REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Squamous-Cell Carcinoma of the Skin

Ashley Wysong, M.D.

From the Department of Dermatology, University of Nebraska Medical Center, Omaha. Dr. Wysong can be contacted at ashley.wysong@unmc.edu or at the Department of Dermatology, 985645 Nebraska Medical Center, Omaha, NE 68198.

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Skin cancer is the most frequently diagnosed cancer in the United States and worldwide. One in five Americans will have skin cancer in their lifetime.[1] Nonmelanoma skin cancers, also called keratinocyte carcinomas, are the most common type of cancer treated in the United States, with more than 5 million incident cases per year.[2] Precise estimates of incidence are challenging, since keratinocyte carcinoma is not reported in national cancer registries such as the Surveillance, Epidemiology, and End Results registry. Cutaneous squamous-cell carcinoma is the second most common type of skin cancer, with more than 1 million new cases per year,[2,3] outnumbering all top five reportable cancers treated in the United States combined.

The overall prognosis for patients with cutaneous squamous-cell carcinoma is excellent. Nodal metastases develop in 1.9 to 5.2% of cases, and overall mortality is 1.5 to 3.4%.[3-7] However, patients with metastases tend to have much poorer outcomes.[6] Among immunosuppressed patients, the risk of cutaneous squamous-cell carcinoma is increased by a factor of 65 to 250, with a higher incidence of local recurrence and metastasis in 6 to 15% of cases.[8,9] Cutaneous squamous-cell carcinoma accounts for an increasing number of deaths from skin cancer in the United States, with estimates suggesting that the absolute numbers of patients with nodal metastasis and of deaths are equal to or exceed those for melanoma or leukemia.[3,10] Both the incidence of cutaneous squamous-cell carcinoma and the burden of disease are on the rise. This evidence-based review provides clinicians with current information about epidemiologic features, clinicopathological risk factors, staging, management, and prevention.[2,11,12]

Epidemiology and Clinical Presentation

Cutaneous squamous-cell carcinoma accounts for 20% of all cutaneous cancers.[1] The incidence over the past several decades has been increasing worldwide among White populations, an increase that is hypothesized to be associated with the aging population, higher levels of sun exposure, the use of tanning beds, and increased focus on skin cancer screening and detection.[13,14] In addition, a growing proportion of persons with cutaneous squamous-cell carcinoma, such as organ-transplant recipients, have underlying immunosuppression.

Cutaneous squamous-cell carcinoma can develop on any surface of the skin. It is more common in men than in women (3:1 ratio), and the risk increases dramatically with age.[15] Specifically, the incidence among persons older than 75 years of age is 5 to 10 times that among those younger than 55 years of age.[16] Patients typically present with scaly, erythematous, or bleeding lesions, most often on sun-exposed areas, and the appearance of these lesions differs according to histologic subtype (Fig. 1). Cutaneous squamous-cell carcinoma is the most common type of skin cancer in Black persons and the second most common type in White, Asian, and Hispanic persons.[17] The overall incidence among Black persons is estimated

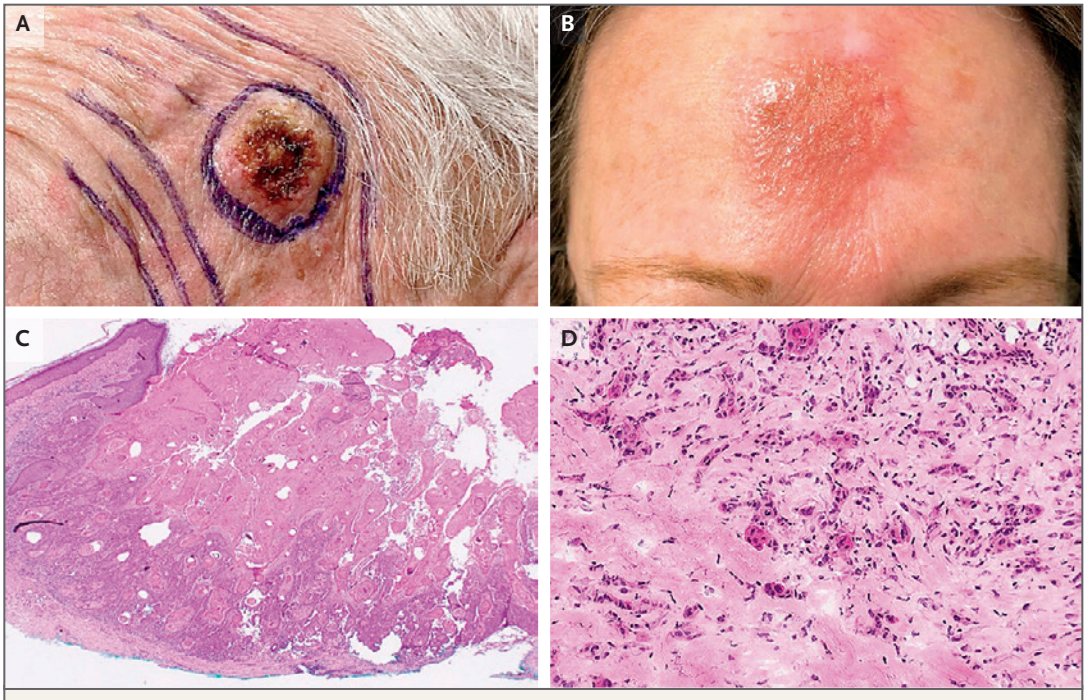

Figure 1. Typical Clinical and Histologic Features of Cutaneous Squamous-Cell Carcinoma.

Panel A and Panel C (hematoxylin and eosin stain) show well-differentiated cutaneous squamous-cell carcinoma, and Panel B and Panel D (hematoxylin and eosin stain) show poorly differentiated cutaneous squamous-cell carcinoma.

to be 3 cases per 100,000, as compared with 150 to 360 per 100,000 among non-Hispanic White persons in the United States.[17,18] Areas of the body that are not exposed to the sun, such as the palms of the hands, soles of the feet, nails, and anogenital regions, as well as areas of chronic inflammation or scarring, are common locations for cutaneous squamous-cell carcinoma in non-White populations. Most cases of cutaneous squamous-cell carcinoma are localized to the skin.

ENVIRONMENTAL, CLINICAL, AND GENETIC RISK FACTORS

Certain environmental, genetic, and clinical factors put patients at increased risk for cutaneous squamous-cell carcinoma. The most important factors are cumulative exposure to ultraviolet radiation, age, and systemic immunosuppression.

Ultraviolet radiation is the most important environmental risk factor for the development of cutaneous squamous-cell carcinoma. Specific patterns of total and cumulative ultraviolet exposure lead to the highest rates of cutaneous squamous-cell carcinoma.[19] Ultraviolet B causes direct DNA damage through the formation of dipyrimidine dimers that lead to malignant transformation.[19] Ultraviolet A (UVA) also plays an etiologic role through indirect DNA damage and the formation of free radicals. Psoralen plus UVA and tanning beds, both primary emitters of UVA, have been shown to be associated with an increased risk of cutaneous squamous-cell carcinoma.[20,21] For persons who have undergone indoor tanning of any duration, as compared with those who have never undergone indoor tanning, the relative risk of cutaneous squamous-cell carcinoma is 1.67.[21] Other environmental risk factors include exposure to ionizing radiation and exposure to arsenic or radon.

Many genetic factors play a role in the development of cutaneous squamous-cell carcinoma. Inherited phenotypic characteristics — such as light skin, red or blonde hair, and light-colored eyes — are associated with an increased risk of cutaneous squamous-cell carcinoma.[22] A family history of cutaneous squamous-cell carcinoma is associated with a risk that is two to four times that in persons without a family history.[23] Inherited disorders such as xeroderma pigmentosum,

epidermolysis bullosa, albinism, and other rare genetic syndromes also increase the risk of cutaneous squamous-cell carcinoma, often with an earlier age at onset for those with such disorders than for those without.[22] Genomewide association studies have identified germline mutations, or single-nucleotide polymorphisms, that may put persons at risk.[24-26] Cutaneous squamous-cell carcinoma has a high tumor mutational burden, with mutations commonly seen in TP53, NOTCH1 or NOTCH2, CDKN2A, PI3K, and cell-cycle pathways.[27]

Innate, acquired, and iatrogenic immunosuppression can increase the risk of cutaneous squamous-cell carcinoma, the number of lesions, and the aggressiveness of any single lesion. Acquired immunosuppression, most commonly due to receipt of a solid-organ transplant, human immunodeficiency virus (HIV) infection, chronic lymphocytic leukemia, lymphoma, or long-term immunosuppressive therapy, puts patients at increased risk for cutaneous squamous-cell carcinoma. Specifically, the incidence of disease has been reported to be higher by a factor of 5 to 113 among organ-transplant recipients than among immunocompetent persons.[28]

Other risk factors for the development of cutaneous squamous-cell carcinoma include chronic inflammation (from burn scars, chronic ulcers, sinus tracts, or inflammatory dermatoses), smoking, hypothyroidism, and drugs (e.g., voriconazole, hydrochlorothiazide, BRAF inhibitors, and tumor necrosis factor inhibitors), as well as human papillomavirus (HPV, a risk factor for periungual and anogenital squamous-cell carcinoma in particular).[29]

STAGING, WORKUP, AND PROGNOSIS

Staging of cutaneous squamous-cell carcinoma has changed dramatically in the past 10 years, with several refinements integrating clinical and pathological risk factors for local recurrence and metastasis in order to improve risk stratification, distinctiveness between tumor stages, and monotonicity. Individual clinical and pathological factors associated with increased rates of local recurrence and metastasis are shown in Figure 2.[30-34] Given the high number of cases of cutaneous squamous-cell carcinoma diagnosed annually, it is important to identify persons at increased risk for a poor outcome who would benefit from enhanced workup, management, and surveillance strategies. Four tumor (T) staging systems for cutaneous squamous-cell carcinoma use clinical and pathological tumor features to predict clinical outcomes, including local recurrence and the development of metastases.[35-38] In addition, the National Comprehensive Cancer Network (NCCN) stratifies cutaneous squamous-cell carcinoma into risk categories to help guide management and surveillance but does not provide prognostic information.[39] Features of the staging systems and risk factors for local recurrence, nodal metastasis, distant metastasis, and disease-specific death are outlined in Table 1.[35-38]

The American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, 8th edition, is the most widely used staging system for solid-organ tumors. However, the Brigham and Women's Hospital (BWH) and Salamanca refinements of the AJCC definition of T3 tumors have been shown to improve risk stratification both in studies at single academic centers[40,41] and in population-based studies.[42,43] The BWH refinement is believed to have the highest specificity, positive predictive value, and concordance index, with all three staging systems having a similar negative predictive value.[43] BWH stage T2a, T2b, and T3 tumors are associated with an increased risk of nodal metastasis, with a 10-year cumulative incidence of 5%, 24%, and 60%, respectively.[40] In one validation study, BWH stage T2b tumors accounted for only 5% of the cases in the retrospective cohort analyzed but for 72% of nodal metastases and 83% of deaths from cutaneous squamous-cell carcinoma.[44]

Immunosuppressed patients are at increased risk for metastasis, with a systematic review and meta-analysis showing a pooled risk estimate for metastasis among organ-transplant recipients of 7.3% (95% confidence interval [CI], 6.2 to 8.4) on the body and 11.0% (95% CI, 7.7 to 14.8) in the head and neck areas.[9] A population-based study involving more than 11,000 patients with cutaneous squamous-cell carcinoma showed that immunosuppression in organ-transplant recipients and patients with hematologic cancer was associated with an increased multivariable hazard ratio of 5.0 and 2.7, respectively, for metastasis.[7] Although the overall risk of metastasis and poor outcomes is increased in immunosuppressed populations, recent data suggest that

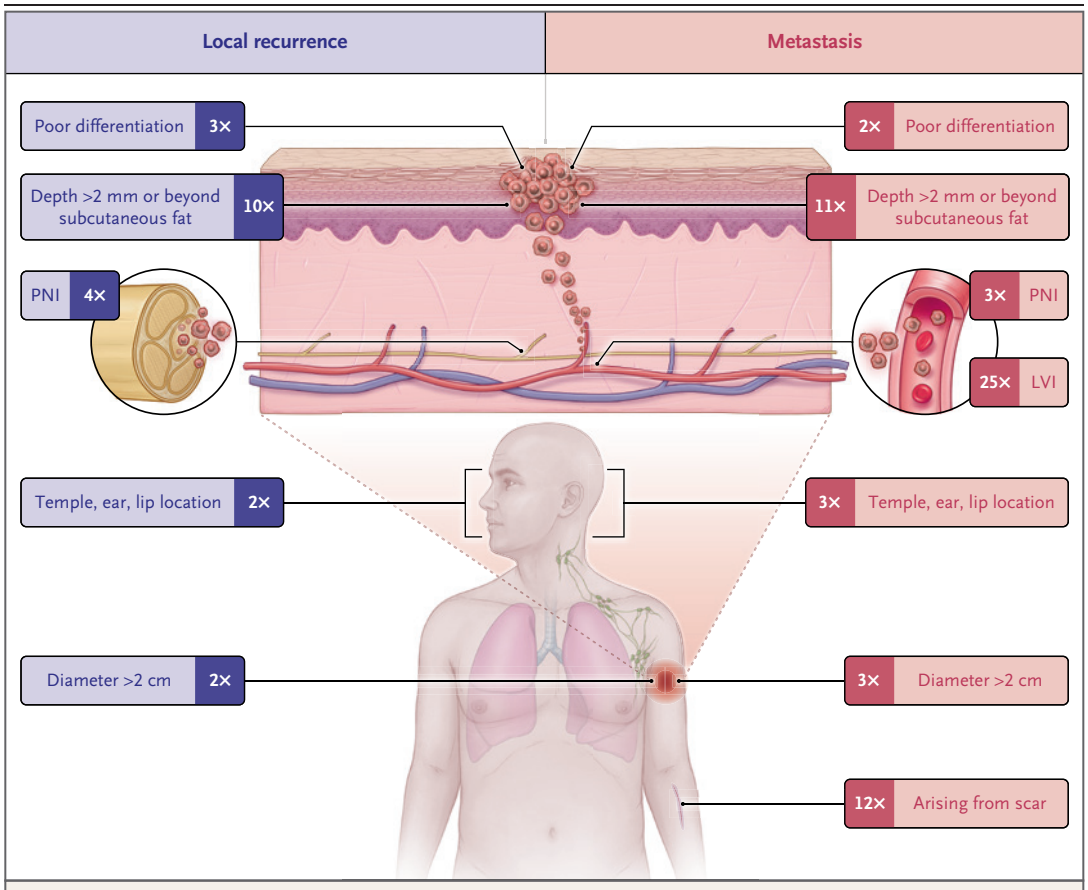

Figure 2. Clinical and Pathological Risk Factors for Local Recurrence and Metastasis in Patients with Cutaneous Squamous-Cell Carcinoma.

LVI denotes lymphovascular invasion, and PNI perineural invasion.

immune status may not independently predict metastasis and death when the analysis is controlled for the stage of any given tumor.[45] Other risk factors that are not considered in current staging systems but are relevant for predicting poor outcomes of cutaneous squamous-cell carcinoma include recurrence, lymphovascular invasion, and in-transit metastasis.[32,46]

Staging systems based on clinical and pathological features alone may be limited in their ability to accurately stratify all patients with cutaneous squamous-cell carcinoma. Gene expression profiling, which uses tumor biology as a prognostic factor, has been shown to be an independent predictor of metastatic risk, with a significantly improved positive predictive value, as compared with traditional staging, and similar negative predictive value, sensitivity, and specificity.[47] A 40-gene expression profile test has been developed and validated to stratify cases of primary cutaneous squamous-cell carcinoma into three classes (1, 2A, and 2B), with event rates for the development of metastasis at 3 years of 8.9%, 20.4%, and 60.0%, respectively.[47] Since this prognostic test was developed on the basis of retrospective cohorts, validation in a prospective study is needed, as well as additional data on how best to integrate gene expression profiling into clinical practice.

Currently, there are no evidence-based or consensus guidelines for imaging in cutaneous squamous-cell carcinoma. Clinical indications for radiologic imaging at baseline include assessment of the extent of the primary tumor (i.e., bony invasion, orbital invasion, or involvement of muscle or fascia or other critical structures) and evaluation for potential perineural spread or metastatic disease. All patients with

Table 1. Tumor Staging and Risk Factors for Cutaneous Squamous-Cell Carcinoma.

Tumor Stage	Staging System*				
	AJCC	BWH	Salamanca Refinement	Tübingen	NCCN
Low risk					
T1	Tumor diameter <2 cm	0 risk factors	Tumor diameter <2 cm	Tumor diameter ≤2 cm, tumor thickness ≤6 mm	Tumor diameter ≤2 cm on trunk and arms and legs; well-defined, primary tumor, well or moderately differentiated, depth ≤6 mm
T2	Tumor diameter ≥2 cm and <4 cm		Tumor diameter ≥2 cm and <4 cm		
T2a		1 risk factor			
High risk					
T2b		2 or 3 risk factors			**High risk**: tumor diameter >2 cm and ≤4 cm on trunk and arms and legs; location on head, neck, hands, or feet, pretibial area, or anogenital areas, regardless of diameter; poorly differentiated, recurrent, immunosuppression, site of prior radiation therapy or chronic inflammatory process, rapid growth, neurologic symptoms, perineural involvement. **Very high risk**: tumor diameter >4 cm at any location, poor differentiation, desmoplastic squamous-cell carcinoma, depth >6 mm or invasion below subcutaneous fat, perineural invasion of a nerve lying below dermis or measuring ≥0.1 mm, lymphatic or vascular invasion
T3	Tumor diameter ≥4 cm or minor bone erosion, perineural invasion, or deep invasion	≥4 high-risk factors or bone invasion			
T3a			Tumor thickness >6 mm (with no invasion beyond subcutaneous fat), with or without tumor diameter ≥4 cm		
T3b			Invasion beyond subcutaneous fat or perineural invasion		
T3c			Combination of both T3b risk factors or AJCC T3 definition with ≥3 risk factors		
T4a	Tumor with gross cortical bone or marrow invasion				
T4b	Tumor invading skull bone or involving skull base foramen				

* The American Joint Committee on Cancer (AJCC) *Cancer Staging Manual*, 8th edition, defines deep invasion as invasion beyond subcutaneous fat or at a depth of more than 6 mm. Perineural invasion is defined as invasion in nerves that are 0.1 mm or more in diameter, invasion that is deeper than the dermis, or clinical and radiologic involvement of affected nerves, without involvement or invasion of the base of the cranium. The Brigham and Women's Hospital (BWH) staging system defines high-risk tumors as having a diameter of 2 cm or greater, poorly differentiated histologic features, perineural invasion of 0.1 mm or more, or tumor invasion beyond subcutaneous fat (excluding bone invasion, which automatically upgrades the tumor to stage T3). NCCN denotes National Comprehensive Cancer Network.

cutaneous squamous-cell carcinoma, and particularly those with any high-risk features, should undergo clinical nodal staging. Retrospective studies suggest that patients with BWH stage T2b or higher tumors may benefit from baseline imaging of the draining nodal basins, since 59 to 65% of patients have abnormal results, with management altered in 24 to 33% of patients.[48,49]

Nodal staging is classified in the AJCC staging system on the basis of size, number of nodes involved, and the presence or absence of extranodal extension. AJCC nodal staging can be clinical or pathological in nature, with current systems lacking the ability to risk-stratify patients in terms of disease-specific or overall survival.[50,51] Pathological nodal staging is probably underutilized in patients with high-risk squamous-cell carcinoma, for which systematic reviews have shown sentinel lymph-node biopsy positivity rates of 13 to 21%, with rates of subclinical lymph-node metastasis as high as 30% in cases involving BWH T2b tumors.[44,52-54] Sentinel lymph-node biopsy is the standard of care for melanoma and other solid tumors, with rates of occult nodal metastasis anticipated to be higher than 7 to 10%. Although there is no standard of care for nodal staging in cutaneous squamous-cell carcinoma, the ability to identify metastasis in its earliest forms can limit poor outcomes. Once metastasis is detected, the 5-year survival rate is reduced (50 to 83%)[55] and may be even lower in immunosuppressed populations.[56] An NCCN panel recently updated recommendations to include consideration of pathological nodal staging for patients who have recurrent cutaneous squamous-cell carcinoma or two or more other risk factors putting them at very high risk.[39]

MANAGEMENT

The general approaches to management of cutaneous squamous-cell carcinoma are outlined in Table 2.[39,57-59]

TREATMENT OF THE PRIMARY TUMOR

The majority of localized, low-risk cases of cutaneous squamous-cell carcinoma can be managed with destructive or surgical techniques performed in most outpatient office settings while the patient is under local anesthesia.[39,58] Specifically, curettage and electrodessication is a destructive technique used for small, low-risk lesions, excluding terminal hair-bearing areas. With this technique, which involves the use of a curette to manually scrape the lesion and an electrosurgical device to remove cancerous cells without pathological assessment, the cure rate is as high as 95% for appropriately selected lesions.[60] Standard wide local excision can be performed with surgical margins of 4 to 6 mm, with cure rates of 90 to 98%.[60]

Surgery remains the mainstay of treatment for localized, high-risk cutaneous squamous-cell carcinoma. However, wider surgical margins (6 to 10 mm) and more exhaustive histologic assessment are recommended. Specifically, Mohs micrographic surgery or resection with peripheral and deep exhaustive margin assessment is recommended to achieve local control for high-risk and very-high-risk cutaneous squamous-cell carcinoma.[39] Mohs micrographic surgery has been shown to be highly effective for control of primary cutaneous squamous-cell carcinoma, with very low rates of local recurrence (1.2 to 4.1%), nodal metastasis, and disease-specific death.[60-62] Appropriate use criteria have been developed, validated, and endorsed by the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery, and American Society for Mohs Surgery.[63] High-risk features, such as positive margins, extensive perineural involvement, or involvement of large or named nerves, warrant multidisciplinary consultation and consideration of adjuvant therapy.

RADIATION THERAPY

For patients who are not surgical candidates, radiation therapy of the primary tumor may be considered. The use of adjuvant radiation therapy in patients with cutaneous squamous-cell carcinoma, particularly in the case of clear histologic margins, is heavily debated, with limited consensus guidelines and a lack of long-term prospective data. The NCCN and the American College of Radiology recommend consideration of adjuvant radiation therapy to the tumor basin, after multidisciplinary consultation, in patients who have positive margins after undergoing Mohs micrographic surgery with peripheral and deep exhaustive margin assessment and in patients with extensive peripheral-nerve involvement,

Table 2. Guideline-Based Management and Risk-Adjusted Follow-up Recommendations for Primary Cutaneous Squamous-Cell Carcinoma.*

Risk Level	Surgery	Workup	Radiation Therapy	Systemic Therapy	Follow-Up
Low	Curettage and electrodesiccation (excluding terminal hair-bearing areas), wide local excision (margins, 4–6 mm), Mohs micrographic surgery	Clinical lymph-node evaluation	For patients who are not surgical candidates or who have positive margins	For patients who are not surgical candidates	Skin self-examination monthly; full-body skin examination every 3–12 mo for 2 yr, then every 6–12 mo for 3 yr, then annually
High	Mohs micrographic surgery or PDEMA preferred, wide local excision (margins, 5–10 mm)	Consideration of nodal staging (imaging) for BWH T2b or T3 tumors or AJCC T3 or higher-grade tumors	For patients who are not surgical candidates or who have positive margins, recurrent disease, or extensive or named-nerve perineural invasion	Multidisciplinary consideration of systemic therapy if there is residual disease after resection or if surgery is not feasible	Skin self-examination monthly; full-body skin examination plus clinical nodal examination every 3–6 mo for 2 yr, then every 6–12 mo for 3 yr, then annually
Very high	Mohs micrographic surgery or PDEMA preferred, wide local excision (margins, 5–10 mm)	Consideration of nodal staging (imaging or sentinel lymph-node biopsy)	For patients who are not surgical candidates or who have positive margins	Multidisciplinary consideration of systemic therapy alone in complicated cases of locally advanced squamous-cell carcinoma in which curative surgery or radiation therapy is not feasible	Skin self-examination monthly; full-body skin examination plus clinical nodal examination every 3–6 mo for 2 yr, then every 6 mo for 3 yr, then every 6–12 months

* PDEMA denotes peripheral and deep exhaustive margin assessment.

involvement of large nerves (≥0.1 mm in diameter) or named nerves, or other high-risk features.

Data on the benefit of adjuvant radiation therapy in cutaneous squamous-cell carcinoma are limited. A retrospective study involving patients with cutaneous squamous-cell carcinoma of the head and neck showed that adjuvant radiation therapy was associated with improved overall survival (hazard ratio, 0.59; 95% CI, 0.38 to 0.90), as well as with improved disease-free survival in a subset analysis of tumors with peripheral-nerve involvement (hazard ratio, 0.47; 95% CI, 0.23 to 0.93).[64] A retrospective cohort study involving 508 patients with high-T-stage cutaneous squamous-cell carcinoma showed that adjuvant radiation therapy after surgery with clear margins resulted in a lower 5-year cumulative incidence of both local recurrence (3.6%) and locoregional recurrence (7.5%) than clear-margin surgery alone (8.7% and 15.3%, respectively).[65] However, other studies have shown no benefit of adjuvant radiation therapy over surgical monotherapy in cohorts with clear histologic margins.[40,66] Further prospective studies are necessary to identify patients with cutaneous squamous-cell carcinoma who may benefit from adjuvant radiation therapy.

Nodal metastasis limited to a solitary, small lymph node (≤3 cm in diameter), without extranodal extension, can be treated with surgery alone.[39] Radiation therapy is used and is considered the standard of care for nodal disease that is inoperable or not fully resected or that involves multiple nodes or nodes larger than 3 cm with extracapsular extension. Adjuvant radiation therapy in patients with nodal disease has been shown to improve both disease-free and overall survival.[64]

SYSTEMIC THERAPY

Systemic therapy (conventional chemotherapy, immunotherapy, and targeted therapies) is not recommended for the treatment of most primary tumors in patients with cutaneous squamous-cell carcinoma unless neither curative surgery nor radiation therapy is feasible.[39] However, immunotherapy has dramatically changed the landscape of systemic therapeutics for cutaneous squamous-cell carcinoma in the past several years with Food and Drug Administration (FDA) approval of cemiplimab (in 2018) and pembroliz-

umab (in 2020). For patients with recurrent, locally advanced (stage la) disease who are not candidates for surgery and for patients with new or recurrent regional disease or distant metastasis, multidisciplinary consideration of systemic therapy, alone or in combination with radiation therapy, is recommended.[39] Regimens for use with radiation therapy include conventional chemotherapeutic agents (cisplatin and carboplatin with or without paclitaxel), as well as targeted molecular inhibitors in certain circumstances. In many cases, the use of traditional chemotherapy is limited because of preexisting conditions and dose-limiting toxic effects, and responses are often short-lived and without curative effect.[67,68] A systematic review showed that among patients treated with cisplatin, the percentage with a complete response was 22%, the overall response was 45%, and the median disease-free survival was 14.6 months.[69] Cetuximab has shown some promise in treating advanced cutaneous squamous-cell carcinoma, with overall response among 50 to 78% of patients, particularly when given with radiation therapy for a synergistic effect. As with other targeted molecular inhibitors, however, a sustained response to cetuximab is limited.[67,69,70]

Immune checkpoint inhibitors have become the preferred regimen for systemic therapy alone on the basis of phase 2 trial data and FDA support for the use of programmed cell death 1 (PD-1) inhibition in patients with locally advanced, recurrent, or metastatic cutaneous squamous-cell carcinoma.[71-74] Overall response to targeted PD-1 inhibition ranges from 34 to 52% for unresectable stage la disease and metastatic disease, and the agents are well tolerated overall, with grade 3 toxic effects reported in 6 to 51% of patients.[71-76] The most common reported adverse effects of any grade are fatigue (in 27% of patients), diarrhea (in 27%), nausea (in 17%), constipation (in 15%), and rash (in 15%). Many of the worrisome and sometimes long-term toxic effects are autoimmune-related (i.e., thyroiditis [in 7% of patients]).[73] The response has been shown to be higher among patients with a higher tumor mutational burden than among patients who have a lower mutational burden. Responses are observed across all levels of tumor mutational burden, and this factor is not currently used to guide treatment in patients with cutaneous squamous-cell carcinoma.[71,74,75] Improved median overall survival and sustained antitumor immune responses among long-term survivors have been reported for this drug class in the treatment of melanoma. Phase 3 clinical trials and long-term follow-up are needed to evaluate PD-1 inhibition in patients with cutaneous squamous-cell carcinoma.[77,78]

Use of PD-1 inhibitors in organ-transplant recipients and patients with hematologic cancers is controversial, which underscores the need for the development of novel therapeutic targets in these patients, who are at elevated risk for metastasis and poor outcomes.[79] However, immunotherapy is routinely used in patients with chronic lymphocytic leukemia or other hematologic cancers, with the recognition that fewer patients may have a response.[80] Organ-transplant recipients with advanced cutaneous squamous-cell carcinoma may benefit from immunotherapy, after extensive discussion of the potential for graft failure, which is reported to be as high as 48% among kidney-transplant recipients. Clinical trials are ongoing in this area.[81,82] In two phase 2 studies of neoadjuvant PD-1 inhibition in patients with locally advanced cutaneous squamous-cell carcinoma, 51% and 75% of patients, respectively, had a pathological complete response.[83,84] There are numerous ongoing clinical trials of neoadjuvant and adjuvant immunotherapy (including intertumoral delivery), as well as the use of oncolytic viruses and new investigational targeted inhibitors, in patients with high-risk cutaneous squamous-cell carcinoma.[85]

SURVEILLANCE AND SECONDARY PREVENTION

Cutaneous squamous-cell carcinoma recurs most commonly (70 to 80% of the time) within 2 years after the diagnosis. Therefore, ongoing, close clinical surveillance is recommended on the basis of the risks for local recurrence and metastasis (Table 2).[39,57,58] In addition to undergoing medical surveillance, patients are encouraged to perform monthly skin self-examinations and to adopt photoprotective practices.[58] Special populations, such as organ-transplant recipients and patients with chronic lymphocytic leukemia, HIV infection, or other forms of immunosuppression, may warrant heightened surveillance.[86] Skin cancer has been identified as a chronic disease in high-risk persons who have five or

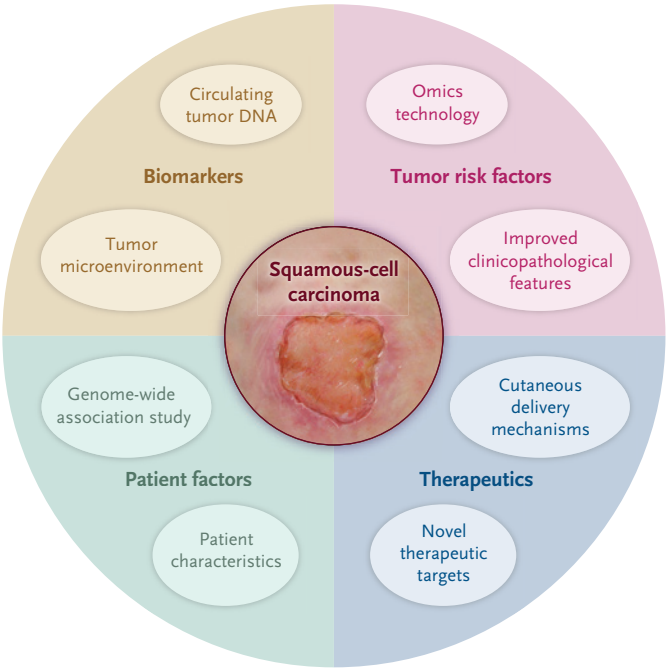

Figure 3. Future Directions in Prognosis and Treatment for Patients with Cutaneous Squamous-Cell Carcinoma.

more skin cancers with clinically significant effects on quality of life and high rates of health care utilization.[87] Persons at high risk for multiple lesions warrant close surveillance, as well as secondary prevention measures, which include cyclical therapy (e.g., topical fluorouracil, imiquimod, and photodynamic therapy) for precancerous lesions and field cancerization and systemic medications to prevent new skin cancers.

A randomized, controlled trial of oral nicotinamide showed a 30% reduction in new squamous-cell carcinoma lesions and a 20% reduction in new basal-cell carcinoma lesions at 1 year, as compared with placebo.[88] In prospective studies, oral retinoids (e.g., acitretin, isotretinoin, and etretinate) have been shown to reduce the number of new squamous-cell carcinoma lesions by up to 54% in patients, including organ-transplant recipients and patients with skin cancer classified as chronic disease.[89,90] As a result of cost, adverse effects, and rebound neoplasms, the use of systemic retinoids varies in clinical practice.[89] Use of the HPV vaccine for the prevention of skin cancer is off label and controversial, since HPV is thought to be a cofactor in the development of cutaneous squamous-cell carcinoma rather than a direct carcinogen. However, case reports of a reduction in new skin cancers have been published, particularly in organ-transplant recipients and other high-risk patients with cutaneous squamous-cell carcinoma.[91] Finally, oral capecitabine has been shown to reduce the burden of new skin cancers in a small number of organ-transplant recipients.[92]

CONCLUSIONS AND FUTURE DIRECTIONS

Squamous-cell carcinoma, with more than 1 million new cases annually and mortality now exceeding that for melanoma, represents a major health care burden. The incidence, associated mortality, and economic impact of cutaneous squamous-cell carcinoma will continue to increase with the aging population and rising incidence of exogenous immunosuppression. Traditional surgical methods remain the standard of care for low-risk disease. Although recent advances have been made in the staging, evaluation, and management of cutaneous squamous-cell carcinoma, there are opportunities to improve risk stratification for high-risk tumors and patients. With the ongoing development of new "omic" techniques, there will continue to be improvements in identifying tumors that will metastasize and those that can be cured with outpatient surgery alone.

Future directions include the development of prognostic nomograms with patient-specific factors, a greater understanding of traditional and novel clinicopathological features and tumor biology, and the identification of new tumor biomarkers to help predict metastasis and poor outcomes in patients with cutaneous squamous-cell carcinoma (Fig. 3). Although immune checkpoint inhibitors have had a major impact on the treatment of locally advanced and metastatic disease, new targeted inhibitors are needed, particularly for organ-transplant recipients and other high-risk populations. Cutaneous squamous-cell carcinoma is uniquely accessible through primary or neoadjuvant intralesional treatments (e.g., PD-1 inhibition and oncolytic viruses), and patients would benefit from the development of additional topical and other skin-directed therapies. Finally, circulating tumor DNA and other biomarkers for identifying early metastasis or recurrence may have a role in cutaneous squa-

mous-cell carcinoma. Secondary prevention can be improved by the development of new topical therapies, devices, and oral medications to treat field cancerization and to help prevent new lesions in high-risk patients and those with skin cancer classified as chronic disease.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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