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Update on the Management of High-Risk Squamous Cell Carcinoma

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Cutaneous squamous cell carcinoma (CSCC) is the second most common malignancy occurring in white patients in the United States and incidence rates are increasing. While the majority of the 87,000-760,000 cases that occur yearly in the U.S. are curable, 4% develop lymph node metastases and 1.5% die from the disease. Given the frequency of occurrence of CSCC, it is estimated to cause as many deaths yearly as melanoma, with the majority occurring in patients with high risk tumors or in those at high risk for metastasis due to a variety of host factors, most commonly systemic immunosuppression. There are currently no standardized prognostic or treatment models to assist clinicians in most effectively identifying and managing these patients. Identification of patients at risk for poor outcomes as well as standardization regarding classification, staging, and treatment of high-risk tumors is critical for optimizing patient care. In this article, available literature on the classification and management of high risk CSCC is briefly summarized, emphasizing new information.

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Cutaneous squamous cell carcinoma (CSCC) accounts for 20% of nonmelanoma skin cancers in the United States, with an estimated 87,000-760,000 cases occurring yearly.[1-8] Incidence rates appear to be increasing over time and are much greater in more Southern U.S. latitudes. CSCC is the second most common cancer overall among white patients.[9] Although most CSCC is curable, 4% result in nodal metastasis and 1.5% in death.[10,11] Precise outcome tallies are unavailable for CSCC because it is excluded from the Surveillance, Epidemiology and End Results (SEER) program data due to its frequency of occurrence and overall low risk of metastasis. However, on the basis of the aforementioned incidence data, it can be estimated that CSCC results in 1300-11,000 deaths annually in the United States, the higher estimates being from more recent studies. These numbers fall in the same range as the number of deaths from melanoma (8700 in 2010 estimated by SEER data). Given these concerning figures, standardization of the identification of high risk cases, classification, staging and management is needed to optimize patient outcomes. External environmental forces, primarily ultraviolet (UV) radiation from sunlight, appear to be the primary causative factors that lead to cellular changes resulting in cutaneous squamous cell carcinoma (CSCC). However, study of the molecular and genetic factors that allow CSCCs to form in response to UV insult is in its infancy. Contributors, such as age, skin pigmentation, immune status, and effectiveness of DNA repair and melanin production all play a role, to varying degrees.[12-14] Exposure to medical or natural ultraviolet radiation (UVB > UVA) with resultant mutations in the p53 tumor-suppressor gene and clonal expansion of keratinocytes is considered the first step in CSCC formation. CSCC risk correlates with latitudes nearer the equator, outdoor occupation,[9,14] and having fair skin, which lacks melanin protection against UV penetration. Infectious contributors include high-risk strains of the human papilloma virus (HPV) (with degradation and dysfunction of p53 and Rb genes via viral E6 and E7 proteins), HIV/AIDS, and chronic infections, such as osteomyelitis. Similarly, chronically inflamed skin is at increased risk, as in chronic radiation dermatitis, in sinus tracts, ulcers and burn scars. Chemical carcinogens linked to CSCC formation include arsenic and polycyclic aromatic hydrocarbons.[3,13,15-22]

Host immune status and local immunobiology play a critical role in the behavior of CSCCs; our understanding of this has been strengthened by new insights on local immune dysregulation within tumors. Although a connection between decreased T-cell activity and CSCC formation has been postulated given the high risk of developing these tumors in patients on immunosuppressive drugs or with chronic lymphocytic leukemia (CLL), counterintuitively, CSCCs tend to be heavily infiltrated with T cells. It has been shown, however, that these T cells are

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mostly T regulatory (Treg) cells. Treg cells tend to suppress the activation and proliferation of effector T cells, which kill tumor cells. Thus, CSCC tumors appear to evade a normal host response.[23] Our understanding of the role of the local immune milieu in CSCC pathogenesis will grow in importance as we attempt to design topical and systemic therapies that selectively destroy CSCC tumor cells.

Identification of High-Risk Squamous Cell Carcinoma

Identification of tumors at high risk for recurrence or metastasis is essential if outcomes are to be optimized. The National Comprehensive Cancer Network (NCCN) recently published their consensus guidelines for defining and managing high risk CSCC based on available data and expert opinion.[24] However, as there is no prognostic model available, it is unknown how various risk factors combine to impact risk of recurrence or death. Therefore, estimating risk of such poor outcomes for an individual patient remains challenging.

Different studies and guidelines have used different definitions of high-risk CSCC. For example, the NCCN considers any one risk factor sufficient to warrant excision with a 10-mm margin or complete margin evaluation (such as Mohs surgery). The risk factors are as follows: large diameter (≥2 cm or 1 cm on cheeks, forehead, scalp, or neck, or 6 mm on other areas of face, genitalia, hands, feet), depth ≥4 mm or beyond the papillary dermis, ill-defined margins, recurrence after definitive treatment, immunosuppression, prior radiation, chronic inflammation, rapid growth, neurological symptoms, perineural or vascular invasion, moderately or poorly differentiated histology, infiltrative or acantholytic pattern, or mucin production. The American Joint Committee on Cancer (AJCC) uses more stringent criteria to define high risk CSCC. To meet T2 criteria, a tumor must be >2 cm in diameter or have 2 or more high-risk features. The AJCC high-risk features are depth (>2 mm or beyond papillary dermis), perineural invasion, location on the ear or lip, or poorly or undifferentiated histology. A tumor must have invasion of bone to meet T3 or T4 criteria.[25]

Neither the NCCN nor AJCC definitions of high risk CSCC have been validated with outcome data, though they are derived from expert review of studies published to date comprised mostly of case series data. The lack of a clear definition of high-risk CSCC, as well as lack of a prognostic model, makes clinical decision-making difficult with regard to use of staging and adjuvant therapy. Even experienced clinicians vary widely in their management of high-risk CSCC[26]. Below we will summarize the available data.

Tumor Factors

Location, Diameter, Histology, Thickness, Invasion, Variants

CSCCs arising in skin that has been previously injured, such as a scar, chronic wound, ulcer, or burn site are associated with a greater risk of recurrence and metastasis.[27-30] Five-year survival rates have been reported to be 52% with recurrence rates approaching 58%.[31] There is a risk of metastasis from anogenital CSCC, with a wide range of rates reported at 15%-74%.[32-35] The prognostic significance of anatomic tumor location at other sites is less clear, as there are conflicting data in the literature. In one prospective study, location on the ear was associated with a 3-fold greater risk of metastasis.[10] Retrospective reviews of available data suggest that location on the lip and ear have higher rates of metastases than other sun exposed sites at 14% and 9%, respectively.[27] In our own retrospective cohort study as well as a 1989 study by Dinehart et al,[36] ear or lip location alone did not portend an increased risk of metastasis although smaller diameter tumors (<2 cm) were more capable of metastasis in these locations (A. Jambusaria-Pahlajani, et al. manuscript in review; Dinehart and Pollack[36]). On the basis of the available data, NCCN guidelines recommend considering CSCC on mucosal surfaces, genitalia and "mask areas" of the face (eyelids and brows, periorbital, nose, lips, chin, pre and postauricular, temple and ear) as well as those occurring in prior radiation fields and on chronically injured skin to be at high risk for recurrence or metastasis.[24]

Tumor diameter has been correlated with higher risk of metastasis with most series using 2.0 cm as a cutoff size.[27,29,37] For CSCC of the lip and ear, tumors <2.0 cm in size have been reported to metastasize.[36] As a result, and based on available data for basal cell carcinoma (BCC), the NCCN panel elected to stratify diameter criteria based on location. Tumors on the "mask area" of the face >0.6 cm, on the forehead, cheeks, neck and scalp >1.0 cm, and on the trunk and extremities >2.0 cm are considered high risk.[24]

In addition to diameter and location, tumors with ill-defined clinical borders or rapid growth are considered high risk according to NCCN guidelines. Local recurrence is associated with distant metastatic disease; 30-50% of metastatic tumors occur in patients with a prior local recurrence[27,38] and thus recurrent tumors are also considered high risk by the NCCN panel.

Histologic Characteristics

CSCC tumor features, determined from case series and small prospective studies, which have been shown to be associated with increased rates of recurrence, metastasis and death include perineural invasion (PNI), depth or involvement of the subcutaneous tissues, and loss of differentiation.[27,39] PNI, particularly of named nerves or those larger than 0.1 mm in diameter, is associated with an increased risk of recurrence and metastasis[27,40] and is associated with disease-specific mortality.[39] Patients with symptomatic involvement or invasion of nerves >0.1 mm in diameter have worse outcomes, with death from disease as high as 32%.[41] NCCN guidelines include both PNI and vascular involvement as high risk factors.[24] In addition, the panel finds that "any suggestion of neurologic involvement in the region of a squamous cell cancer," such as symptoms of pain or dysesthesia, places a tumor in the high-risk category.

While the millimeter depth that defines a tumor as high risk is not well-classified, increased tumor thickness and in-

vasion of underlying fat, fascia, muscle and bone have been associated with metastatic disease. Depths ranging from 4 to 6 mm have been correlated with 16%-45.7% rates of metastasis.[10,27,42] Similarly, tumors <2 mm thick have a very low risk of metastasis[10] while tumors infiltrating through subcutaneous fat are associated with disease specific mortality.[39] As such, NCCN guidelines recommend that tumors >4 mm deep or those with Clark level ≥ IV (invasion of reticular dermis or beyond) be considered high risk.[24]

Histologic degree of differentiation is directly associated with probability of cure with CSCC. Poorly differentiated tumors have been reported to have a 33% risk of metastasis.[27] Well-differentiated tumors have an 88% cure rate, whereas this drops to 59% in moderately differentiated and only 37% in poorly differentiated cases.[29] In addition, specific subtypes, particularly desmoplastic or infiltrative CSCCs are more likely to develop regional metastasis; the likelihood increases with thicker tumors. Infiltrative CSCCs are 10 times more likely to recur locally and 6 times more likely to exhibit regional lymph node spread when compared with non-infiltrative tumors.[42] Other parameters included in the NCCN guidelines, despite limited data regarding their prognostic significance, include adenoid (acantholytic) and adenosquamous histologic subtypes.[24]

Host Factors

Because of a substantially increased incidence of metastasis from CSCC in patients who are immunosuppressed, this status places tumors in such patients in the "high risk" category, supported by the current NCCN guidelines. Metastatic rates are twice as high in the immunocompromised, reaching 13%.[27] The type of immunodeficiency correlates with varying degrees of increased susceptibility, with the greatest amount of available information coming from the organ transplant population.

When compared with the general population, organ transplant recipients (OTRs) have a 65-fold increased incidence of CSCCs.[42] In addition, the ratio of CSCCs to BCC is reversed, with 3 to 4 CSCCs occurring for each BCC.[44,45] Although the role of HPV remains uncertain in this patient group, as yet uncharacterized viruses may contribute to CSCC formation in the immunocompromised.[46] Heart transplant recipients have 3 times the incidence of CSCC when compared with renal transplants, presumably because of the greater degree of immunosuppression required to prevent rejection.[43] Despite the lesser degree of immunosuppression, a renal transplant patient with common risk factors for CSCC development, such as fair skin and extensive sun exposure, has a cumulative incidence of CSCC that approaches 70% after 20 years.[47] The duration of immunosuppression has a direct impact on incidence, with rates of 7% after one year and 45% after 11 years. Once an OTR develops one CSCC, the risk of developing a second within 5 years is 66%.[48] OTRs present more commonly with tumors exhibiting high-risk behavior, with a greater tendency toward deep invasion, poorly differentiated histology and metastasis.[49] The occurrence of in-transit cutaneous metastases is more common in OTRs, and when it occurs is associated with 30% mortality.[50] In certain OTR subsets, such as light-skinned long-term heart transplant survivors, the risk of mortality from CSCC is substantial. In a cohort of heart transplant patients, 4% developed poorly differentiated CSCC within 10 years of transplant. Within 2 years of diagnosis, 66% of the cohort had died or developed metastatic disease.[51] Reduction of immunosuppression in patients with high-risk CSCC may improve outcomes. Dermatologists should alert transplant physicians to the risks posed by high-risk CSCC when such tumors occur in OTRs.[52]

CLL and small-cell lymphocytic lymphoma (SLL) are also associated with increased risk of CSCC and worse outcomes.[53] In these patients, tumors are generally aggressive with high rates of recurrence (19% at 5 years) and metastasis.[20] Less than 5% of patients with CLL/SLL develop CSCC, but those who do tend to have worrisome tumors, with more than half meeting high risk tumor criteria.[53] One quarter of CSCCs in CLL/SLL patients recur or metastasize despite standard therapy with a staggering 41% of CSCC patients with CLL/SLL dying from SCC.[53] CSCC formation may correlate with their underlying lymphoproliferative disorder; if CSCCs suddenly become more plentiful or aggressive, this may herald progression of hematologic disease or at least increased immune dysfunction. Cooperative management with a treating hematologist/oncologist is crucial.

The role of immunosuppression attributable to the HIV virus in the development of CSCC has not yet been clearly established. There is well-documented evidence of an increased risk of anogenital CSCC in association with HPV in these patients. Reports of a small case series have described a 50% mortality rate at 7 years in HIV patients with aggressive CSCC.[21] Because of these concerning reports, HIV patients are generally considered among the high-risk population, particularly those with AIDS or high viral loads, and it is reasonable to treat them as such until further information becomes available.

Other host factors reportedly associated with aggressive CSCC include exposure to iatrogenic psoralen-ultraviolet-A (PUVA), ionizing radiation, or arsenic. Patients with chronic inflammatory or autoimmune disorders treated with immunosuppression, may also have an increased risk of poor outcomes from CSCC.[54] This may be related to both therapy and the disease itself. Chronic inflammation or tissue injury is a well-known risk factor for recurrence and metastasis, as in burn scars or chronic sinus tracts. CSCC is the leading cause of death in patients with recessive dystrophic epidermolysis bullosa. Management in these young patients is incredibly challenging and there is a striking 80% mortality rate within 5 years of diagnosis of the neoplasm.[55]

Work-Up and Disease Staging of High-Risk Disease

Although the staging of CSCC was recently updated by the AJCC to incorporate data from the literature on high risk status, there is limited information on the outcomes and

management of patients based on this classification system. Tumor stages T3 and T4 require bone invasion, which is relatively rare in CSCC, so most high-risk CSCCs currently fall into the T2 category.

After a diagnosis of a high-risk CSCC, a thorough physical examination of draining nodal basins is required. Any clinically palpable node should be evaluated with fine-needle aspiration (FNA) or excisional biopsy; if FNA is done and is negative, excisional biopsy should follow. Because most patients with lymph node metastasis from CSCC are curable if surgically resectable and amenable to adjuvant radiation, early detection of nodal disease is critical.

When there is no evidence of clinical lymphadenopathy, radiologic imaging is the most common approach used for detecting subclinical nodal disease. There is no established gold standard and sensitivity and specificity data for radiologic staging of CSCC is sorely lacking. Generally, computed tomography (CT) is more useful for detecting nodal disease or bone or cartilage involvement and magnetic resonance imaging (MRI) is preferred for evaluating soft tissue extension, including nerve invasion.[56,57] Although CT and MRI have quite low sensitivity for detecting asymptomatic nerve involvement, when nerve invasion is visible on imaging, it correlates with a poor prognosis (a 5-year survival of 50% vs 86% with negative imaging).[58] There have been 2 small studies evaluating 18-fluorodeoxyglucose—positron emission tomography (FDG-PET) scans and ultrasound-guided FNA indicating they may be useful screening tools in detecting subclinical nodal metastases.[59,60] FDG-PET is useful for detecting metastasis where radiotherapy has resulted in necrosis, fibrosis and dense scarring.[61]

There are no data regarding whether radiologic imaging improves outcomes. However, given the limited risks of radiologic imaging, it should be considered in high-risk CSCC for nodal staging and in selected cases, for preoperative planning to evaluate for deep tissue, nerve, or bone invasion.

There have been no controlled studies evaluating sentinel lymph node biopsy (SLNB) in clinically negative nodal basins of patients with CSCC. Its impact on mortality remains unknown. Case reports and small series to date of high-risk CSCC without palpable lymphadenopathy have a combined SLN positivity of 21%, which is greater than that for melanoma. This indicates that SLNB may be underused in high-risk CSCC, particularly since early detection of nodal disease usually results in cure. False-positive results occurred primarily before the use of combination lymphoscintigraphy with methylene blue dye during SLN localization. False-negative rates are reported at 4%-5% and occurred in patients with prior surgery or radiation to the site, which may have impacted the lymphatic drainage and accuracy of SLN biopsy.[62] Which high-risk CSCC patients may benefit from SLNB remains to be defined, but because cure rates with surgery plus adjuvant radiation are 73%,[63] early identification of nodal disease may positively impact outcomes in high-risk CSCC and the utility of SLNB in high-risk CSCC warrants further investigation.

Metastasis from CSCC most commonly presents 1-2 years after diagnosis of the primary tumor.[10,27,36-38,64] It has been rarely reported to metastasize later, with a delay as long as 8 years.[65] Distant metastasis is thought to occur via hematogenous spread, most commonly reaching the lungs, liver, brain, bones or other cutaneous sites.[9] More commonly, CSCC seems to spread via direct extension along nerves, fascial or bony planes or regionally via the lymphatics.[66] Of CSCCs that metastasize, approximately 80% involve regional lymph nodes.[36,38] This finding, and the knowledge that locoregional disease when treated with combination surgery and radiation therapy results in a 73% 5-year survival,[63] underscores the importance of close follow-up and aggressive management in high-risk cases.

Management of Invasive High-Risk CSCC

Surgical Options

Supported by the 2010 NCCN guidelines, complete circumferential peripheral and deep margin assessment (CCPDMA) with frozen or permanent sections is critical for achieving cure of high-risk CSCC. Even in such high-risk cases, tumors with reported clear surgical margins have very good outcomes with significantly lower rates of local recurrence, metastasis and death than those in which the status of the margin is not defined. The rate of local recurrence with clear margins is 5%, nodal metastasis 5%, distant metastases 1%, and disease specific death 1%.[26]

Standard Excision

As per NCCN treatment guidelines, standard surgical excision (in which a sampling but not the entire marginal surface is evaluated pathologically) is considered adequate for non-high-risk CSCC. The only scenario in which standard excision is recommended for high-risk CSCC is for tumors >2 cm on the trunk and extremities with no other high-risk factors that can be excised with a 1.0-cm clinical margin with a primary closure.[24] For all other high-risk CSCC, Mohs surgery or excision with CCPDMA is advised. CCPDMA refers to procedures in which the tissue is excised by a surgeon and the entire circumferential and deep margin is assessed by a pathologist. In Mohs surgery, the surgeon performs this complete margin assessment.

Mohs Surgery

Mohs surgery or resection with CCPDMA is the recommended therapy for all high-risk CSCC (with the single exception above), as well as tumors located in cosmetically or anatomically sensitive areas. Five-year cure rates support the importance of careful margin evaluation, particularly in recurrent cases. Although no randomized studies of Mohs versus standard excision have been carried out in high-risk CSCC, lower recurrence rates have been reported with Mohs in a systematic review[27] and other studies. Standard excision reportedly cures 92% of primary tumors, while Mohs cures 97%; standard excision has a 77% cure rate for recurrent disease, while Mohs cures 90%-94%.[27,67,68] With the presence of high-risk features, cure rates across all modalities decrease, but are still superior with Mohs.

Multidisciplinary Surgical Approach

The presence of deep or bony invasion, in-transit metastasis or large nerve involvement with CSCC may require a multidisciplinary team to attain surgical clearance. If large named nerve involvement is suspected, an MRI can be obtained preoperatively. A Mohs surgeon can establish the peripheral margin of a large tumor. Then, within the next few days, craniofacial, head and neck, or oncological surgeons track PNI of major nerves, manage parotid involvement and bone extirpation to clear the tumor. Establishing the peripheral margin via Mohs surgery shortens intraoperative wait times for frozen section pathology, thus minimizing the duration of general anesthesia and allowing the head and neck or craniofacial surgeon to focus on clearing the deep margin. In high-risk cases, this alone can be a challenging and time-consuming task.

Nonsurgical Treatment of Primary Tumors

Nonsurgical therapies, such as electrodesiccation and curettage, cryotherapy, topical medications, and photodynamic therapy have variable outcomes based on the experience of the practitioner and do not allow for assessment of tumor margins.[47] These modalities are not sufficient for treating high-risk disease and should be reserved for in situ, low-risk tumors, nonsurgical candidates, and in the treatment of field cancerization, as discussed in the sections to follow.

Radiation therapy (RT)

Radiation can be used as a primary treatment option for CSCCs, but because reported cure rates are higher with surgical therapy, radiation as monotherapy is generally reserved for a specific subset of patients where surgery would lead to unacceptable cosmetic or functional impairment, tumors are inoperable, or the risks of surgery outweigh the benefits.[69] With high-risk CSCC, recurrence rates for RT are high, with local control at 80%-85%.[70] However, when properly implemented, RT may allow for maintenance of oral function and cure rates similar to surgery in treating CSCC of the lower lip.[71] The long-term cutaneous risks of radiation and challenges of scheduling make it less favorable for many patients.[70] RT is contraindicated in the treatment of patients with genodermatoses resulting in an increased tendency toward cutaneous malignancy (eg, Gorlin's syndrome, xeroderma pigmentosum) and in patients with connective tissue disease. It is also contraindicated in cases of verrucous carcinoma, due to a well-documented increased likelihood of metastasis in this setting.[24]

Adjuvant Therapy

Radiation Therapy

Although the data regarding which patients most benefit from adjuvant radiation therapy (ART) is limited, it is clear that patients with surgically negative margins before ART have better outcomes, even with significant PNI.[41] If surgical margins are not clear, radiation is termed salvage rather than adjuvant therapy. Salvage therapy carries higher risks of local, regional and distant recurrence.[70,72] Thus, radiation is not a substitute for meticulous margin control and clear surgical margins should be attained whenever possible before ART. As discussed previously, high-risk CSCC has a high-cure rate with Mohs or CCPDMA. Given this, ART is usually not considered worth the added morbidity and cost.

No randomized studies of ART versus surgical monotherapy have been conducted in CSCC. Case series data for ART in high-risk CSCC is very limited and does not show a benefit with ART, however these data were uncontrolled for tumor stage and are subject to treatment bias. More advanced cases with poorer prognoses likely received ART more often.[26] It is unknown which high-risk CSCC patients benefit from ART. ART may be considered in cases of PNI. However, small nerve invasion may have a low risk of recurrence so ART may not be needed in these cases.[41] ART may also be considered in cases of highly infiltrative or multiply recurrent CSCC in which clear surgical margins, even with Mohs or CCPDMA, are less certain. According to NCCN guidelines, ART is recommended to the primary tumor site when there is substantial PNI, which they define as "involvement of more than just a few small sensory nerve branches or large nerve involvement." Salvage RT is recommended when there are positive margins following Mohs or excision with CCPDMA.[24]

Nodal metastasis should be first treated with complete surgical resection. The addition of ART following lymphadenectomy can result in 5-year disease-free survival rates as high as 73%.[63] As per the NCCN, ART is recommended in all cases of CSCC nodal metastases of the head and neck and should be considered following lymphadenectomy in cases on the trunk and extremities.[24] Dosing guidelines depend on the site, type of radiation used, tumor size, prior treatment and whether there is extracapsular extension within involved nodes.[24]

Chemotherapy

Metastatic CSCC has been treated, with occasional responses, with cisplatin monotherapy or in combination with 5-fluorouracil (5-FU), methotrexate, bleomycin, or doxorubicin. There are limited data on efficacy. 5-FU-related adverse effects are most commonly reported and outcomes are varied. Capecitabine (Xeloda; Roche Laboratories, Inc, Nutley, NJ) is the oral 5-FU prodrug and is selectively metabolized within tumor cells to 5-FU. This local metabolism is aimed at reducing systemic adverse effects. Capecitabine monotherapy[73] as well as in combination with subcutaneous interferon[74] have been used to treat locally advanced CSCC, with some reports of improved outcomes. Phase 2 trials in patients with CSCC of the head and neck using capecitabine with cisplatin or paclitaxel[75,76] or in combination with radiation[77] have shown favorable outcomes.

Epidermal growth factor receptor (EGRF) inhibitors have been used off-label in the treatment of CSCC, owing to the overexpression of EGFR in some tumors.[78] The inhibitors are thought to control proliferation, survival, cell cycle progression, angiogenesis and metastasis. The EGFR inhibitor cetuximab has shown some success in the treatment of inoperable

disease, in-transit metastases and in metastatic CSCC in epidermolysis bullosa. It has also shown some efficacy when used in combination with celecoxib.[79-82] Although another EGFR inhibitor, gefitinib, was reported in a single case to result in palliative tumor shrinkage,[83] phase II,[84] and III[85] trials in metastatic mucosal SCC of the head and neck failed to show a significant survival benefit.

Randomized trials of 13-*cis*-retinoic acid (isotretinoin), for the treatment of existing tumors, have shown no benefit. This is the case when used alone for adjuvant-treatment of mucosal SCC of the head and neck,[86] or in combination with interferon[87] for existing CSCC. There have been no controlled trials evaluating acitretin in treating established tumors. It remains reasonable to consider the use of full dose retinoids for a possible chemotherapeutic or suppressive effect in patients with metastatic or inoperable disease.[52]

Despite the lack of evidence, adjuvant chemotherapy may still be considered in locally advanced or metastatic disease; a multidisciplinary approach in collaboration with medical oncology is needed. NCCN guidelines recommend consideration of cisplatin-based chemotherapeutic regimens and participation in clinical trials for distant metastatic disease or regional recurrence.[24] Further evaluation is needed to determine which patients and which regimens are most likely to improve outcomes.

Follow-Up

Because patients with nodal disease have 5-year survival rates of 73% with the combination of surgery and RT,[63] patients with CSCC should be closely followed for nodal as well as local recurrence. 95% of local recurrences and metastases occur within 5 years of diagnosis,[27] with 70%-80% occurring in the first 2 years. In addition, 30%-50% of patients will develop a second primary nonmelanoma skin cancer within 5 years of the first. The NCCN recommends full skin and lymph node examination by a dermatologist every 3-6 months for the first 2 years, every 6-12 for the next 3 and annually thereafter in cases of local disease. For regional disease, recommended follow up is more aggressive, reported to be every 1-3 months for 1 year, 2-4 months for the second year, 4-6 months until 5 years and then 6-12 months for life; which end of the range depends on the patient and clinical judgment. A neurological examination should be performed if symptoms or signs indicate it is warranted. Management of actinic keratoses, treatment of field cancerization as below and early biopsy of suspicious or persistent lesions is recommended. Although there is no empiric data to support any change in outcomes, imaging of the draining nodal basin can be considered every 6 months for more advanced cases, such as with extensive PNI or in those who are at highest risk of aggressive tumor behavior secondary to their degree of immunosuppression or personal history of tumor behavior.

Management of High-Risk Patients with Diffuse Actinic Damage and/or Multiple CSCCs

Assessment of Immune Status

A diagnosis of CSCC should prompt questioning to identify the presence of any underlying impairment of immune status, placing the patient at higher risk of a poor outcome. Accelerated skin cancer formation, particularly with multiple or high-risk CSCCs, may herald declining immunity. For OTRs, when immunosuppression is reduced, the number of new CSCCs declines and outcomes in patients with known aggressive disease improve.[52] In general, single agent therapy is less correlated with tumor formation than multiagent immunosuppression. Sirolimus, a newer immunosuppressive agent and an inhibitor of the mammalian target of rapamycin (mTOR), is associated with a lower incidence of CSCC when compared with older calcineurin inhibitors. Its use does not appear to compromise graft function.[88,89] In addition, transitioning from traditional calcineurin inhibitors to sirolimus is correlated with thinner tumors showing reduced vascularization.[90] This finding is consistent with the known antiangiogenic properties of mTOR inhibitors.

Nonmelanoma skin cancers have a real impact on the quality of life of transplant patients. It is important to convey to transplant physicians that multiple and high-risk CSCC formation may indicate profound immune dysfunction, that up to 10% of CSCCs in OTRs metastasize and most of these patients will die from their skin cancer.[48,91] Risks may be much greater for certain tumors, although these risks have not been precisely quantified, making management decisions difficult. When CSCC develops in an OTR, the dermatologist should alert the transplant physician and request that medications be reviewed to ensure the patient is on the lowest possible doses safe for the organ graft. Further dose reductions or changes in class of immunosuppression may be considered by transplant physicians if high-risk CSCC develops. The risks posed by high-risk CSCC must be balanced with the risks of a new immunosuppressive regimen on the graft.

For high-risk CSCC in a CLL patient, the hematologist should be notified so the patient's CLL status may be reevaluated. Aggressive CSCC may herald a change in the leukemic state or immune function of the patient.

Treatment of Field Cancerization

Immunosuppressed patients with diffuse actinic damage, who develop multiple CSCCs monthly, should be treated aggressively and preventatively by effectively using field therapies. Surgical clearance of all invasive CSCCs with histologic margin evaluation is considered first-line therapy. CCPDMA should be performed on all high-risk invasive tumors and electrodesiccation and curettage should be avoided. One acceptable approach is the use of disk excision with POMA for low-risk CSCCs on the trunk and extremities. Patients can be seen monthly with multiple tumors removed at each visit. Wounds may be allowed to heal by secondary intention, with minimal risk of infection, even in the immunocompromised.

The initial "clean-up" phase may require 6 months of visits every 4 to 6 weeks.

Once all invasive CSCC has been removed (those which appear to have a dermal component on examination), field treatment of the remaining in situ disease may begin. Hypertrophic actinic keratoses and SCC in situ may be lightly curetted to remove hyperkeratotic overlying scale. This improves the efficacy of topical therapies, such as 5-FU twice a day for a month; this should begin immediately to 1 day after curettage. Imiquimod is less well tolerated in this setting given large surface areas of involvement and flu-like symptoms that occur with systemic absorption. Similarly, cryotherapy has a limited role in field therapy, given the area requiring treatment. Lesions that fail to clear on monthly follow-up must be biopsied or treated with disk excision.[92]

In addition to topical 5-FU as described previously, another option for the treatment of the remaining field of actinic damage is cyclic photodynamic therapy (PDT). In these patients, 20% 5-aminolevulinic acid is applied under plastic wrap occlusion followed by PDT with blue light (417 nm). This is repeated every 2-4 months and has been shown to reduce CSCC formation in OTRs by 95% when compared with the year preceding the initiation of cyclic PDT.[93]

If patients persistently develop multiple tumors after 6-12 months the aforementioned methods have been instituted, the addition of low-dose oral retinoids should be considered for tumor prophylaxis. Retinoids have been reported to slow the development of new tumors, particularly in OTRs, but do not alter the course of existing cancers.[94-98] They promote differentiation, down-regulate proto-oncogenes and regulate growth in the hyperproliferative epidermis.[95,99] Reported effective doses range from 10 to 30 mg/d. Therapy must be continued indefinitely for persistent efficacy, as patients return to baseline on discontinuation of treatment. Low dose therapy is usually sufficient and dose escalation, beginning with 10 mg every other day and increasing to where effect is observed, is an acceptable method of instituting treatment.[52] Once efficacy is reached, it is reasonable to taper to the lowest effective maintenance dose, given that therapy is continued indefinitely. Laboratory measures must be followed as per established standards.

Conclusions

Despite its visibility on the skin, CSCC may account for nearly as many deaths annually in the United States as melanoma. Nearly all of these poor outcomes are thought to occur in a subset of cases with known high-risk factors, termed high-risk CSCC. However, the precise risks associated with various combinations of risk factors have yet to be quantified and subsequently, high-risk CSCC has not yet been clearly or consistently defined. Better prognostic estimates and more precise tumor staging systems are necessary to effectively manage patients afflicted with CSCC. Meanwhile, there is ambiguity and variability in treatment guidelines and therefore in patient care.

Current NCCN guidelines and AJCC staging have been developed from clinician experience and available case series data. On this basis, the identification and classification of tumor and host factors has begun to take form. Current NCCN standards require surgical treatment to clear margins whenever possible, using Mohs surgery or excision with CCPDMA for high-risk CSCC. Consideration of nodal staging and adjuvant radiotherapy or chemotherapy remains largely at the practitioners' discretion because data are limited but should be considered in high-risk cases, particularly those with large-caliber nerve invasion or when clear surgical margins are in question. Close follow up is imperative for early detection and treatment of nodal metastasis which can usually be cured. The development of reliable prognostic models and validated tumor staging systems will greatly aid future treatment decisions in CSCC and facilitate well-designed clinical studies. Such studies should lead to decreased morbidity and mortality from high-risk CSCC and its management.

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