Cutaneous Squamous Cell Carcinoma

Updates in Staging and Management

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KEYWORDS

• Cutaneous squamous cell carcinoma • High-risk skin cancer • AJCC staging
• Squamous cell carcinoma staging • Skin cancer radiologic imaging • Sentinel lymph node biopsy
• PD-1 inhibitor • EGFR inhibitor

KEY POINTS

- Outcomes for cutaneous squamous cell carcinoma (cSCC) are generally favorable, but a subset of cSCC is biologically distinct and requires a different approach because of its higher risk of local recurrence, metastasis, and death.
- Updates to staging systems have improved their prognostic ability, but further study is needed to identify and include the most important risk factors.
- Uniform reporting of clinical and pathologic characteristics is important for clinical risk assessment and future population-based study.
- Although surgical resection with negative margins remains the goal of treatment, radiation and new systemic therapies have shown promise for advanced disease.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is one of the most common cancers in the United States. Together with basal cell carcinoma (BCC), these cancers of epidermal keratinocyte lineage are often referred to as nonmelanoma skin cancer, or more specifically, keratinocyte carcinoma to differentiate their origins from melanoma and other skin cancers, such as Merkel cell carcinoma, adnexal carcinoma, and dermatofibrosarcoma protuberans.[1] Although cSCC and BCC have many similarities, a subset of cSCC is biologically distinct and requires a different approach because of its higher risk of local recurrence, metastasis, and death. This article focuses on the recent literature regarding identification of this high-risk subset, efforts to improve the prognostic ability of staging systems, and updates in management. Much of these data and expert opinion are incorporated in recent cSCC guidelines.

Incidence

Approximately 5.4 million cases of BCC and cSCC occur annually in the United States, with increasing incidence over time.[2] Although cSCC was previously estimated to represent about 20% of keratinocyte carcinomas, recent data suggest a 1:1 ratio of cSCC to BCC.[2–4] Because cSCC development is associated with older age and greater cumulative ultraviolet (UV) radiation exposure, these numbers are expected to increase as the population ages.

Disease-related Outcomes

Outcomes for cSCC are generally favorable, with low rates of local recurrence (LR; 3%–5.2%), NM

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(NM; 1.5%–4%), and disease-specific death (DSD; 1.5%–2.8%).[5–11] Poor outcomes typically occur in elderly patients with multiple comorbidities but may be underreported because cSCC is not always identified as the official cause of death. In 2012, an estimated 3932 to 8791 deaths could be attributed to cSCC, with the highest mortality rates in the southern and central United States rivalling renal and oropharyngeal cancer and melanoma.[5] However, cSCC is not included in national cancer registries, limiting understanding of its true impact. In this context, increased focus has been placed on identifying high-risk patients that may benefit from a more intensive diagnostic and therapeutic approach.

Risk Factors

Over the past 80 years, numerous studies have identified risk factors for poor outcomes. Rowe and colleagues[12] reviewed all studies of cSCC outcomes from 1940 to 1992 and identified the following risk factors for LR and metastasis: treatment modality, prior treatment, location, size, depth, histologic differentiation, perineural involvement, host immunosuppression, and precipitating factors other than UV light. Recent studies have built on this work by further examining the following risk factors:

- Increased tumor size[6,7,12–16]
- Location on ear, lip, or genitals[7,12,15,17]
- Poorly differentiated, desmoplastic, or acantholytic histologic subtype[6–10,12,13,15,18,19]
- Perineural involvement[7,12,16,18,20–24]
- Lymphovascular involvement[10,18]
- Increased depth of invasion[6–8,12,14–16,18,25]
- Immunocompromised status[8,12,26–28]

These studies vary in the definition and reported magnitude of each risk factor, making a standard definition of high risk elusive (**Fig. 1**). For instance, some studies report tumor depth as Breslow thickness (measured from the granular layer to deepest point of invasion), whereas others consider anatomic depth to subcutaneous fat, muscle, bone, or cartilage. Perineural invasion may be reported as a binary variable (present or absent) or a continuous variable based on nerve diameter. Risk factors such as tumor depth and perineural or lymphovascular invasion tend to co-occur, potentially minimizing their individual contribution in multivariate analyses. Despite the heterogeneity in current data, great strides have been made in assessing the risk of poor outcomes.

STAGING SYSTEMS

Standardized staging systems help physicians provide prognostic information to patients, design treatment plans based on tumor risk, communicate with other physicians, and study new treatment paradigms through clinical trials. These staging systems help physicians reassure patients with favorable prognoses and better evaluate, manage, and monitor those at risk for adverse outcomes.

The ideal staging system is easily applicable to daily clinical practice and shows distinctiveness, homogeneity, and monotonicity. Distinctiveness means that disease-related outcomes should differ between stages, homogeneity refers to similar outcomes in patients within the same stage, and monotonicity implies worsening outcomes with increasing stage.[29]

Tumor Staging

At present, there are 2 major cSCC staging systems in the United States: the American Joint Committee on Cancer (AJCC) system and the Brigham and Women's Hospital (BWH) system (**Table 1**). The International Union Against Cancer (UICC) also has a staging system for cSCC that has been consistent with the AJCC system and is not discussed further in this article. Before 2010, the first 6 editions of the AJCC manual grouped cSCC in a chapter with all nonmelanoma skin cancers and included only tumor size and bony invasion as high-risk features.[29] The seventh edition added more risk factors but was criticized for its complexity and poor prognostic ability.[25,30,31] Retrospective cohorts showed that the bulk of poor outcomes occurred in tumor (T) stage T2 (69% of LRs, 83% of NM, and 92% of DSDs) and that T3 and T4 were too rare to be useful.[16,22]

The eighth edition was published in 2017 and reclassified cSCC in the head and neck chapter.[32,33] There are separate AJCC tumor classifications for cSCC on the eyelid, vulva, penis, and perianal region but none for tumors on other sites of the body. Changes from AJCC 7 include expansion of T3 and removal of poorly differentiated histology as a risk factor (see **Table 1**).

Validation of AJCC 8 with population-level data in the United States is challenging because national registries exclude cSCC. Karia and colleagues[34] attempted to validate the AJCC 8 T classification with a 10-year retrospective cohort of 680 primary head and neck cSCCs treated at BWH from 2000 to 2009. AJCC 8 showed a significant improvement in homogeneity and monotonicity compared with AJCC 7 based on expansion of the T3 and T4 categories, which together accounted for 17.8% of total cases

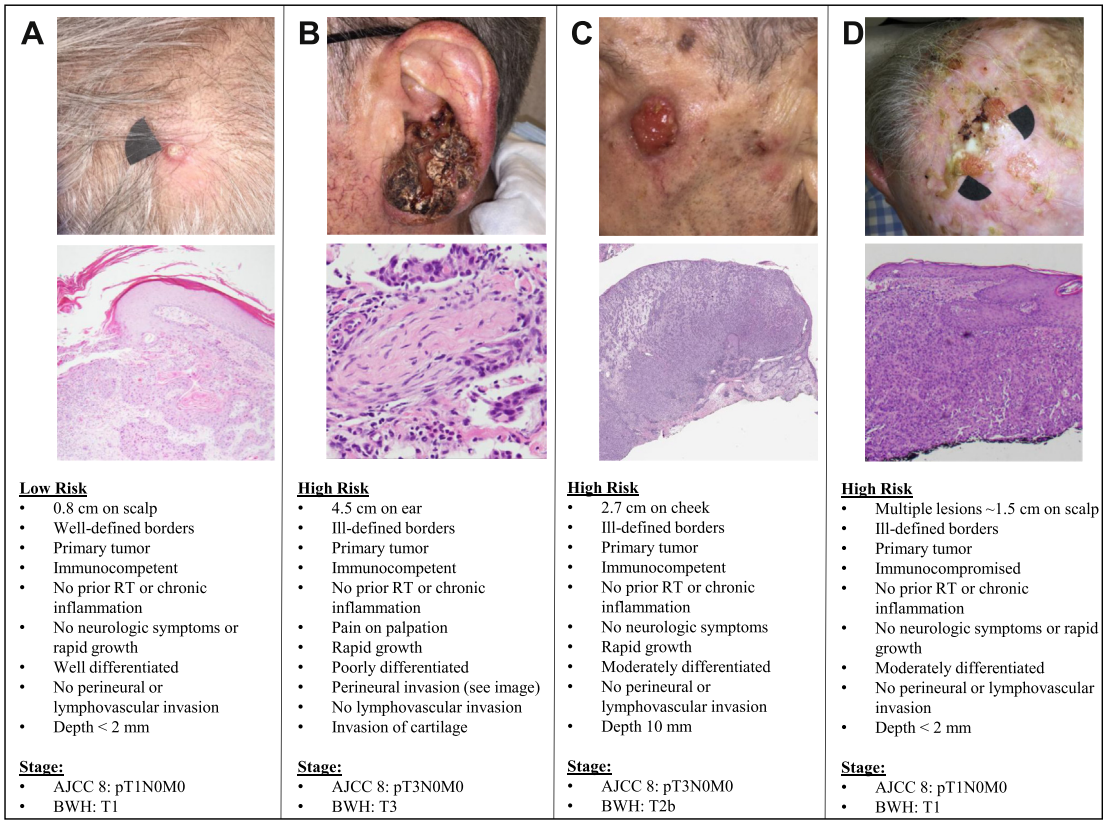

Fig. 1. Risk assessment of cutaneous squamous cell carcinoma. (*A*) Example of low-risk squamous cell carcinoma with well-differentiated pathology (H&E, original magnification ×4). (*B–D*) Examples of squamous cell carcinoma with a variety of high-risk features. Pathology images stained with hematoxylin and eosin (H&E, original magnification [B] ×10; [C] ×1.25; [D] ×2). AJCC, American Joint Committee on Cancer staging; BWH, Brigham and Women's Hospital staging; RT, radiation therapy. See **Table 1** for AJCC and BWH criteria.

and 70.4% of disease-related poor outcomes compared with only 0.7% and 16.9%, respectively, in AJCC 7. Furthermore, T2, T3, and T4 cases together included 85.9% of poor outcomes. Despite these improvements, several weaknesses were identified, including similar risk of disease-related outcomes between AJCC 8 T2 and T3, making these categories indistinct. The investigators suggest that some T2 tumors may still warrant adjuvant therapy or nodal staging. Of note, most of the poor outcomes in AJCC 8 T1 and T2 were cases of poorly differentiated tumors, but this parameter was thought to be too inconsistently defined in clinical practice to be included by the AJCC 8 committee. Consistently reporting clinical tumor size and reproducibly grading histologic differentiation and depth will be critical for future population-based validation.

An alternative tumor staging system was proposed by Jambusaria-Pahlajani and colleagues[22] based on retrospective analysis of 256 tumors at BWH. Their multivariate analysis determined the strongest independent predictors of the following poor outcomes: LR, NM, DSD, or all-cause death. The resulting high-risk features determine staging (see **Table 1**). The model eliminates the rare T4 category and better stratifies stage T2 such that T2b tumors have a statistically significantly increased risk of NM, DSD, and all-cause death. The 4 selected risk factors were confirmed on multivariate analysis of a larger cohort of 1818 tumors from the same center.[16]

Their group also compared the BWH system with AJCC 7 and UICC 7, showing better homogeneity with only 40% of poor outcomes in T1 and T2a compared with 86% in AJCC 7 T1/T2 and 70% in UICC 7 T1/T2. BWH staging also showed better monotonicity with 60% of poor outcomes in T2b and T3 compared with only 14% in AJCC 7 T3/T4 and 30% in UICC 7 T3/T4. Of note, their model does not include N or M criteria because

Table 1
Overview of United States staging systems for cutaneous squamous cell carcinoma

	AJCC 7	AJCC 8 (Head and Neck Only)	BWH
T1	Tumor diameter ≤2 cm with <2 high-risk features	Tumor diameter <2 cm	0 high-risk features
T2	Tumor diameter >2 cm or tumor any size with ≥2 high-risk features	Tumor diameter ≥2 cm but <4 cm	T2a: 1 high-risk feature T2b: 2–3 high-risk features
T3	Tumor with invasion of maxilla, mandible, orbit, or temporal bone	Tumor diameter ≥4 cm or tumor any size with any 1 high-risk feature	All 4 high-risk features
T4	Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base	T4a: gross cortical bone or marrow invasion T4b: skull base invasion or skull base foramen involvement	Not applicable
High-risk features	• Tumor depth >2 mm (or Clark level IV or higher) • Perineural invasion of any size • Location (ear or nonglabrous lip) • Histologic differentiation (poorly differentiated or undifferentiated)	• Deep invasion (beyond subcutaneous fat or >6 mm) • Minor bone erosion • Perineural invasion: tumor cells within the nerve sheath of a nerve ◦ Deeper than the dermis, or ◦ Measuring ≥0.1 mm, or ◦ Clinical or radiographic involvement of named nerves without skull base invasion	• Poorly differentiated histology • Tumor diameter ≥2 cm • Perineural invasion • Deep tumor invasion (beyond subcutaneous fat but excluding bone invasion, which qualifies as T3)

Abbreviation: T, tumor staging.
Data from Refs.[22,30,32]

of the rarity of these events. The investigators assert that their system provides greater separation of high-risk and low-risk tumors, although it may not have had the power to detect other important factors that are not uniformly reported on pathology reports, such as immunosuppression or depth of invasion.

A recent population-based study in Norway[11] attempted to validate AJCC 7, AJCC 8, BWH, and a proposed staging model by Breuninger and colleagues[25] based on tumor diameter, thickness, and other risk factors. They found a lower metastatic rate compared with previous studies (1.5% of 6721 patients), possibly reflecting a more generalizable population than cohorts from tertiary referral systems. In their analysis, the Breuninger system was best able to discriminate between patients who developed metastasis and those who did not. AJCC 8 was an improvement over AJCC 7, but both showed worse discrimination than Breuninger and BWH. The investigators also commented on the simplicity of the BWH and Breuninger systems, which is an important determinant of adoption in daily clinical practice. Continued refinement of T staging is vital for improved prognosis because most cSCCs (about 96%) do not metastasize.

Nodal Staging

Nodal (N) and distant metastasis is rare in cSCC but significantly affects prognosis when it occurs. This article highlights 4 nodal staging systems: AJCC 8, the parotid system by O'Brien and colleagues,[35] the N1S3 system, and the ITEM (immunosuppression, treatment, extranodal spread, and margin status) system. These systems stratify patients into higher stages based on increasing number of affected nodes and node size. AJCC 8 recently added extranodal extension (ENE) as an adverse risk factor, resulting in 7 nodal categories compared with 6 in AJCC 7. A recent retrospective cohort of 382 patients with metastatic cSCC in Australia showed AJCC 8 had poor prognostic ability, because there was no significant difference in disease-specific survival or

overall survival between N1 and N2a, N2b, N2c, or N3b.[36] The investigators note that although studies support ENE as an independent risk factor, it is too common in metastatic cSCC (78% of cases) to make it appropriately discriminatory. Another weakness of AJCC 8 is its joint consideration of both cutaneous and mucosal squamous cell carcinoma (SCC) of the head and neck. Moeckleman and colleagues[37] found that AJCC 8 better stratified patients with mucosal SCC than those with cSCC.

The O'Brien staging system proposes separation of parotid and neck metastasis based on a retrospective cohort showing significantly worse survival with parotid and neck disease compared with parotid involvement alone.[35] Further analysis with larger cohorts is needed to validate the system and determine whether the added complexity is worthwhile.

The N1S3 system is a simpler alternative developed by Forest and colleagues[38] in 2010 from a cohort of 215 patients in Australia and then later validated with a separate group of 250 patients. Multivariate analysis revealed number and size of nodes as independent predictors of disease-specific survival (DSS), yielding 3 distinct prognostic groups:

- I: single lymph node less than or equal to 3 cm with 90% DSS
- II: single lymph node greater than 3 cm or multiple nodes less than or equal to 3 cm with 75% DSS
- III: multiple nodes greater than 3 cm with 42% DSS

In addition, the ITEM prognostic score stratifies patients with metastatic cSCC into low-risk, moderate-risk, and high-risk groups based on a weighted ranking system (1.8 for immunosuppression, negative 1.8 for treatment with surgery and radiation therapy [RT] compared with surgery alone, 4.8 for ENE, and 1.0 for involved surgical margins).[39] In this model, number and size of lymph nodes were not independent predictors of survival. The 5-year risk of death from disease for the low-risk, moderate-risk, and high-risk patients was 6%, 24%, and 56%, respectively.

Note that the most widely used staging systems do not account for patient characteristics known to increase risk of poor outcomes, such as immunosuppression, tumors associated with chronic scars or inflammatory disease, and treatment history (primary vs recurrent).[40] Future studies may lead to their incorporation into staging systems.

MANAGEMENT

Diagnosis

National Comprehensive Cancer Network (NCCN) guidelines recommend that skin biopsies include deep reticular dermis to enable complete histologic evaluation.[41] American Academy of Dermatology (AAD) guidelines recommend that important clinical information be conveyed to pathologists, including age, sex, anatomic location, recurrent versus primary lesion, size of lesion, immunosuppression, and relevant history (especially radiation, burn, or organ transplant).[42] Similarly, to ensure optimal identification of high-risk features, pathology reporting should uniformly include degree of differentiation; presence of aggressive histologic subtypes; depth of invasion (in millimeters); Clark level of invasion; perineural invasion (PNI); lymphovascular invasion (LVI); invasion of fascia, muscle, or bone; number of high-risk features; margin status; and AJCC TNM stage. Some clinicians argue that it is impractical to report all of these features in routine clinical practice, but standardized reporting would significantly improve the ability to evaluate the impact of high-risk features. Future study is needed to determine the frequency of standardized clinical histories and pathology reports and barriers to their completion.

Risk Stratification

On diagnosis of cSCC, clinical evaluation should include inspection and palpation of the involved site and regional draining lymph node basins. According to NCCN guidelines, patients should be stratified based on the presence of clinical or radiographic lymph node involvement. In the absence of nodal disease, local cSCC is divided into low-risk and high-risk tumors based on location, size, treatment history, presence of rapid growth or neurologic symptoms, patient characteristics (immunocompromised status, site of prior RT, or chronic inflammatory process), histologic differentiation, depth of invasion, and presence of PNI or LVI. These factors were selected based on available evidence and expert opinion and are intended to provide guidance on treatment rather than accurate prognostic information.

Local Control for Low-risk Tumors

Low-risk tumors may be treated with curettage and electrodessication (except in terminal hair-bearing regions or when adipose tissue is reached) or standard excision with 4-mm to 6-mm clinical margins and postoperative margin assessment. These recommendations are based primarily on expert consensus and retrospective and

observational studies showing 95% to 96% cure rates.[12,43,44] RT as primary treatment may be considered only for nonsurgical candidates older than 60 years because of the risk of long-term secondary malignancy. Superficial therapies, such as topical fluorouracil, topical imiquimod, photodynamic therapy, and cryotherapy, should be reserved for cSCC in situ.[41]

Local Control for High-risk Tumors

Standard excision with wider margins, Mohs micrographic surgery (MMS), and RT are treatment options for high-risk tumors. There is no specific recommendation for margins on standard excision given the heterogeneity of the high-risk group, and few prospective studies have compared standard excision with MMS. One meta-analysis showed lower recurrence rates with MMS compared with standard excision, with 3.1% versus 8.1% for primary tumors and 10% versus 23.3% for locally recurrent tumors.[12] The improved cure rates of MMS were amplified with higher-risk tumors, because those with perineural involvement had LR of 0% with MMS compared with 47.2% with standard excision. Even in the context of newer adjuvant treatments (discussed later), surgical clearance with negative margins remains the primary goal.

Adjuvant Treatment for Local Control

NCCN guidelines recommend consideration of adjuvant therapy if postoperative margins are positive and further surgery is contraindicated, or if margins are negative and there is extensive perineural involvement. In these situations, RT or multidisciplinary tumor board consultation should be considered. Data have been mixed about the benefits of adjuvant RT, but retrospective studies are limited by selection bias because only the highest-risk patients are considered for adjuvant therapy.[45,46]

Regional Control

Regional nodal disease is associated with increased risk of LR and mortality.[15,19] Haisma and colleagues[15] reported a 5-year DSS rate of 37.3% and overall survival rate of 22.5% in patients with NM compared with 98.8% and 71.4%, respectively, in patients without NM. On clinical or radiologic identification of nodal involvement and confirmation with fine-needle aspiration (FNA) or core biopsy, NCCN guidelines recommend regional lymph node dissection for operable disease, which has shown excellent 5-year DSS of 97% in patients with low nodal tumor burden.[47] RT or systemic therapy may be considered for inoperable NM.

Increased nodal disease burden with multiple involved nodes or ENE may warrant adjuvant RT to the nodal basin. A retrospective study of 167 metastatic head and neck SCCs from Australia showed that patients undergoing lymph node dissection and adjuvant nodal basin RT had a trend toward a lower rate of locoregional recurrence (20% vs 43%) and significantly better 5-year disease-free survival rate (73% vs 54%) than surgery alone.[48] In contrast, Forest and colleagues[38] found no improvement in overall survival with adjuvant nodal RT. More data are needed, because current studies are limited by retrospective design, patient heterogeneity, and treatment selection bias.

Role of Radiologic Imaging

Because the overall risk of cSCC metastasis is low, routine radiologic imaging is not recommended. Imaging should be considered to evaluate locoregional and distant disease, bony or soft tissue invasion, perineural spread, or postoperative recurrence.[49] Ruiz and colleagues[50] retrospectively studied the use of radiologic imaging in high-risk cSCCs (BWH stage T2b or T3) over a 13-year period.[50] In their cohort, imaging was performed in 46% of patients.

Computed tomography (CT), MRI, ultrasonography, and PET/CT have all been used in the work-up of mucosal and cutaneous SCC, with CT identified as the most commonly used modality in retrospective cohorts (79%–83% of cases).[50,51] The best imaging modality depends on the clinical question and available resources (**Table 2**).[49,50,52,53] For evaluation of NM, a 2012 meta-analysis compared CT, MRI, PET/CT, and ultrasonography. CT was superior to ultrasonography in specificity, but there were no other differences in sensitivity or specificity.[53] A 2007 meta-analysis of head and neck mucosal SCC showed higher sensitivity and specificity for ultrasonography with FNA (87% and 98%, respectively) compared with CT and MRI.[54] A retrospective cohort study of 31 patients found that addition of PET/CT resulted in no change in management in 77% despite improved sensitivity for NM.[55] Its high cost may also limit its utility.

Ruiz and colleagues[50] found that imaging in high-risk cSCC cases (defined as BWH stage T2b or T3) resulted in treatment changes in 33%. Furthermore, 5-year disease-free survival rate was higher in patients that were imaged (78%) compared with those that were

Table 2
Comparison of imaging modalities for evaluation of cutaneous squamous cell carcinoma

Imaging Modality	CT	MRI	Ultrasonography	PET/CT
Optimal Use in cSCC	Bone or lymph node disease	Perineural, CNS, deep soft tissue, bone marrow, or lymph node disease	Superficial lymph node disease and image-guided FNA	Distant metastasis
Advantages	Less expensive, more widely available, and faster image acquisition than MRI	No exposure to ionizing radiation	Least expensive, no exposure to contrast dye or ionizing radiation, rapid image acquisition	Functional and anatomic information, distinguish postoperative scar tissue from recurrence
Disadvantages	Exposure to contrast dye and ionizing radiation	Less widely available, longer acquisition time, more expensive than CT	Operator and technique dependent, limited visualization of deep structures	Most expensive
Sensitivity for Head and Neck Nodal Disease (%)[a]	52	65	66	66
Specificity for Head and Neck Nodal Disease (%)[a]	93	81	78	87

Abbreviation: CNS, central nervous system.
[a] Only statistically significant difference is CT with superior specificity compared with ultrasonography.
Data from Refs.[49,50,53]

not (51%), raising the possibility that earlier detection of nodal disease may improve outcomes.

Although there are no specific guidelines for imaging in cSCC, some groups have proposed criteria:

- Que and colleagues[40] recommend CT imaging of draining lymph node basins for BWH stage T2b or T3 tumors and AJCC 8 stage T4 tumors because these patients have 20% risk of NM.
- Breuninger and colleagues[25] recommend ultrasonography for tumors greater than 2 mm in thickness or CT or MRI for infiltrative or destructive tumors.
- NCCN guidelines recommend consideration of CT with contrast and/or ultrasonography in those with significant risk of NM.[41]
- In Europe, ultrasonography is recommended as the initial imaging modality for regional nodal basins in high-risk cSCC, especially for superficial basins such as parotid and cervical nodes.[25,56]

Imaging is not a substitute for clinical palpation of regional nodal basins. Compared with clinical palpation, MRI showed no advantage in a prospective study of 60 patients in Taiwan who later underwent lymphadenectomy.[57] Clinical palpation and MRI had similar sensitivity, specificity, and rate of occult cervical metastasis, underscoring the importance of clinical evaluation.

Sentinel Lymph Node Biopsy

The potential benefit of early detection has led to increased interest in sentinel lymph node biopsy (SLNB) for cSCC. Retrospective studies and meta-analyses have shown the feasibility of SLNB in this patient population along with low false-negative rates (2.6%–7.1%).[58–62] In their review of 173 patients, Allen and Stolle[60] found a sensitivity of 79%, specificity of 100%, and negative predictive value of 96%. Fukushima and colleagues[63] showed that 7% of 41 patients with negative PET/CT or ultrasonography had occult micrometastases on SLNB. Sensitivity of SLNB is improved with use of combined radioisotope and blue dye for identification of the sentinel node (SN) and

serial sections with immunohistochemistry to identify microscopic foci of disease. SN positivity rates varied in these studies between 11.3% and 24%, possibly reflecting varying definitions of high-risk tumors selected for this procedure.[58–62,64] These rates are in keeping with the 10% risk threshold generally thought to warrant SLNB for melanoma. Furthermore, complications from SLNB are rare and mild, including dye allergy, lymphedema, infection, hematoma, seroma, or wound dehiscence. A meta-analysis by Schmitt and colleagues[61] determined that there was a statistically higher rate of SLNB positivity in BWH T2b tumors than T2a tumors (29.4% vs 7.1%). They propose that high-risk lesions T2b or higher be considered for SLNB. They found no such clear cutoff by AJCC 7 criteria, but their review was published before AJCC 8.

One difficulty in applying SLNB to cSCC is that many tumors are staged intraoperatively or postoperatively. In these situations, SLNB may still be considered based on extrapolation from data in melanoma management.[65] At our institution, previous surgery at the melanoma primary site is not a contraindication for SLNB; however, the accuracy and utility of SLNB likely decreases with complex reconstruction or location on head, neck, or trunk where multiple lymph node basins could be involved. Delayed repair or reconstruction that minimizes lymphatic disruption may be considered in these high-risk cases. Microstaging saucerization or excisional biopsies may also be helpful to evaluate high-risk pathologic features before definitive surgical intervention. Prospective studies are needed to determine optimal patient selection and evaluate the effect of SLNB on patient outcomes.

Systemic Treatment

New systemic therapies may help the subset of patients with poor outcomes from cSCC. Historically, combinations of 5-fluorouracil (5-FU)/cisplatin, 5-FU/carboplatin, and paclitaxel/carboplatin showed 80% remission in observational studies. However, responses are short lived, and side effects are often intolerable for the elderly population affected by cSCC. Epidermal growth factor receptor (EGFR) inhibitors target the Ras-Raf mitogen-activated protein kinase (MAPK) pathway, which controls cell cycle progression and proliferation. Cetuximab is now Food and Drug Administration (FDA) approved for locally or regionally advanced mucosal SCC of the head and neck and is used off label for cSCC. Phase II trials of cetuximab monotherapy and phase III trials for gefitinib monotherapy have shown some benefit for unresectable cSCC.[66,67] The addition of cetuximab to traditional platinum/fluorouracil chemotherapy or RT has also shown promise.[68–70]

Immunotherapy with anti–programmed cell death protein 1 (PD-1) inhibitors has also shown efficacy for cSCC, leading to FDA approval of cemiplimab in September 2018. Improved immune surveillance with PD-1 blockade seems to be particularly beneficial in solid tumors with high mutational burden and PD-L1 expression, such as melanoma, non-small cell lung cancer, and cSCC. Phase I data for cemiplimab showed a 52% response rate for unresectable locally advanced or metastatic cSCC,[71] and early data for the phase II cohort with metastatic cSCC showed objective response in 47% over a median of 7.9 months.[72] Data for the phase II trial in locally advanced disease have not yet reached the time point for primary analysis. These treatments have been well tolerated, with fatigue, diarrhea, and rash being the most common adverse effects. Caution in transplant patients has been recommended given the risk of allograft rejection.[73,74]

Further study is needed to determine which patients will benefit from systemic therapy and the role of adjuvant or neoadjuvant therapy.

Immunocompromised Patients

Immunocompromised patients require special mention. Although immunosuppression is not generally included in staging systems, numerous studies have shown higher risk of cSCC development and worse outcomes for cSCC in immunocompromised individuals.[8,12,26–28,75] NCCN guidelines discuss several strategies for treatment of SCC in such high-risk patients that rapidly develop multiple cSCCs. First, destructive techniques that allow treatment of multiple lesions at a single visit may be beneficial. Similarly, field treatment of precancers with 5-FU, imiquimod, or photodynamic therapy may be helpful. In addition, dose reduction of immunosuppression therapy or use of mammalian target of rapamycin (mTOR) inhibitors have shown benefit.[76,77]

Follow-up Monitoring

Patients with cSCC are more likely than the general population to develop another cSCC and are also at higher risk of developing BCC and melanoma. Long-term surveillance and education about sun protection are important in these patients. Furthermore, because most LR occurs within 2 years of treatment, frequent follow-up is recommended during this time.[7,12,75] NCCN recommends physical examination every 3 to

12 months during the first 2 years, every 6 to 12 months for another 3 years, then annually for life. Patients with metastatic disease may be monitored with CT scans, with frequency every 3 to 6 months depending on individual patient risk factors. Importantly, these recommendations should be adjusted depending on individual patient risk.

SUMMARY

The increasing incidence of cSCC in the United States and a renewed focus on high-risk tumors have resulted in exciting new staging and treatment paradigms. Although significant strides have been made, further study is needed to identify, evaluate, and manage the subset of patients at risk for poor outcomes.

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