specified; SLN, sentinel lymph node; XRT, radiotherapy.

*High-risk factors: (1) Clark level ≥ 5, (2) depth > 2 mm, (3) perineural invasion, (4) location (ear; lip), (5) differentiation (poor; undifferentiated).

Table 4. Characteristics of patients contributing to rate of false omission.
While the findings of a 4.7% false omission rate and associated 95% NPV is promising, the publication bias inherent to a systematic review warrants mention. Negative outcomes often go unreported and are unavailable in the published literature. In an attempt to minimize this bias, we augmented the traditional database searches with grey data found in AHNS, ACS, ASCO, and ADA abstracts. Bibliography cross-referencing of all 38 screened manuscripts was also completed by hand. An additional weakness is that data analysis is limited due to inadequate and inconsistent reporting of covariates. Despite contacting 3 different authors, several well-designed studies did not meet inclusion criteria due to lack of information. This review was unable to take into account surgeon volume/experience, which is a known factor in SLNB success.25,30 Lastly, the mean patient follow-up of 21 months is respectable, but should not be considered long-term. One patient had only 2 months follow-up and was eliminated from the analysis; similarly 1 case study had only 3 months follow-up and was excluded.35 Longer follow-up may identify additional patients who fail regionally in the setting of a SLNB, thus increasing the rate of false omission. However, at the present time, H&N cSCC studies with longer follow-up have not been published.

Conclusion

This systematic review is the largest to date and successfully demonstrates that SLNB is feasible and reliable for staging H&N cSCC patients. One hundred percent of H&N cSCC patients underwent successful SLNB without significant morbidity. In all, 4.76% of patients experienced regional recurrence in a previously mapped negative nodal basin. This false omission rate mirrors that of H&N melanoma where SNB is already considered standard of care. This systematic review also serves to highlight the inconsistencies in cSCC SLNB reporting. Currently SLNB is a staging modality to assess regional disease. In order to fully elucidate risk factors for occult metastasis and which patients may benefit from the staging procedure, prospective, multi-institutional trials are required. Variables related to radiographic work-up, high-risk features, SLNB technique, and treatment must be standardized and diligently documented in order to successfully conduct a meaningful trial. Similar trials will be required to answer additional SLNB questions related to impact on survival, therapeutic implications, and cost-benefit ratio.

Acknowledgments

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Author Contributions

Mostafa M. Ahmed, substantial contributions to acquisition of data, revising it critically for important intellectual content, and final approval of the version to be published; Brian A. Moore, substantial contributions to analysis and interpretation of data, revising it critically for important intellectual content, and final approval of the version to be published; Cecelia E. Schmalbach, substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; and final approval of the version to be published.

Disclosures

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