Nodal staging of high-risk cutaneous squamous cell carcinoma

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Background: While progress has been made in defining the clinical and histopathologic features of high-risk cutaneous squamous cell carcinoma (HRcSCC), optimal staging guidelines remain elusive.

Objective: We seek to guide clinical practice regarding nodal staging options for patients with HRcSCC via review of evolving definitions of HRcSCC, nodal staging options, and how nodal staging may impact treatment and affect outcomes.

Methods: This was a retrospective review of the published peer-reviewed literature regarding risk stratification, nodal staging, and treatment and outcomes for patients with HRcSCC via PubMed.

Results: For patients without clinical lymphadenopathy, based on literature from head and neck SCC, preoperative nodal staging with ultrasonography may be more useful than computed tomography or magnetic resonance imaging. Early nodal disease is usually curable, and therefore obtaining a sentinel lymph node biopsy specimen may be considered in those with negative imaging while we await studies of nodal staging outcomes.

Limitations: More data are needed to validate the relationships between primary tumor stage and sentinel lymph node biopsy status and to determine if early detection of nodal disease impacts survival for patients with HRcSCC.

Conclusion: It is reasonable to consider nodal staging for patients with HRcSCC (Brigham and Women's Hospital stage T2b and T3) in the absence of clinically palpable lymphadenopathy via radiographic imaging and, if negative, sentinel lymph node biopsy. (J Am Acad Dermatol 2019;81:548-57.)

Key words: nodal staging; sentinel lymph node biopsy; squamous cell carcinoma.

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While the treatment outcomes and prognosis for the majority of patients diagnosed with cutaneous squamous cell carcinoma (cSCC) are excellent, a small but increasingly well-defined subset of tumors are at substantial risk for recurrence and metastasis.[1] Brantsch et al[1] and Schmults et al[2] have estimated a 4% risk of nodal metastasis for cSCC in single-hospital cohort studies of German and U.S. patients, respectively. Robust data from Australia place this risk at approximately 5% to 6%.[3,4]

Much work has been done to define the clinical and histopathologic features of the subset of patients with cSCC who are at high risk for nodal metastasis, and tumor staging systems have been developed to predict the risk of nodal metastasis and death.[1,5-8] Classic high-risk features for tumor recurrence and metastasis are shown in Table I.[1,6-8] The American Joint Committee on Cancer (AJCC) published a staging system for cSCC in 2010 (Table II),[9] giving cSCC its own staging system for the first time. While the AJCC recently published revised staging for cSCC located on the head and neck in its 8th edition (Table II),[10] little outcome data are available to validate AJCC staging. An alternate T staging system, hereafter referenced as Brigham and Women's Hospital (BWH) staging, was proposed in 2013 and validated in a subsequent larger study.[5,11] This BWH system, outlined in Table II, stratifies AJCC 7th edition stage T2 tumors into low- and high-risk groups and offers improved prognostic discrimination. BWH stage T2b tumors were a low percentage (5%) of the cohort analyzed yet they accounted for 70% of nodal metastases and 83% of deaths from cSCC. The T2b subgroup had a risk of nodal metastasis of approximately 21% (95% confidence interval 13-27%). Later work investigating tumor staging as a predictor of sentinel lymph node biopsy (SLNB) results demonstrated sentinel lymph node (SLN) positivity in 8 of 23 (34.7%) patients with BWH T2b and T3 tumors, lending further evidence that this patient group may have a significant risk of nodal metastasis.[12] Only BWH staging has evaluated nodal metastatic risk relative to stage and risk factors and defined a group with a risk of nodal metastasis in excess of 20%, and high-risk cSCC (HRcSCC) herein refers to BWH T2b/T3 tumors.

CAPSULE SUMMARY

- Nodal metastasis for cutaneous squamous cell carcinoma occurs in 4% to 6% of patients, and sentinel lymph node biopsy specimens are positive in 29.4% of Brigham and Women's Hospital stage T2b tumors.
- Nodal staging may be considered with high-risk cutaneous tumors without palpable lymphadenopathy via imaging and, if negative, sentinel lymph node biopsy.

While nodal status is a valuable prognostic variable that correlates with poor outcomes, survival is superior for regional and nodal metastasis compared with distant metastasis (83% 5-year disease-specific survival for N1 disease vs 11% for distant disease).[13] With nodal metastasis, the risk of disease-specific death increases with the number and size of lymph nodes involved.[14] In a retrospective cohort study of patients with metastatic head and neck cSCC, only 1 of 19 (5.3%) patients with a single small (≤3 cm) involved node without extracapsular extension treated with surgery alone developed regional failure.[15] Moreover, a 92% 5-year disease-specific survival was reported for this cohort of patients. The identification of this low-risk group and the high cure rates with treatment of early nodal disease suggest that simpler treatment and improved outcomes are possible if nodal metastases can be identified at their earliest stage. This is further supported by the recent demonstration that both time to disease progression and overall survival decrease if the ratio of positive lymph nodes to excised lymph nodes is > 0.21.[16]

Much remains undiscovered in terms of assigning proper therapeutic interventions for patients at each nodal stage. However, it is clear that the ability to identify cSCC metastatic to regional lymph nodes in its earliest forms has the potential to favorably impact morbidity and mortality. Our purpose herein is to review the options for nodal staging for patients with HRcSCC.

MODALITIES FOR EVALUATING REGIONAL METASTASIS IN HRcSCC

Clinical examination

Patients with HRcSCC should receive a comprehensive history and physical examination including a full-body skin examination, evaluation of peritumoral nerve function, and regional lymph node examination via manual palpation, generally every 6 to 12 months or more often depending on the risk profile of the tumor(s).[17] The predictive value and limitations of clinical lymph node examination are outlined in Table III.[18-23] While clinical lymph node examination is clearly a cost-effective modality, data

Table I. High-risk features of cutaneous squamous cell carcinoma

Classically defined high-risk features	AJCC 7th ed staging high-risk features (2010)	BWH staging high-risk features
Diameter ≥2 cm	Tumor size >2 cm*	Clinical tumor diameter ≥2 cm
Location on the ear or lip	Location on the ear or lip	
Recurrent tumors		
Patient immunosuppression		
Depth beyond the dermis	Depth >2 mm or Clark level ≥ IV	Tumor invasion beyond the subcutaneous fat
Poorly differentiated histology	Poorly differentiated histology	Poorly differentiated histology
Perineural invasion	Perineural invasion	Perineural invasion of nerve(s) ≥0.1 mm in caliber
Lymphovascular invasion		

AJCC, American Joint Committee on Cancer; *BWH*, Brigham and Women's Hospital.
*While tumor size >2 cm is not defined as an "additional high-risk feature" according to the AJCC 7th ed staging, presence of this feature alone upstages from T1 to T2.

regarding its use are from head and neck and oropharyngeal SCC, which while in many cases has similar lymphatic drainage patterns to cSCC of the head and neck may potentially limit applicability when considering cSCC as a whole.

In the event of clinically palpable nodes, fine-needle aspiration (FNA) or obtaining a biopsy specimen for diagnostic confirmation, computed tomography (CT), or ultrasonography (US) for preoperative staging, followed by regional lymph node dissection is recommended.[17]

Imaging

There are limited data regarding radiologic nodal staging specific to cSCC, which may explain the variability in practice regarding when to initiate nodal staging.[24] Data to date regarding radiologic nodal staging in cSCC are summarized in Table IV.

Among patients who are clinically negative for lymphadenopathy, the utility of radiologic imaging lies in its ability to identify lymph nodes that are abnormal in size, presumably because of tumor infiltration. Limitations include false negatives, which result from the inability to detect micrometastasis, and false positives, which may result in additional unnecessary procedures.

A single study has evaluated the impact of radiologic imaging on HRcSCC outcomes. In 108 patients with BWH T2b/T3 tumors, imaging (80% CT) was used for 48 tumors among 45 patients, mostly for nodal staging. Imaging altered management in 16 tumors (33%), including 9 where CT alone was used, 2 where positron emission tomography (PET) CT alone was used, and 5 where a combination of CT, PET CT, or magnetic resonance imaging (MRI) was used. Imaged patients received adjuvant radiation more often and had a lower risk of nodal metastasis (13% vs 30%).[25] Nearly twice as many patients who underwent imaging received adjuvant therapy (imaging 23%, no imaging 12%; $P = .119$), which may support the concept that those who received nodal imaging may have earlier identification and treatment of advanced disease, resulting in a lower risk of subsequent nodal metastasis. Though relatively higher-risk patients (within an already high-risk BWH T2b/T3 group) may have received imaging more often, the finding that such imaged patients did better (rather than worse, as may be expected if they were at higher risk at baseline) lends some support to the concept that early detection of metastasis may positively impact outcomes.

The imprecision of noninvasive imaging for regional nodal staging in the absence of palpable lymphadenopathy has been reported for patients with cSCC of the penis and vulva.[26,27] In a small single-institution cohort study of 54 patients with cSCC who underwent preoperative imaging with either US or PET/CT before SLNB, 13 patients (24%) had results suggestive of nodal metastasis but only 1 had a positive SLN. Conversely, of the 41 patients with negative imaging studies, 3 had a positive SLN.[28]

The use of whole-body fluorodeoxyglucose PET (alone without CT) in the staging of HRcSCC is unclear. In a study of 9 patients with cSCC who underwent whole-body PET scans at the time of diagnosis, 3 (33%) had lymph node metastases and 1 had a distant metastasis to lung, all of which were confirmed histologically.[29] A retrospective study of 31 patients with head and neck cSCC with regional nodal metastases who underwent staging CT or MRI in addition to fluorodeoxyglucose PET-CT within 4 weeks of each other found that the addition of PET-CT to CT or MRI altered the management in 23% of cases.[30]

Table II. Summary of staging systems for cutaneous squamous cell carcinoma

Summary of the 7th edition AJCC staging for cutaneous squamous cell carcinoma		Summary of the 8th edition AJCC staging for cutaneous squamous cell carcinoma		Brigham and Women's Hospital T staging for cutaneous squamous cell carcinoma	
Stage	**Definition**	**Stage**	**Definition**	**Stage**	**Definition**
T0	No evidence of primary tumor	T1	Tumor <2 cm in greatest dimension	T0	In situ SCC
Tis	Carcinoma in situ	T2	Tumor ≥2 cm, but <4 cm in greatest dimension	T1	0 risk factors*
T1	Tumor ≤2 cm in greatest dimension with <2 high-risk features*	T3	Tumor ≥4 cm in greatest dimension or minor bone erosion or perineural invasion or deep invasion†	T2a	1 risk factor*
T2	Tumor >2 cm in greatest dimension with or without one additional high-risk feature, or any size with ≥2 high-risk features*	T4a	Tumor with gross cortical bone/marrow invasion	T2b	2-3 risk factors*
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone	T4b	Tumor with skull base invasion and/or skull base foramen involvement	T3	4 risk factors* or bone invasion
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base				

AJCC, American Joint Committee on Cancer; *SCC*, squamous cell carcinoma.
Adapted from Edge et al,[9] Amin et al,[10] and Karia et al.[11]
*See Table I for AJCC 7th edition and Brigham and Women's Hospital risk factors.
†Deep invasion defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm in caliber or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

US can detect subtle changes in nodal architecture that occur before lymph node enlargement. Based on our experience, limitations of US include the inability to assess deep nodes (which is less problematic for cSCC than other forms of cancer because most nodal metastases from cSCC are superficial) and high dependence on operator experience. While German data have shown a high sensitivity for US performed by dermatologists in detecting nodal metastases in patients with melanoma (it detects 71% of SLNB-positive cases preoperatively), demonstrating the utility of this modality in the surveillance of cutaneous nodal basins,[31] caution should be exercised in extrapolating US data from melanoma to cSCC. There is a relative paucity of data assessing the ability of US to detect purely micrometastatic nodal disease in cSCC.

In 2007, a metaanalysis was performed comparing US, US-guided fine needle aspiration (USgFNA), CT, and MRI for the detection of cervical lymph node metastases among patients with head and neck SCC, which often shares nodal metastatic basins with cSCC of the head and neck (USgFNA results are reported below).[32] While all studies included in the analysis reported histopathology findings of specimens obtained to be used as reference standard, it was not specified whether lymph node biopsy alone versus lymph node dissection (versus both) was performed. Of the noninvasive modalities, US had a higher mean diagnostic odds ratio, sensitivity, and specificity (40, 87%, and 86%, respectively) than either CT (14, 81%, and 76%) or MRI (7, 81%, and 63%).[32] The prevalence of lymph node metastases ranged from 20% to 77%, and therefore mucosal and cutaneous tumors were not analyzed separately—it is difficult to know if results would be the same for HRcSCC patients alone. However, lymph node metastases from cSCC may be more superficial and easier to detect on US than those from mucosal SCC. The findings are encouraging for a minimally invasive staging modality.

In a study of 44 patients with primary vulvar cSCC and suspected (and subsequently histologically confirmed) inguinal lymph node metastasis, preoperative US alone had a higher sensitivity and a

Table III. Clinical lymph node examination

Study	Year	Study design	Key findings
Biron et al[18]	2013	Retrospective cohort	Oral cavity SCC. Clinical examination TN 82.6%, TP 83.8%, FN 17.4%, FP 16.2%, SN 83%, and SP 84%. Overall accuracy of clinical examination 68%
Ross et al[19]	2004	Prospective cohort	Head and neck SCC. Clinical examination FN 44%. Only clinically neck node-negative patients were assessed, so false positives cannot be determined
Greenberg et al[20]	2003	Retrospective cohort	Oral tongue SCC. Clinical examination TN 66%, TP 69%, FN 34%, FP 31%, SN 67%, and SP 68%
Bergman et al[21]	1994	Retrospective cohort	Oral SCC. Clinical examination TN 80%, TP 60%, FN 20%, FP 40%, SN 75%, SP 67%, PPV 60%, and NPV 80%. Clinical examination was correct in 70% of cases. All lymph nodes inaccurately labeled negative by clinical examination were <1 cm
Friedman et al[22]	1990	Retrospective cohort	Advanced head and neck SCC. Clinical examination TN 61%, TP 86%, FN 39%, FP 14%, SN 71.7%, and PPV 85.7%
Shah et al[23]	1990	Retrospective cohort	Oral cavity SCC. Clinical examination FN 34%, FP 31%, SN 70%, and SP 65%. Total accuracy 68%

FN, False negative; *FP*, false positive; *NPV*, negative predictive value; *PPV*, positive predictive value; *SCC*, squamous cell carcinoma; *SN*, sensitivity; *SP*, specificity; *TN*, true negative; *TP*, true positive.

negative predictive value than CT, but lower specificity and positive predictive value.[27] Notably, routine preoperative CT imaging did not provide additional value because the findings did not alter surgical planning.

USgFNA

USgFNA combines noninvasive imaging with immediate biopsy and rapid histologic confirmation of metastases. Because USgFNA is typically used when there is clinically or radiologically detected lymphadenopathy, there is a much higher pretest probability of identifying nodal metastasis associated with USgFNA compared with other modalities. In the study above of vulvar cSCC with suspected nodal disease, USgFNA had superior sensitivity, specificity, negative predictive value, and positive predictive value compared with CT, and superior specificity, negative predictive value, and positive predictive value compared with US.[27] Results of the 2007 metaanalysis described above showed that USgFNA had the highest diagnostic accuracy with a pooled sensitivity of 80% and specificity of 98%.[32] While this suggests that preoperative nodal staging with USgFNA may be more useful than CT for SCC of the head and neck, how these data correlate to purely cSCC remains unclear.

Summary of radiologic data for cSCC nodal staging

The optimal radiologic imaging modality for initial staging and surveillance of lymph nodes is open to further research. Although the results above are encouraging for US and USgFNA, these modalities are operator-dependent and persons trained in US of cutaneous nodal basins are not available at all institutions. The main limitation of all forms of radiologic nodal staging in the absence of palpable lymphadenopathy is the inability to detect micrometastasis as imaging generally cannot detect lesions <5 mm. False positive and incidental findings may lead to unnecessary workup and additional procedures. Though PET has the added advantage of detecting distant organ metastases, such metastases are rare in cSCC at the time of primary tumor presentation.

SLNB

As with nodal screening in other cancers, patients with HRcSCC with positive or suspicious nodes on screening CT or US should proceed to FNA, core biopsy, or excisional biopsy of the suspicious lymph node(s) as per the information above. This section addresses whether SLNB should be considered in patients with negative imaging studies in order to detect subradiologic nodal disease. There is accumulating evidence with respect to SLNB for cSCC as a promising option to detect microscopic metastasis, as is outlined in Table V. The largest prospective cohort of SLNB for cSCC, reported by Gore et al[33] in 2016, demonstrated a 14% SLN positivity rate (8/57).[33] The number of high-risk clinical factors, perineural invasion, and lymphovascular invasion were each associated with

Table IV. Radiographic staging

Study	Year	Study design	Key findings (SN/SP/FP/FN)
Hughes et al[26]	2009	Literature review	Penile cancer. Noninvasive radiologic imaging modalities (unenhanced CT and MRI) as well as USgFNA were unreliable in staging impalpable regional lymph nodes. LNMRI and PET/CT failed to detect micrometastases (<2 mm). SN/SP/FP/FN not reported
De Bondt et al[32]	2007	Metaanalysis	Head and neck SCC. USgFNA had the highest diagnostic accuracy with a pooled SN/SP/FP/FN of 80%/98%/2%/20%; CT of 81%/76%/24%/19%; US of 87%/86%/14%/13%; MRI of 81%/63%/37%/19%; and USPIO-MRI 74%/88%/12%/26%, respectively
Fukushima et al[28]	2014	Single-institution cohort study	cSCC. Using nodal status (metastasis positive vs negative) detected by SNLB as the criterion standard, preoperative imaging with US or PET/CT had SN/SP/FP/FN 25%/76%/24%/75%, respectively
Cho et al[29]	2005	Retrospective analysis	cSCC. 3/9 (33%) HRcSCC cases had nodal metastasis and 1/9 (11%) had distant metastasis to lung revealed on FDG PET and confirmed histopathologically. SN/SP/FP/FN not reported
Supriya et al[30]	2014	Retrospective case cohort study	cSCC of the head and neck. FDG PET/CT failed to detect nodal metastasis in 4/31 cases. This additional imaging modality did not change the management in 24/31 (77%) of patients. FDG PET/CT results compared to the final pathology results after resection in 25 patients showed SN/SP/FP/FN/PPV/NPV 54%/76%/24%/46%/61% and 71%, respectively
Tomaszewski et al[52]	2014	Retrospective case series	cSCC. PET/CT can distinguish nodal cSCC from leukemic infiltration with high specificity in this small case series, with SN/SP/FP/FN 45%/99.6%/0.4%/55%, respectively
Land et al[27]	2006	A mixed retrospective and prospective case review	Vulvar SCC. All cases with histologically proven nodal status were analyzed to compare the preoperative imaging status with the histology. The calculated SN/SP/FP/FN/NPV/PPV for CT were 58%/75%/25%/42%/75%/58%; US: 87%/69%/31%/13%/94%/48%; and USgFNA: 80%/100%/0%/20%/93%/100%, respectively. For the groin nodes, USgFNA is superior to CT in assessing disease status

cSCC, Cutaneous squamous cell carcinoma; *CT*, computed tomography; *FDG*, fluorodeoxyglucose; *FN*, false negative; *FP*, false positive; *HRcSCC*, high-risk cutaneous squamous cell carcinoma; *LNMRI*, lymphotropic nanoparticle-enhanced magnetic resonance imaging; *MRI*, magnetic resonance imaging; *PET*, positron emission tomography; *SLNB*, sentinel lymph node biopsy; *SN*, sensitivity; *SP*, specificity; *TN*, true negative; *TP*, true positive; *US*, ultrasound; *USgFNA*, ultrasound-guided fine needle aspiration; *USPO*, ultrasmall superparamagnetic iron oxide.

increased risk of SLN positivity. Patients with a positive SLN had a statistically significantly higher disease-specific mortality rate than those with a negative SLN, indicating that SLNB may serve as a prognostic tool. The study included only patients who underwent SLNB and therefore did not compare treatment and outcomes between patients receiving versus not receiving SLNB, and therefore the impact of SLNB utilization on outcomes could not be assessed.

Individual case series and case reports with <20 patients per publication have a combined SLN positivity rate ranging from 0% to 80% for cSCC.[34-47] One such small series of 17 patients with cSCC with varying risk profiles undergoing SLNB is among the first to evaluate disease outcomes including subsequent recurrence and metastasis (but not death). SLNB was positive in 2 of 17 patients with cSCC. There was a 40% (6/15) risk of recurrence after negative SLNB. Only 1 recurrence occurred in

Table V. Sentinel lymph node biopsy for cutaneous squamous cell carcinoma

Study	Year	Study design	Tumor site	Key findings
Navarrete-Dechent et al[50]	2015	Systematic review	Various	SLNB positive: 13.9% (32/231)/ FN: 4.6% (10/215)
Gore et al[33]	2016	Prospective	Cutaneous SCC	SLNB positive: 14% (8/57)
Krediet et al[47]	2015	Retrospective case series	Head and neck, lower extremities, trunk	SLNB positive: 11.7% (2/17)/FN: 35.2% (6/17)
Schmitt et al[12]	2014	Systematic review	Various	SLNB positive: 12.3% overall, 34.7% (8/23) for BWH T2b and T3 tumors
Ahmed et al[49]	2014	Systematic review	Various	SLNB positive: 13%/SN 77%/SP 100%/NPV 92.5%
Fukushima et al[28]	2014	Prospective case series	Head and neck, extremities, trunk, genitalia	SLNB positive: 7.4% (4/54), 12.9% if considering only T2 and above
Takahashi et al[46]	2014	Retrospective case series	Head and neck, extremities, trunk, genitalia	SLNB positive: 23.1 % (6/26)/FN: 0/26
Kwon et al[45]	2011	Retrospective case series	Head, extremities, perineum	SLNB positive: 0% (0/6)
Rastrelli et al[44]	2010	Retrospective case series	Head and neck, extremities, trunk	SLNB positive: 5% (1/20)/FN: 2/20
Renzi et al[43]	2007	Prospective case series	Not specified	SLNB positive: 4.5% (1/22)
Resendiz-Colosia et al[42]	2007	Prospective case series	Head and neck, extremities, trunk	SLNB positive: 20% (4/20)/FN: 0/20
Ross et al[48]	2006	Systematic review	Various	SLNB positive: 21%/FN: 4%
Cecchi et al[41]	2006	Case series	Head, extremities	SLNB positive: 16.6% (1/6)/FN: 0/6
Hatta et al[40]	2005	Prospective case series	Lower extremity	SLNB positive: 0% (0/4)/FN: 0/4
Nouri et al[39]	2004	Prospective case series	Head and neck	SLNB positive: 12% (1/8)/FN: 0/8
Eastman et al[38]	2004	Prospective case series	Extremities	SLNB positive: 80% (4/5)/FN: 0/5
Wagner et al[37]	2004	Prospective case series	Head and neck, extremities, perineum, vulva	SLNB positive: 29.4% (5/17)/FN: 1/17
Reschly et al[36]	2003	Prospective case series	Head and neck, extremeties, trunk	SLNB positive: 44.4% (4/9)/FN: 0/9
Michl et al[35]	2003	Retrospective case series	Head and neck, trunk, extremeties, genitalia (2)	SLNB positive: 18.1% (2/11)/FN: 0/11
Altinyollar et al[34]	2002	Prospective case series	Lower lip	SLNB positive: 16.6% (3/18)/FN: 0/18

BWH, Brigham and Women's Hospital; *FN*, false negative; *FP*, false positive; *SLNB*, sentinel lymph node biopsy; *SN*, sensitivity; *SP*, specificity; *TN*, true negative; *TP*, true positive.

the SLN basin, with the remainder occurring in other nodal basins (2), the orbit or surrounding skin (2), and the lung (1). These data are consistent with other reports that SLNB has a low false-negative rate but that recurrences outside the nodal basin are possible, so further study of the impact of SLNB on overall outcomes is needed.[47]

Another systematic review of 130 patients who underwent SLNB from 19 reports correlated cSCC T stage with SLNB outcome using both the AJCC 7th edition and BWH T staging systems.[12] There was no positive SLNB among patients with T1 lesions. The majority of SLN positive cases were T2 lesions >2 cm. Overall, 12.3% of patients had a positive SLNB. The BWH T staging system identified a higher risk category, with a SLNB positivity of nearly 30% in the BWH T2b group. There was a statistically significant difference between the SLNB positivity rates of BWH T2a and T2b groups (7.1% vs 29.4%; $P = .02$). Further systematic reviews of SLNB for cSCC have reported SLNB positivity ranging from 13% to 21%.[48-50]

DISCUSSION

The importance of risk stratification among patients with cSCC is clear, and the process of defining meaningful prognostic markers among the subset of patients with HRcSCC continues to evolve.

Among patients with cSCC who were diagnosed in the BWH cohort study from 2000 to 2009, the risk of nodal metastasis using the BWH T staging system is 0.1% (95% CI 0-0.4%) for BWH T1 tumors and 3% (1-5%) for BWH T2a tumors.[11] The risk increases to 21% (13-27%) for BWH T2b tumors and 67% (30-90%) for BWH T3 tumors.[11] That metastatic risk can be stratified using this system—based entirely upon the clinical and pathologic features of tumor size and depth, histologic growth pattern, and the presence or absence of perineural tumor growth—underscores the importance that these parameters be identified and defined before treatment whenever possible. Synoptic reporting of risk factors of cSCC in clinical notes and dermatopathology reports becomes an essential element in achieving accurate risk stratification. Not infrequently, risk stratification may change during treatment as additional high-risk features of a tumor are identified intraoperatively. For example, more aggressive or poorly differentiated histology or perineural invasion may be noted during Mohs micrographic surgery for a tumor that on original pathology had no high-risk features. In these circumstances, both final tumor staging and the decision to proceed with nodal staging should be based on the features of the tumor that give it the highest tumor stage.

Given the elevated probability for nodal metastasis in the presence of ≥2 risk factors in the BWH model, it may be reasonable to consider nodal staging for tumors BWH stage T2b or higher in the absence of clinically palpable lymphadenopathy. Several radiologic imaging modalities may be helpful in detecting nodal metastasis, but limitations, including relatively high false negative rates likely caused by an inability to detect micrometastases and high operator dependence in the case of US, remain. Though data are limited, US has a higher diagnostic odds ratio, sensitivity, and specificity than MRI or CT and has the added advantage of immediate biopsy via FNA when a pathologic node is detected. Literature to date has shown the ability of SLNB to identify nodal metastasis among a relatively high percentage of patients with HRcSCC. It remains to be seen whether earlier detection via SLNB results in sufficient outcome benefits (over noninvasive CT and US) to warrant its widespread use. SLNB is generally safe, with a pooled risk of hematoma, seroma, and infection of 5.1% (95% CI 2.2-9.3%) when performed for head and neck tumors.[51] Logistical challenges and questions regarding the accuracy of SLNB remain for HRcSCC, particularly when tumors are upstaged intraoperatively (usually during Mohs micrographic surgery) to BWH T2b. In such cases, SLNB is performed by injecting dye and radioactive tracer into the dermis around the tumor resection bed—which is sometimes several centimeters in dimension—rather than around the clinical perimeter of a small intact tumor, as in melanoma. While data from melanoma literature suggest that previous wide excision does not appear to negatively impact the detection of lymph node metastases,[52] the impact of such technical variations has not been studied for HRcSCC. In effort to preserve preoperative lymphatic drainage patterns, tissue undermining should not be performed before SLNB because undermining severs the draining lymphatic vessels in the subcutaneous fat. It should be noted that this recommendation is based on opinion and experience and not on higher quality evidence. Wounds can be stabilized by application of a matrix wound dressing while patients await SLNB and reconstruction.

The current evidence suggests that we are now able to better predict which patients with cSCC are at high risk for metastasis, that we have the tools to accurately detect metastases among this subset of patients, and that patients with early limited nodal cSCC have a high (92%) 5-year survival rate with conventional treatment. As such, it is reasonable to consider nodal staging for patients with HRcSCC (BWH T2b and T3) in the absence of clinically palpable lymphadenopathy via radiographic imaging and, if negative, SLNB.

Prospective studies are needed to validate the relationships between tumor stage and SLN status and to determine if early identification of nodal metastasis, such as identification of micrometastases via SLNB, will impact disease-free, disease-specific, and overall survival for patients with HRcSCC.

REFERENCES

1. Brantsch KD, Meisner C, Schonfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol*. 2008;9:713-720.
2. Schmults CD, Karia PS, Carter JB, Han J, Qureshi AA. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single-institution cohort study. *JAMA Dermatol*. 2013;149:541-547.
3. Czarnecki D, Staples M, Mar A, Giles G, Meehan C. Metastases from squamous cell carcinoma of the skin in southern Australia. *Dermatology*. 1994;189:52-54.
4. Joseph MG, Zulueta WP, Kennedy PJ. Squamous cell carcinoma of the skin of the trunk and limbs: the incidence of metastases and their outcome. *Aust N Z J Surg*. 1992;62:697-701.
5. Jambusaria-Pahlajani A, Kanetsky PA, Karia PS, et al. Evaluation of AJCC tumor staging for cutaneous squamous cell carcinoma and a proposed alternative tumor staging system. *JAMA Dermatol*. 2013;149:402-410.
6. Clayman GL, Lee JJ, Holsinger FC, et al. Mortality risk from squamous cell skin cancer. *J Clin Oncol*. 2005;23:759-765.

7. Mullen JT, Feng L, Xing Y, et al. Invasive squamous cell carcinoma of the skin: defining a high-risk group. *Ann Surg Oncol*. 2006;13:902-909.
8. Rowe DE, Carroll RJ, Day CL Jr. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. *J Am Acad Dermatol*. 1992;26:976-990.
9. Edge S, Byrd DR, Compton CC, et al., eds. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010.
10. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
11. Karia PS, Jambusaria-Pahlajani A, Harrington DP, et al. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. *J Clin Oncol*. 2014;32:327-334.
12. Schmitt AR, Brewer JD, Bordeaux JS, Baum CL. 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. *JAMA Dermatol*. 2014;150:19-24.
13. Brunner M, Veness MJ, Ch'ng S, Elliott M, Clark JR. Distant metastases from cutaneous squamous cell carcinoma--analysis of AJCC stage IV. *Head Neck*. 2013;35:72-75.
14. Clark JR, Rumcheva P, Veness MJ. Analysis and comparison of the 7th edition American Joint Committee on Cancer (AJCC) nodal staging system for metastatic cutaneous squamous cell carcinoma of the head and neck. *Ann Surg Oncol*. 2012; 19:4252-4258.
15. Ebrahimi A, Clark JR, Lorincz BB, Milross CG, Veness MJ. Metastatic head and neck cutaneous squamous cell carcinoma: defining a low-risk patient. *Head Neck*. 2012;34:365-370.
16. Tseros EA, Gebski V, Morgan GJ, Veness MJ. Prognostic significance of lymph node ratio in metastatic cutaneous squamous cell carcinoma of the head and neck. *Ann Surg Oncol*. 2016;23:1693-1698.
17. Miller SJ, Alam M, Andersen J, et al. Basal cell and squamous cell skin cancers. *J Natl Compr Canc Netw*. 2010;8:836-864.
18. Biron VL, O'Connell DA, Seikaly H. The impact of clinical versus pathological staging in oral cavity carcinoma—a multi-institutional analysis of survival. *J Otolaryngol Head Neck Surg*. 2013;42:28.
19. Ross GL, Soutar DS, MacDonald DG, et al. Improved staging of cervical metastases in clinically node-negative patients with head and neck squamous cell carcinoma. *Ann Surg Oncol*. 2004;11:213-218.
20. Greenberg JS, El Naggar AK, Mo V, Roberts D, Myers JN. Disparity in pathologic and clinical lymph node staging in oral tongue carcinoma. Implication for therapeutic decision making. *Cancer*. 2003;98:508-515.
21. Bergman SA, Ord RA, Rothman M. Accuracy of clinical examination versus computed tomography in detecting occult lymph node involvement in patients with oral epidermoid carcinoma. *J Oral Maxillofac Surg*. 1994;52:1236-1239.
22. Friedman M, Mafee MF, Pacella BL Jr, et al. Rationale for elective neck dissection in 1990. *Laryngoscope*. 1990;100:54-59.
23. Shah JP, Candela FC, Poddar AK. The patterns of cervical lymph node metastases from squamous carcinoma of the oral cavity. *Cancer*. 1990;66:109-113.
24. Jambusaria-Pahlajani A, Hess SD, Katz KA, Berg D, Schmults CD. Uncertainty in the perioperative management of high-risk cutaneous squamous cell carcinoma among Mohs surgeons. *Arch Dermatol*. 2010;146:1225-1231.
25. Ruiz ES, Karia PS, Morgan FC, Schmults CD. The positive impact of radiologic imaging on high-stage cutaneous squamous cell carcinoma management. *J Am Acad Dermatol*. 2017;76:217-225.
26. Hughes B, Leijte J, Shabbir M, Watkin N, Horenblas S. Non-invasive and minimally invasive staging of regional lymph nodes in penile cancer. *World J Urol*. 2009;27:197-203.
27. Land R, Herod J, Moskovic E, et al. Routine computerized tomography scanning, groin ultrasound with or without fine needle aspiration cytology in the surgical management of primary squamous cell carcinoma of the vulva. *Int J Gynecol Cancer*. 2006;16:312-317.
28. Fukushima S, Masuguchi S, Igata T, et al. Evaluation of sentinel node biopsy for cutaneous squamous cell carcinoma. *J Dermatol*. 2014;41:539-541.
29. Cho SB, Chung WG, Yun M, Lee JD, Lee MG, Chung KY. Fluorodeoxyglucose positron emission tomography in cutaneous squamous cell carcinoma: retrospective analysis of 12 patients. *Dermatol Surg*. 2005;31:442-446.
30. Supriya M, Suat-Chin N, Sizeland A. Use of positron emission tomography scanning in metastatic head and neck cutaneous squamous cell cancer: does it add to patient management? *Am J Otolaryngol*. 2014;35:347-352.
31. Voit CA, Gooskens SL, Siegel P, et al. Ultrasound-guided fine needle aspiration cytology as an addendum to sentinel lymph node biopsy can perfect the staging strategy in melanoma patients. *Eur J Cancer*. 2014;50:2280-2288.
32. de Bondt RB, Nelemans PJ, Hofman PA, et al. Detection of lymph node metastases in head and neck cancer: a meta-analysis comparing US, USgFNAC, CT and MR imaging. *Eur J Radiol*. 2007;64:266-272.
33. Gore SM, Shaw D, Martin RC, et al. Prospective study of sentinel node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck. *Head Neck*. 2016;38(suppl 1):E884-E889.
34. Altinyollar H, Berberoglu U, Celen O. Lymphatic mapping and sentinel lymph node biopsy in squamous cell carcinoma of the lower lip. *Eur J Surg Oncol*. 2002;28:72-74.
35. Michl C, Starz H, Bachter D, Balda BR. Sentinel lymphonodectomy in nonmelanoma skin malignancies. *Br J Dermatol*. 2003;149:763-769.
36. Reschly MJ, Messina JL, Zaulyanov LL, Cruse W, Fenske NA. Utility of sentinel lymphadenectomy in the management of patients with high-risk cutaneous squamous cell carcinoma. *Dermatol Surg*. 2003;29:135-140.
37. Wagner JD, Evdokimow DZ, Weisberger E, et al. Sentinel node biopsy for high-risk nonmelanoma cutaneous malignancy. *Arch Dermatol*. 2004;140:75-79.
38. Eastman AL, Erdman WA, Lindberg GM, Hunt JL, Purdue GF, Fleming JB. Sentinel lymph node biopsy identifies occult nodal metastases in patients with Marjolin's ulcer. *J Burn Care Rehabil*. 2004;25:241-245.
39. Nouri K, Rivas MP, Pedroso F, Bhatia R, Civantos F. Sentinel lymph node biopsy for high-risk cutaneous squamous cell carcinoma of the head and neck. *Arch Dermatol*. 2004;140: 1284.
40. Hatta N, Morita R, Yamada M, Takehara K, Ichiyanagi K, Yokoyama K. Implications of popliteal lymph node detected by sentinel lymph node biopsy. *Dermatol Surg*. 2005;31:327-330.
41. Cecchi R, Buralli L, De Gaudioc C. Sentinel lymphonodectomy in non-melanoma skin cancers. *Chir Ital*. 2006;58:347-351.

42. Reséndiz-Colosia JA, Valenzuela-Flores AA, Torres-Nuñez G, et al. Lymphatic mapping and sentinel lymph node biopsy in patients with high risk squamous cell carcinoma of the skin [in Spanish]. *Gac Med Mex*. 2007;143:209-214.
43. Renzi C, Caggiati A, Mannooranparampil TJ, et al. Sentinel lymph node biopsy for high risk cutaneous squamous cell carcinoma: case series and review of the literature. *Eur J Surg Oncol*. 2007;33:364-369.
44. Rastrelli M, Soteldo J, Zonta M, et al. Sentinel node biopsy for high-risk cutaneous nonanogenital squamous cell carcinoma: a preliminary result. *Eur Surg Res*. 2010;44:204-208.
45. Kwon S, Dong ZM, Wu PC. Sentinel lymph node biopsy for high-risk cutaneous squamous cell carcinoma: clinical experience and review of literature. *World J Surg Oncol*. 2011;9:80.
46. Takahashi A, Imafuku S, Nakayama J, Nakaura J, Ito K, Shibayama Y. Sentinel node biopsy for high-risk cutaneous squamous cell carcinoma. *Eur J Surg Oncol*. 2014;40:1256-1262.
47. Krediet JT, Beyer M, Lenz K, et al. Sentinel lymph node biopsy and risk factors for predicting metastasis in cutaneous squamous cell carcinoma. *Br J Dermatol*. 2015;172:1029-1036.
48. Ross AS, Schmults CD. Sentinel lymph node biopsy in cutaneous squamous cell carcinoma: a systematic review of the English literature. *Dermatol Surg*. 2006;32:1309-1321.
49. Ahmed MM, Moore BA, Schmalbach CE. Utility of head and neck cutaneous squamous cell carcinoma sentinel node biopsy: a systematic review. *Otolaryngol Head Neck Surg*. 2014;150:180-187.
50. Navarrete-Dechent C, Veness MJ, Droppelmann N, Uribe P. High-risk cutaneous squamous cell carcinoma and the emerging role of sentinel lymph node biopsy: a literature review. *J Am Acad Dermatol*. 2015;73:127-137.
51. Moody JA, Ali RF, Carbone AC, Singh S, Hardwicke JT. Complications of sentinel lymph node biopsy for melanoma - A systematic review of the literature. *Eur J Surg Oncol*. 2017;43:270-277.
52. Tomaszewski JM, Lau E, Corry J. Utility of positron emission tomography/computed tomography for nodal staging of cutaneous squamous cell carcinoma in patients with chronic lymphocytic leukemia. *Am J Otolaryngol*. 2014;35:66-69.