Cutaneous squamous cell carcinoma

Management of advanced and high-stage tumors

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Learning objectives
After completing this learning activity, participants should be able to evaluate evidence-based literature concerning cSCC preventive therapies; discuss general indications for Mohs surgery in the setting of cSCC; and work up high-risk cSCC and arrive at potential treatment options.

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While the majority of cutaneous squamous cell carcinomas (cSCCs) can be treated surgically, the additional work-up and treatments indicated for high-risk cSCC remain undefined. In recent years, improvements in tumor staging systems have allowed for the more accurate stratification of tumors into high- and low-risk categories. This insight, along with the publication of cSCC guidelines, brings us closer to the development of a consensus approach. The second article in this continuing medical education series addresses in question and answer format the most common questions related to advanced and high-stage cSCCs, with a simplified flowchart. The questions include the following: 1) Does my patient have high-risk cSCC?; 2) What is the next step for patients with cSCC and palpable lymphadenopathy?; 3) In patients with no clinically evident lymphadenopathy, who are candidates for lymph node staging?; 4) What forms of radiologic imaging can help detect subclinical lymph node metastases?; 5) What is the role of sentinel lymph node biopsy in cSCC?; 6) Which patients with cSCC need adjuvant radiation therapy?; 7) Is adjuvant chemotherapy an option for patients with high-stage cSCC after surgery?; 8) Are targeted and immunologic therapies an option for advanced cSCC?; 9) How often should I follow up with my patient after he/she has been diagnosed with a high-risk cSCC?; 10) What are the options for chemoprophylaxis in a patient with an increased risk of cSCC?; and 11) What chemopreventive measures can be started in coordination with medical oncology or transplant physicians? (J Am Acad Dermatol 2018;78:249-61.)

Key words: 5-fluorouracil; imiquimod; ingenol mebutate; acitretin; American Joint Commission on Cancer; Brigham and Women's Hospital staging system; capecitabine; *CDKN2A*; cetuximab; chemotherapy; classification; cSCC; CT; cutaneous squamous cell carcinoma; familial cancer syndromes; high-risk; management; MRI; N1S3 staging; nicotinamide; nivolumab; *NOTCH1*; p53; PD-1; pembrolizumab; photodynamic therapy; radiation therapy; Ras; retinoids; risk factors; sentinel lymph node biopsy; sirolimus; staging.

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Abbreviations used:

5-ALA:	5-aminolevulinic acid
5-FU:	5-fluorouracil
AJCC-8:	American Joint Committee on Cancer, 8th edition
AK:	actinic keratosis
ART:	adjuvant radiation therapy
BWH:	Brigham and Women's Hospital
cSCC:	cutaneous squamous cell carcinoma
CT:	computed tomography
EGFR:	epidermal growth factor receptor
MRI:	magnetic resonance imaging
PDT:	photodynamic therapy
SLNB:	sentinel lymph node biopsy

QUESTIONS AND ANSWERS REGARDING THE MANAGEMENT OF HIGH-RISK CUTANEOUS SQUAMOUS CELL CARCINOMA

1. Does my patient have high-risk cutaneous squamous cell carcinoma?

There is no single universal definition of high-risk cutaneous squamous cell carcinoma (cSCC). The risk factors incorporated in the cSCC staging systems (detailed in the first article in this continuing medical education series) can be used as a guide in selecting high-risk patients. In both the Brigham and Women's Hospital (BWH) and the American Joint Committee on Cancer, 8th edition (AJCC-8) staging systems, T1 is considered low-risk disease. BWH T2a also appears to be low-risk while BWH T2b and T3 cases carry a risk of nodal metastases in excess of 20%. AJCC-8 has not yet been evaluated with regard to metastatic risks associated with T2, T3, and T4 cases.

Risk factors not accounted for in either staging system but clinically relevant in risk assessment include immune status, lymphovascular invasion, association with scar or chronic inflammatory disease, and treatment history (ie, primary vs. recurrent cSCC).

2. What is the next step for patients with cSCC and palpable lymphadenopathy?

The diagnosis of a high-risk cSCC should involve inspection and palpation of the involved site and the regional lymph nodes. For patients with palpable lymphadenopathy, clinicians can proceed to ultrasound-guided fine-needle aspiration or biopsy confirmation of involved lymph nodes. Ultrasound-guided fine-needle aspiration is reported to have a sensitivity of 80% and specificity of 98%.[1] A positive fine-needle aspiration or biopsy specimen usually prompts lymphadenectomy of the associated nodal basin with or without adjuvant radiation therapy (ART).

3. In patients with no clinically evident lymphadenopathy, who are candidates for lymph node staging?

The risk of nodal metastases is 21% to 30% for BWH T2b tumors and 50% to 67% for BWH T3 tumors.[2,3] We cannot definitively determine which patient population requires nodal staging, and therefore BWH T2b tumors appear to have a nodal metastasis risk higher than the 10% threshold for sentinel lymph node biopsy (SLNB) used for melanoma.[4] In light of this evidence, we recommend nodal staging in the form of radiologic imaging for AJCC-8 T4 and BWH T2b and T3 cSCCs. Radiologic imaging will be discussed in question 4; SLNBs will be discussed in question 5.

4. What forms of radiologic imaging can help detect subclinical lymph node metastases?

Radiologic imaging may be a useful tool in the management of high-stage cSCC and can alter management in ≤33% of patients with BWH T2b/T3 stage cSCC.[5] Patients who receive no imaging are often at higher risk of nodal metastases, local recurrence, and death from disease. Computed tomography (CT) is superior for bony and nodal assessment while magnetic resonance imaging (MRI) is more suitable for soft tissue and nerve examination.[6] The use of positron emission tomography/CT increases the sensitivity of nodal detection but is an expensive imaging tool and does not alter management in the majority (77%) of patients with head and neck cSCC with regional nodal metastases.[7] In our practice, we obtain CT imaging of the draining lymph node basin(s) in high-stage cSCC (BWH T2b and T3) cases given the risk of nodal metastases in excess of 20%.

In Europe, ultrasonography is the most commonly used modality for nodal staging in high-risk cSCCs.[8] Breuninger et al[9] recommend ultrasonography to evaluate lymph nodes for tumors >2 mm in thickness and CT or MRI for imaging infiltrative or destructive tumors. Ultrasonography can discriminate extranodal spread of head and neck SCC with comparable accuracy and higher specificity than MRI[1] at a lower cost. In the United States, ultrasound is used less frequently than CT and MRI for cSCC lymph node staging. The accuracy of ultrasonography in pathologic lymph node detection is technique- and operator-dependent. A more in-depth review of radiologic imaging can be found in MacFarlane et al[6] and Humphreys et al.[10]

5. What is the role of SLNBs in cSCC?

Radiologic imaging of the draining nodal basin, generally considered pathologic if ≥1 node(s) are