Staging for Cutaneous Squamous Cell Carcinoma as a Predictor of Sentinel Lymph Node Biopsy Results
Meta-analysis of American Joint Committee on Cancer Criteria and a Proposed Alternative System

Adam R. Schmitt, BA; Jerry D. Brewer, MD; Jeremy S. Bordeaux, MD, MPH; Christian L. Baum, MD

IMPORTANCE The appropriate clinical setting for the application of sentinel lymph node biopsy (SLNB) in the management of cutaneous squamous cell carcinoma (cSCC) is not well characterized. Numerous case reports and case series examine SLNB findings in patients who were considered to have high-risk cSCC, but no randomized clinical trials have been performed.

OBJECTIVE To analyze which stages in the American Joint Committee on Cancer (AJCC) criteria and a recently proposed alternative staging system are most closely associated with positive SLNB findings in nonanogenital cSCC.

DESIGN, SETTING, AND PARTICIPANTS Medical literature review and case data extraction from private and institutional practices to identify patients with nonanogenital cSCC who underwent SLNB. Patients were eligible if sufficient tumor characteristics were available to classify tumors according to AJCC staging criteria and a proposed alternative staging system. One hundred thirty patients had sufficient data for AJCC staging, whereas 117 had sufficient data for the alternative system.

EXPOSURE Nonanogenital cSCC and SLNB.

MAIN OUTCOMES AND MEASURES Positive SLNB findings by cSCC stage, quantified as the number and percentage of positive nodes.

RESULTS A positive SLN was identified in 12.3% of all patients. All cSCCs with positive SLNs were greater than 2 cm in diameter. The AJCC criteria identified positive SLNB findings in 0 of 9 T1 lesions (0%), 13 of 116 T2 lesions (11.2%), and 3 of 5 T4 lesions (60.0%). No T3 lesions were identified. The alternative staging system identified positive SNLB findings in 0 of 9 T1 lesions (0%), 6 of 85 T2a lesions (7.1%), 5 of 17 T2b lesions (29.4%), and 3 of 6 T3 lesions (50.0%). Rates of positive SLNB findings in patients with T2b lesions were statistically higher than those with T2a lesions ($P = .02$, Fisher exact test) in the alternative staging system.

CONCLUSIONS AND RELEVANCE Our findings suggest that most cSCCs associated with positive SLNB findings occur in T2 lesions (in both staging systems) that are greater than 2 cm in diameter. The alternative staging system appears to more precisely delineate high-risk lesions in the T2b category that may warrant consideration of SLNB. Future prospective studies are necessary to validate the relationship between tumor stage and positive SLNB findings and to identify the optimal staging system.
nonmelanoma skin cancer is the most common cancer worldwide, with the incidence continuing to rise. An estimated 3.5 million nonmelanoma skin cancers are diagnosed annually in the US population, with 75% occurring on sun-exposed areas of the head and neck. Basal cell carcinoma accounts for approximately 80% of nonmelanoma skin cancers in the United States and United Kingdom, and squamous cell carcinoma (SCC) accounts for most of the remaining 20%. The incidence of cutaneous SCC (cSCC) varies widely by geographic location, with rates increasing at lower latitudes. A recent report estimates that as many as 3932 to 8791 deaths resulted from cSCC in 2012. Still, cSCC is often curable, especially when detected at an early stage.

The American Joint Committee on Cancer (AJCC) developed the seventh edition of the AJCC Cancer Staging Manual (AJCC-7) to reflect data demonstrating the prognostic value of various risk factors. Changes include the elimination of the 5-cm threshold to distinguish T2 lesions from T3 lesions because this cutoff point has no proven prognostic value. The 2-cm cutoff continues to differentiate T1 from T2 lesions, but the presence of 2 or more of the following high-risk features increases the T stage independently of tumor size: differentiation (poorly differentiated or undifferentiated), primary anatomical site on the ear or the non–hair-bearing lip, thickness of greater than 2 mm, Clark level of at least IV, and perineural invasion (Table 1). The nodal staging has been revised to reflect evidence that survival decreases with increased nodal size and with the number of involved nodes. A recent publication examined outcomes data related to the AJCC-7 criteria and found that most poor outcomes occurred in T2 lesions. Through elegant modeling, Jambusaria-Pahlajani et al have proposed an alternative staging system that eliminates the T4 designation owing to its extreme rarity but distinguishes between T2a and T2b lesions and appears to offer more precise prognostic data (Table 2). Sentinel lymph node biopsy (SLNB) is used to detect micrometastases in disease with clinically negative nodes. The procedure has been shown to be a safe and effective tool for guiding treatment and determining prognosis in melanoma and breast cancer. Wagner and colleagues found that SLN histological characterization may be the most important negative predictor of early recurrence and survival in AJCC stages I and II melanoma. They also reported a false-negative rate of 4.5% for SLN staging. Sentinel lymph node biopsy is used by most surgeons and major cancer centers as the preferred method of axillary node staging in breast cancer and is the means of axillary nodal assessment recommended by the American Society of Clinical Oncology and the National Comprehensive Cancer Network.

Although no randomized clinical trials have been performed yet, numerous case reports and case series examine the use of SLNB in patients who were considered to have high-risk cSCC. The purpose of this study was to analyze which stages in the AJCC-7 criteria and the alternative staging system are most closely associated with positive SLNB findings.

### Methods

We conducted a literature review of SLNBs performed for cSCC. We searched the MEDLINE database for articles published through November 1, 2012, using the following keywords: squamous or nonmelanoma AND cutaneous or skin AND sentinel or lymphoscintigraphy. References within cited articles were also reviewed to identify additional studies that met the inclusion criteria. We included only those publications involving humans that were available in English. Articles were excluded if the cSCC data could not be separated from data from other tumors, such as Merkel cell carcinoma, melanoma, or oral SCC.

Data were extracted for patients with cSCC who underwent SLNB. The following data were collected when available: age, sex, anatomical location of the primary SCC, clinical diameter, depth, Clark level, perineural invasion, differentiation, and SLNB results. Based on these data, we staged each case according to the AJCC-7 criteria and the alternative staging system. Tumors without sufficient information for staging, cases of anogenital cSCC, and cases in which an SLN could not be identified were excluded from this study. We included reports in which at least a T stage could be determined according to the AJCC-7 TNM and the alternative staging systems.

### Results

The literature search yielded 138 articles, of which 19 reports of SLNB for nonanogenital cSCC met the inclusion criteria. Thirteen of these reports were case series and 6 were case reports with sufficient information to include 130 patients in our review. A positive SLN was identified in 16 patients (12.3%) (Table 3).
AJCC-7 Staging System
Under the AJCC-7 criteria, 13 of 116 SLNs (11.2%) were positive in patients with T2 tumors, as were 3 of 5 (60.0%) in patients with T4 tumors (Table 4). All primary cSCCs with positive SLNs were greater than 2 cm in diameter. Of the 116 T2 tumors, 109 were greater than 2 cm in diameter, and all 13 positive SLNs in the T2 group were found among these 109 patients. Three false-negative SLNB findings—corresponding with a false-negative probability of 2.6% (3 of 114)—were reported, and they were associated with primary tumor diameters of 1.0, 3.5, and 5.0 cm.

Alternative Staging System
We evaluated the same 130 cases identified for the AJCC staging analysis in the context of the alternative staging system. Owing to differences in the high-risk criteria between the staging systems, only 117 cases had sufficient data to undergo staging (Table 4). Fourteen cases overall (11.9%) had positive SLNB findings. No positive SLNs were identified in the 9 T1 lesions. The proportions of positive SLNB findings were 6 of 85 T2a lesions (7.1%), 5 of 17 T2b lesions (29.4%), and 3 of 6 T3 lesions (50.0%). The difference in the proportions of positive SLNB findings between the T2a and T2b cases was statistically significant (P = .02, Fisher exact test).

Discussion
Our findings showed that 12.3% of patients who were considered to have high-risk cSCC had microscopic nodal metastases detected by SLNB. Although the term high risk is relatively ambiguous, this cohort of patients appears to fit that label when published metastatic rates of 4% to 5% for all patients with cSCC are considered.20-23 Most of the tumors in the present study were categorized as T2 lesions in the AJCC and alternative staging systems. Although T3 and T4 lesions had a high rate of positive SLNB findings, such cases are extremely rare. Therefore, efforts to identify appropriate patients for consideration of SLNB should probably focus on the T2 category. If this supposition is true, should all T2 lesions be considered for SLNB?

Previous studies have attempted to define high-risk features of cSCC that are associated with recurrence and metastasis. Among these factors are tumor diameter,10,12,32,34-36 tumor thickness or Clark level,10,12,34,35 localization at the ear or lip,10,12,33 host immunosuppression,10,38,39 perineural invasion,10,12,34,35,40 and histological differentiation.10,12,35,37 The AJCC-7 staging criteria define high-risk features as the lack of histological differentiation (poorly differentiated or undifferentiated), a primary anatomical site on the ear or the non-hair-bearing lip, thickness greater than 2 mm, Clark level of at least IV, and perineural involvement (Table 1).13 The presence of any 2 of these criteria is sufficient to assign a T2 stage regardless of tumor diameter. In the present data set, no positive SLNB finding was identified in T2 lesions less than 2 cm in diameter, although the sample size was relatively small.
Pahlajani et al appears to stratify the risk of T2 tumors more well-known risk factor for metastatic disease. 2 cm in diameter also measured thicker than 4 mm, another they pointed out, however, that 60% of lesions smaller than in their study population had primary lesions larger than 2 cm. SCC metastasis, although none have examined the risk demonstrated that the 2-cm cutoff is an independent risk factor for of positive SLNB findings. Of course, any SCC has the potential to warrant consideration of SLNB.41-43 then our data suggest that T2 AJCC lesions that are at least 2 cm in diameter may also warrant consideration of SLNB. Prior studies have demonstrated that the 2-cm cutoff is an independent risk factor for SCC metastasis, although none have examined the risk of positive SLNB findings. Of course, any SCC has the potential to metastasize regardless of its size. Vaness et al reported that only 30% of 266 patients with metastatic disease in their study population had primary lesions larger than 2 cm. They pointed out, however, that 60% of lesions smaller than 2 cm in diameter also measured thicker than 4 mm, another well-known risk factor for metastatic disease.

The alternative staging system proposed by Jambusaria-Pahlajani et al44 appears to stratify the risk of T2 tumors more accurately with regard to local recurrence, nodal metastasis, and disease-specific death. However, no prior data on the risk for positive SLNB findings exist. The high-risk factors that Jambusaria-Pahlajani et al44 have identified include tumor diameter greater than 2 cm, poorly differentiated histological characteristics, perineural invasion, and tumor invasion beyond the subcutaneous fat (excluding bone invasion) (Table 2). The rate of positive SLNB findings among all T2 tumors staged by their alternative system was similar to the rate of the larger cohort of 130 cases undergoing staging by AJCC-7 criteria (10.8% vs 11.2%, respectively). As with the AJCC-7 system, no T1 lesion in the alternative staging system had a positive SLNB. At the other end of the spectrum, T3 lesions, although rare, had a 50.0% rate of nodal positivity. Although T2a lesions accounted for most cases, only 6 of 85 (7.1%) had a positive SLNB finding. Meanwhile, the T2b lesions accounted for nearly as many positive SLNB findings but with 80% fewer cases (5 of 17). This rather robust stratification of risk between T2a and T2b lesions is also apparent in the outcomes data published by Jambusaria-Pahlajani et al.44 Furthermore, if we use the 10% risk threshold for SLNB as is applied with melanoma,41,42,47 these data suggest that T2b but not T2a tumors may warrant consideration of SLNB. Future prospective studies may help clarify the distinction between these subsets.

Although SLNB effectively detects occult metastasis, whether it will improve survival in patients with high-risk cSCC is not known. Cutaneous SCC may lend itself particularly well to SLNB because of its predictable metastatic pattern. Most metastases—an estimated 80%—spread first to a single regional lymph node.13,48,49 After metastasizing to nodes, cSCC may spread to the lungs, liver, brain, skin, or bone.13,48 Early detection of micrometastases through SLNB may reduce disease-related morbidity and mortality and may avoid the need for more invasive procedures, such as elective neck dissection, for determining nodal metastasis status. Sentinel lymph node biopsy may also be helpful in guiding tumor staging, the choice of further treatment vs observation, and prognosis.

Sentinel lymph node biopsy has been shown to be safe, minimally invasive, and effective in identifying SLNs in patients with cSCC.26,50,51 In a systematic review of the English-language medical literature, Ross and Schmults50 found that complications are rare, typically mild, and localized and that reported complications are usually limited to hematoma, seroma, cutaneous lymphatic fistula, wound infection, and dehiscence. An SLN could be found in 82 of 85 nonanogenital cases (96%), with 1 false-negative finding (1 of 20 [5%]) reported. The authors of the original report attributed this false-negative finding to a combination of the complex lymphatic drainage in the head and neck region and altered lymphatic drainage owing to the patient’s previous surgical treatment.26 Three of the 114 negative SLNB findings (2.6%) included in our study had false-negative results. One of these patients was described originally by Wagner et al26 and cited by Ross and Schmults50 in their review. The finding in another case was presumed by Sahn and Lang52 to be false-negative because the patient had a palpable lymph node just 6 months after a negative SLNB finding. No lymphadenectomy was performed, but metastatic disease was confirmed by fine-needle aspiration biopsy findings.52 The final patient with false-negative results included here underwent neck dissection after the negative SLNB results and was found to have metastatic disease.30 The primary tumor diameters in these false-negative SLNB findings were 5.0, 3.5, and 1.0 cm, respectively.

Regardless of whether SLNB is performed, long-term follow-up is advisable for patients considered to have high-risk tumors; most studies have a follow-up of less than 5 years, which may not be sufficient to detect the true rates of recurrence and metastasis.10,53 Further studies are required to define the role of SLNB in the management of high-risk cSCC and in determining the prognostic value of various risk factors. The proposed alternative staging system appears to be more pre-

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### Table 4. SLN+ by T Stage in Patients With Nonanogenital cSCC in 2 Staging Systems

<table>
<thead>
<tr>
<th>T Stage</th>
<th>No. of SLN+ Tumors/Total No. of Tumors (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC staging system**</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>0/9</td>
</tr>
<tr>
<td>T2</td>
<td>13/116 (11.2)</td>
</tr>
<tr>
<td>T3</td>
<td>0/0</td>
</tr>
<tr>
<td>T4</td>
<td>3/5 (60.0)</td>
</tr>
<tr>
<td>Alternative staging system***</td>
<td></td>
</tr>
<tr>
<td>T0</td>
<td>Not included</td>
</tr>
<tr>
<td>T1</td>
<td>0/9</td>
</tr>
<tr>
<td>T2a</td>
<td>6/85 (7.1)</td>
</tr>
<tr>
<td>T2b</td>
<td>5/17 (29.4)</td>
</tr>
<tr>
<td>T3</td>
<td>3/6 (50.0)</td>
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Abbreviations: AJCC, American Joint Committee on Cancer; cSCC, cutaneous squamous cell carcinoma; SLN+, positive sentinel lymph node.

* Described in Table 1; adapted from the seventh edition of the AJCC staging manual.13

** Described in Table 2; adapted from Jambusaria-Pahlajani et al14

(n = 7). Among the T2 lesions greater than 2 cm in diameter, 13 of 109 (11.9%) had a positive SLNB finding. These results suggest that the T2 category in the AJCC-7 system may represent a heterogeneous population with a risk stratification that may lie at the 2-cm cutoff. Future prospective studies are necessary to investigate this potential. If we use melanoma as a model of care wherein a 10% risk threshold is generally sufficient to warrant consideration of SLNB,41-43 then our data suggest that T2 AJCC lesions that are at least 2 cm in diameter may also warrant consideration of SLNB. Prior studies have demonstrated that the 2-cm cutoff is an independent risk factor for SCC metastasis, although none have examined the risk of positive SLNB findings. Of course, any SCC has the potential to metastasize regardless of its size. Veness et al reported that only 30% of 266 patients with metastatic disease in their study population had primary lesions larger than 2 cm. They pointed out, however, that 60% of lesions smaller than 2 cm in diameter also measured thicker than 4 mm, another well-known risk factor for metastatic disease.

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cise than the AJCC-7 staging system for identifying which patients may have sufficiently high-risk tumors to warrant consideration of SLNB.

Conclusions

The data are incomplete about the utility of SLNB in patients with cSCC, and published studies are limited to case series and case reports. Findings thus far, however, suggest that SLNB accurately identifies SLNs and is well tolerated. Sentinel lymph node biopsy can provide early detection of subclinical nodal metastases, although the survival benefit is not yet known. Although no consensus has formed about which characteristics warrant the use of this procedure in patients with cSCC, our findings suggest that T2 tumors that are larger than 2 cm in the AJCC-7 criteria and T2b tumors in the alternative staging system may be considered for SLNB given their associated rates of positive SLNB findings of 11.9% and 29.4%, respectively. Although the alternative staging system appears to more precisely stratify the risk of T2 lesions, future prospective studies are necessary to validate the relationship between tumor stage and positive SLNB findings and to identify the optimal staging system.

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Study concept and design: Brewer, Baum.

Acquisition of data: Schmitt, Baum.

Analysis and interpretation of data: Schmitt, Bordeaux, Baum.

Drafting of the manuscript: Schmitt, Baum.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Schmitt.

Study supervision: Brewer, Bordeaux, Baum.

Conflict of Interest Disclosures: None reported.

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REFERENCES


George Papanicolaou; 10 years later, she married Arthur Allen, another physician. During her career, she became an expert in tropical medicine and in melanocytic nevi. Because she was affected by familial polyposis, in 1956 she experienced an untimely death from colon cancer, before her eponym was popular. Only after her death, in fact, did the discussion about the term and the real entity of Spitz nevus or juvenile melanoma start.

Author Affiliation: Università degli Studi di Milano, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milano, Italy.

Corresponding Author: Gianluca Nazzaro, MD, Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milano Via Pace, 9 Milano, Italy (Gianluca.nazzaro@gmail.com).