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Guidelines of care for the management of cutaneous squamous cell carcinoma

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Cutaneous squamous cell carcinoma (cSCC) is the second most common form of human cancer and has an increasing annual incidence. Although most cSCC is cured with office-based therapy, advanced cSCC poses a significant risk for morbidity, impact on quality of life, and death. This document provides evidence-based recommendations for the management of patients with cSCC. Topics addressed include biopsy techniques and histopathologic assessment, tumor staging, surgical and nonsurgical management, follow-up and prevention of recurrence, and management of advanced disease. The primary focus of these recommendations is on evaluation and management of primary cSCC and localized disease, but where relevant, applicability to recurrent cSCC is noted, as is general information on the management of patients with metastatic disease. (J Am Acad Dermatol 2018;78:560-78.)

Key words: biopsy; curettage; metastasis; phototherapy; radiotherapy; squamous cell carcinoma; staging; surgery; surveillance; topical therapy.

DISCLAIMER

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care, or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding

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the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

SCOPE

This guideline addresses the management of patients with cutaneous squamous cell carcinoma (cSCC) from the perspective of a US dermatologist. Other forms of SCC, such as head and neck (ie, mucosal) SCC are outside the scope of this document, as is a discussion of cSCC in situ (Bowen disease). The primary focus of the guideline is on the most commonly considered and utilized approaches for the surgical and medical treatment of cSCC, but it also includes recommendations on appropriate biopsy techniques, staging, follow-up, and prevention of cSCC. A detailed discussion of specific chemotherapeutic or radiotherapeutic approaches for distant metastatic SCC falls outside the scope of this guideline. However, general recommendations regarding the management of patients with advanced or metastatic SCC are included to provide guidance and facilitate consultation with a physician or multidisciplinary group with specific expertise in SCC, such as a surgical, medical, or radiation oncologist, head and neck surgeon, plastic surgeon, or dermatologist specializing in SCC.

METHODS

An expert work group was convened to determine the audience and scope of the guideline, and to identify important clinical questions in the biopsy, staging, treatment, and follow-up of cSCC (Table I). Work group members completed a disclosure of interests that was updated and reviewed for potential relevant conflicts of interest periodically throughout guideline development. If a potential conflict was noted, the work group member recused himself or herself from discussion and drafting of recommendations pertinent to the topic area of the disclosed interest.

An evidence-based approach was used and available evidence was obtained by using a systematic search and review of published studies from PubMed and the Cochrane Library databases from January 1960 through April 2015 for all identified clinical questions. A secondary search was subsequently undertaken to identify and review published studies from April 2015 to August 2016 to provide the most current information. Searches were prospectively limited to publications in the English language. As cSCC is traditionally known as a form of nonmelanoma skin cancer (NMSC), a term that also includes basal cell carcinoma (BCC), searches were collectively undertaken for literature on cSCC and BCC simultaneously, by using a set of search terms applicable to both cSCC and BCC. A parallel American Academy of Dermatology (AAD) guideline on BCC has also been developed.[1] MeSH (Medical Subject Headings) terms used in various combinations in the literature search included *carcinoma*, *basal cell carcinoma*, *squamous cell carcinoma*, *skin neoplasms*, *stage(ing)*, *grade(ing)*, *score(ing)*, *biopsy*, *pathology*, *prognosis*, *signs and symptoms*, *risk factors*, *curettage*, *electrodesiccation*, *excision*, *incomplete*, *cryosurgery*, *Mohs (micrographic) surgery*, *topical*, *fluorouracil*, *imiquimod*, *laser*, *radiotherapy*, *radiation*, *photochemotherapy*,

Table I. Clinical questions used to structure the evidence review

- What is the standard grading system for BCC and cSCC?
- What are the standard biopsy techniques for BCC and cSCC?
- What pathologic and clinical information is useful in the pathology report for BCC and cSCC?
- What are the benefits harm and effectiveness/efficacy of available treatments for BCC and cSCC?
  - Surgical treatment
    - Standard excision
    - Mohs micrographic surgery
    - Curettage and electrodesiccation
    - Cryosurgery
  - Topical therapy
    - Fluorouracil
    - Imiquimod
    - Other
  - Energy devices
    - Laser
    - Photodynamic therapy (MAL* and ALA)
    - Radiation therapy
- What are effective treatment options for the management of advanced BCC and cSCC?
  - Hedgehog inhibitors*
- What are the effective methods for follow-up and preventing recurrence and new primary keratinocyte cancer formation?
  - Oral and topical retinoids
  - Celecoxib
  - α-Difluoromethylornithine
  - Selenium
  - β-Carotene

ALA, Aminolevulinic acid; *BCC*, basal cell carcinoma; *cSCC*, cutaneous squamous cell carcinoma; *MAL*, methylaminolevulinate.
*BCC only.

Abbreviations used:

AAD:	American Academy of Dermatology
AJCC:	American Joint Committee on Cancer
BCC:	basal cell carcinoma
BWH:	Brigham and Women's Hospital
C&E:	curettage and electrodesiccation
CT:	computed tomography
5-FU:	5-fluorouracil
MM:	malignant melanoma
MMS:	Mohs micrographic surgery
NCCN:	National Comprehensive Cancer Network
PI:	principal investigator
RCT:	randomized controlled trial
cSCC:	cutaneous Squamous Cell carcinoma
SLNB:	sentinel lymph node biopsy
SOTR:	solid organ transplant recipient

phototherapy, *metastasis*, *vismodegib*, *sonidegib*, *prevention*, *prevention and control*, and *recurrence*.

A total of 1120 articles were reviewed for possible inclusion; 188 were retained on the basis of relevancy and the highest level of available evidence for the outlined clinical questions. Evidence tables were generated for these 188 studies and utilized by the work group in developing recommendations. Other current guidelines on cSCC were also evaluated.[2-4]

The available evidence was evaluated by using a unified system called the Strength of Recommendation Taxonomy (SORT), which was developed by editors of the US family medicine and primary care journals (ie, *American Family Physician*, *Family Medicine*, *Journal of Family Practice*, and *BMJ USA*).[5] Evidence was graded using a 3-point scale based on the quality of study methodology (eg, randomized control trial [RCT], case-control, prospective/retrospective cohort, case series, etc), and the overall focus of the study (ie, diagnosis, treatment/prevention/screening, or prognosis) as follows:

I. Good-quality *patient-oriented evidence* (ie, evidence measuring outcomes that matter to patients: morbidity, mortality, symptom improvement, cost reduction, and quality of life).
II. Limited-quality patient-oriented evidence.
III. Other evidence, including consensus guidelines, opinion, case studies, or *disease-oriented evidence* (ie, evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

Clinical recommendations were developed on the basis of the best available evidence tabled in the guideline. These are ranked as follows:

A. Recommendation based on consistent and good-quality patient-oriented evidence. Recommendation based on consistent and good-quality patient-oriented evidence.
B. Recommendation based on inconsistent or limited-quality patient-oriented evidence.
C. Recommendation based on consensus, opinion, case studies, or disease-oriented evidence.

In situations in which published evidence-based data were not available, expert opinion of the authors was utilized to generate clinical recommendations.

This guideline has been developed in accordance with the AAD/AAD Association *Administrative Regulations for Evidence-Based Clinical Practice Guidelines*, which includes the opportunity for review and comment by the entire AAD membership and final review and approval by the AAD Board of Directors.[6] An additional multidisciplinary panel of invited reviewers was utilized to provide cross-specialty comments on the draft guideline. This guideline will be considered current for a period of 5 years from the date of publication, unless reaffirmed, updated, or retired at or before that time.

INTRODUCTION

cSCC is the second most common skin cancer and the second most common form of keratinocyte carcinoma after BCC. Like BCC, cSCC is increasing in incidence throughout the world. In the United States, lifetime risk for development of cSCC is estimated at 9% to 14% for men and 4% to 9% for women.[7] Each year in the United States, at least 200,000 to 400,000 new cases of cSCC are expected, and disease-related death occurs in more than 3000 people with cSCC.[8] A Canadian study also detected an increase in annual incidence in cSCC of more than 200% in both men and women from 1960 to 2000.[9] According to a study of US health care workers that analyzed prospective questionnaires obtained from more than 250,000 participants enrolled in 3 large cohort studies from 1976 to 2008, the incidence of invasive cSCC increased over 18 years of follow-up.[10]

Although many factors can increase the risk for cSCC, cumulative sun exposure, especially in childhood and youth, is of greatest importance. In recent years, immunosuppression, including that associated with organ transplantation,[11] has emerged as an increasingly important contributor to tumorigenesis.

cSCC can develop on any skin surface. In fair-skinned individuals, who are at highest risk, sun exposed areas, including the head and neck and the backs of the arms and hands, are common anatomic sites.[12] Awareness is growing that patients with skin of color are also at risk, with tumors in these patients sometimes emerging in sun-protected sites or in areas of chronic inflammation.[13]

The treatment of cSCC has long been a substantial component of the clinical practice of dermatologists, who are well versed in the numerous available therapeutic options. These clinical practice guidelines provide evidence-based recommendations for clinical treatment and management of patients with cSCC. Information pertaining to widely utilized therapies, ranging from curettage and electrodesiccation (C&E) to Mohs micrographic surgery (MMS), is reviewed. The quality of the evidence regarding emerging treatment modalities, such as topical and systemic medications and devices, is also discussed. Recommendations regarding staging, biopsy technique, prevention, and follow-up are made on the basis of the best available literature.

Recently, the diagnosis and treatment of cSCC among older adults with limited life expectancy has become an important and valid topic of discussion.[14,15] A clear distinction between advanced age and limited life expectancy is critical to this debate, as they are by no means synonymous. Every dermatologist is familiar with healthy, energetic nonagenarians, who justifiably desire and deserve treatment of their cSCC with a modality that provides optimal cure rate and quality of life. Conversely, significant medical comorbidities at any age may justify a therapeutic option that may have a lower long-term cure rate but is most appropriate with regard to quality of life. In select circumstances and after careful consideration with their health care provider, patients may understandably prefer observation over any form of treatment. A thorough understanding of the entire spectrum of therapies available for cSCC and the evidence on which each treatment recommendation is based is critical to selecting and providing care optimally tailored to individual patients.

Although many recommendations in these guidelines reaffirm prevailing knowledge and current practice, some recommendations highlight alternative therapeutic or preventive options that are less widely considered or are supported by insufficient evidence. As the incidence of keratinocyte carcinoma in the United States continues to increase,[16] a thorough understanding of the management of cSCC and the evidence on which recommendations are based is critically important for optimal patient care.

GRADING AND STAGING

A universally accepted staging system for risk stratification of cSCC is not yet available. Until 2010, cSCC was grouped in the American Joint Committee on Cancer (AJCC) staging manual with a multitude of other cutaneous malignancies.[17] In the seventh edition of the staging manual, which was published in 2010, cSCC was specifically addressed in the chapter "Cutaneous Squamous Cell Carcinoma and Other Cutaneous Carcinomas."[18] In the recently published eighth edition, cSCC is included in the chapter "Cutaneous Squamous Cell Carcinoma of the Head and Neck."[19] Although the chapter focuses primarily on cSCC, the staging system applies to all histologic subtypes of carcinoma limited to the head and neck, with the exception of Merkel cell carcinoma.

Table II. Brigham and Women's Hospital tumor classification system

Category	Definition
T0	In situ SCC
T1	0 risk factors*
T2a	1 risk factor
T2b	2-3 risk factors
T3	4 risk factors or bone invasion

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SCC, Squamous cell carcinoma.
*Risk factors include tumor diameter 2 cm or larger, poorly differentiated histology, perineural invasion, and tumor invasion beyond the subcutaneous fat (excluding bone, which automatically upgrades to T3).

Several studies have evaluated various aspects of the seventh edition of the AJCC staging system for cSCC and consistently identified unsatisfactory prognostication among stage groups.[20] In 2013, Brunner et al noted the heterogeneous nature of stage group IV, and in 2014 they pointed out that nodal classification demonstrated less prognostic significance in cSCC than in mucosal SCC.[21,22] In 2013, Jambusaria-Pahlajani et al proposed an alternative tumor classification system for cSCC on the basis of a retrospective cohort study.[23] This alternative Brigham and Women's Hospital (BWH) system classifies tumor categories on the basis of presence of several clinical and pathologic risk factors, as summarized in Table II. The BWH system was validated by an expanded retrospective cohort from the same group, as well as by an independent systematic literature review.[24,25] Although the BWH system does not address nodal and metastasis classifications and advanced stage groups as the AJCC staging system does, it appears to provide superior prognostication for patients with localized cSCC. Further validation by independent cohorts, as well as clinical trials regarding nodal staging and adjuvant therapy, will be needed to determine the clinical utility of the proposed staging system.

Current National Comprehensive Cancer Network (NCCN) clinical practice guidelines for cSCC provide

Table III. National Comprehensive Cancer Network stratification of low versus high risk cSCC

Parameters	Low risk	High risk
Clinical		
Location*/size†	Area L <20 mm Area M‡ <10 mm	Area L ≥20 mm Area M ≥10 mm Area H§
Borders	Well defined	Poorly defined
Primary vs recurrent	Primary	Recurrent
Immunosuppression	No	Yes
Site of prior radiation therapy or chronic inflammatory process	No	Yes
Rapidly growing tumor	No	Yes
Neurologic symptoms	No	Yes
Pathologic		
Degree of differentiation	Well to moderately differentiated	Poorly differentiated
High-risk histologic subtype‖	No	Yes
Depth (thickness or Clark level)¶	<2 mm, or I, II, III	≥2 mm or IV, V
Perineural, lymphatic, or vascular involvement	No	Yes

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cSCC, Cutaneous squamous cell carcinoma.

*Area L consists of trunk and extremities (excluding hands, feet, nail units, pretibia, and ankles); area M consists of cheeks, forehead, scalp, neck, and pretibia; and area H consists of central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, preauricular and postauricular skin/sulci, temple, ear, genitalia, hands, and feet.

†Greatest tumor diameter, including peripheral rim of erythema.

‡Location independent of size may constitute high risk.

§Area H constitutes high-risk on the basis of location, independent of size.

‖Adenoid (acantholytic), adenosquamous (showing mucin production), desmoplastic, or metaplastic (carcinosarcomatous) subtypes.

¶A modified Breslow measurement should exclude parakeratosis or scale/crust and should be made from base of the ulcer is present. If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow-margin excisional biopsy.

an approach to stratifying high-risk and low-risk tumors, similar to that used for BCC.[3] This stratification, summarized in Table III, takes both clinical and pathologic parameters into account and is based on a combination of available evidence and expert opinion. The NCCN risk stratification is primarily intended to provide health care providers with practical clinical guidance on how to treat cSCC rather than to provide accurate prognostication and assess outcome as the BWH system does. For this reason, treatment recommendations throughout the currently presented guidelines are based on the NCCN risk stratification (for the recommendations, see Table IV; for the level of evidence/strength of the recommendations, see Table V[2,3,20-50]).

On the basis of the low overall risk for nodal and distant metastases in cSCC, staging imaging studies are rarely indicated. Although very limited data are available on the value of such studies in cSCC, imaging to evaluate for nodal metastasis (eg, computed tomography, F-fluorodeoxyglucose positron emission tomography/computed tomography, or ultrasound) may be considered for high-risk tumors (eg, BWH category ≥T2b). Imaging may also be considered to assess for deep structural involvement with extensive localized disease.[51] A thorough clinical examination of the regional lymph node basins should always be performed.

Table IV. Recommendations for grading and staging of cSCC

Stratification of localized SCCs using the NCCN guideline framework is recommended for clinical practice.
Clinicians should refer to the BWH tumor classification system to obtain the most accurate prognostication of patients with localized cSCC.

BWH, Brigham and Women's Hospital; *cSCC*, cutaneous squamous cell carcinoma; *NCCN*, National Comprehensive Cancer Network; *SCC*, squamous cell carcinoma.

The value of sentinel lymph node biopsy (SLNB) in cSCC is currently unknown. Tumor size and thickness, as well as angiolymphatic and perineural invasion, have been proposed as risk factors for sentinel lymph node positivity, but small study sizes limit the assessment of prognostic parameters. Retrospective and prospective case series have demonstrated successful detection of occult nodal metastases and suggested a prognostic role in patients with high-risk tumors.[52,53] However, the effect of SLNB on management and outcome of

Table V. Level of evidence and strength of recommendations for grading and staging, biopsy, clinical information, and pathology report for the treatment of cSCC

Recommendation	Strength of recommendation	Level of evidence	References
Grading and staging			
AJCC	B	II	20-25
BWH	B	II	23-25
NCNN	C	III	2,3
Biopsy	C	II, III	26-32
Clinical information provided to pathologist			
Age	A	I, II	33-35
Sex	B	II	34,36
Anatomic location	B	I, II	34-43
Recurrent lesion	A	I, II	41,44,45
Size of lesion	A	I, II	23,37-45
Immunosuppression	B	I, II	20,23,39,43,46
History, especially radiation, burn, organ transplant	B	II	20,41,47,48
Pathology report elements			
Degree of differentiation*	B	I, II	23,35,37,39-44
Presence of aggressive histologic subtype†	B	I, II	39,40
Depth of invasion, mm	A	I, II	23,33,39,42-45
Clark level of invasion	B	II	40,41
Perineural invasion	A	I, II	23,33,37,40-45
Lymphovascular invasion	A	I, II	37,44
Invasion of fascia, muscle, or bone	A	I, II	23,33,44,45
No. of high-risk features‡	C	III	Expert opinion
Margin status	B	II	20,34,36
TNM stage (AJCC)	A	I	23,33
Inflammation	A	I	33,44
Infiltrative strands, single cells, small nests	B	II	40
Diameter of largest involved nerve	B	II	49,50

AJCC, American Joint Committee on Cancer; *BWH*, Brigham and Women's Hospital; *cSCC*, cutaneous squamous cell cancer; *NCCN*, National Comprehensive Cancer Network; *TNM*, tumor, node, metastasis.
*Well differentiated, moderately differentiated, poorly differentiated, or undifferentiated.
†Acantholytic, adenosquamous, or carcinosarcomatous subtypes.
‡High-risk features include thickness greater than 2 mm, Clark level IV or V, poorly differentiated/undifferentiated, site on mucosa lip or ear, perineural invasion, and lymphovascular invasion.

patients with cSCC is unknown; enrollment of high-risk patients in clinical trials is encouraged, when available.

BIOPSY

The available literature does not identify a single optimal biopsy technique for sampling lesions suspected of being cSCC. Recommended biopsy techniques for cSCC include punch biopsy, shave (eg, by tangential technique) biopsy,[a] and excisional biopsy. Excisional biopsy is distinguished from excision with margins in that the intent of the former is to determine and/or confirm diagnosis, whereas the intent of the latter is to remove the tumor. For all techniques, the biopsy specimen size and depth should be adequate to provide the recommended clinical information and pathology report elements to permit accurate diagnosis and guide therapy, including by identifying an aggressive growth pattern if present. Repeat biopsy may be considered if the initial biopsy specimen is inadequate for accurate diagnosis. The recommendations for biopsy of suspected cSCC are shown in Table VI, and the level of evidence/strength of the recommendation is presented in Table V.

Selection of the specific biopsy technique is contingent on the clinical characteristics of the suspected tumor, including morphology, expected histologic subtype and depth, natural history, and anatomic location; patient-specific factors, such as bleeding and wound healing diatheses; and patient preference and physician judgment. Most investigations that have compared biopsy methods for detection of NMSC have studied BCC rather than

[a]Shave biopsies are not necessarily superficial, tangential shaves of tissue. We use the term *shave* for biopsies that are saucerize or scoop techniques that may penetrate deep into the dermis.

Table VI. Recommendations for the biopsy of suspected cSCC

The recommended biopsy techniques for cSCC are punch biopsy, shave biopsy, and excisional biopsy. The biopsy technique used will depend on the characteristics of the suspected malignancy (morphology, location, etc) and the judgment of the physician.
The biopsy size and depth should be adequate to provide the recommended clinical information and pathology report elements to permit accurate diagnosis and guide therapy.
Repeat biopsy may be considered if the initial biopsy specimen is inadequate for accurate diagnosis.

cSCC, Cutaneous squamous cell cancer.

cSCC.[26-32] However, given the similarity in the depth and anatomic distribution of many BCC and cSCC tumors, the findings of these studies are likely applicable also to biopsy of cSCC. Specifically, it is likely that initial punch or shave biopsies can detect the relevant histologic characteristics for the vast majority of sampled cSCC tumors. When recurrent tumor, deep invasion, or other aggressive features are suspected, more extensive tissue resection or multiple scouting biopsies may be needed to detect these features if more superficial methods are insufficient. The need to obtain information through biopsy is counterbalanced by the patient and physician preferences to minimize biopsy-associated discomfort, trauma, risk for wound infection or dehiscence, scar, or loss of function, particularly on the head, neck, and other vital, functional, sensory, or cosmetically sensitive sites.

Clinical and pathologic information

A presumptive diagnosis of cSCC is based on the physician's interpretation of clinical information, including appearance and morphology, anatomic location, and patient-reported history. Clinical diagnosis is routinely confirmed by biopsy findings before treatment. When the clinician is submitting biopsy tissue for histopathologic diagnosis, and when possible and appropriate, key elements of the patient demographics, clinical presentation, and history should be provided to the pathologist (Table VII; for level of evidence/strength of recommendations, see Table V). These include patient age and biologic sex,[33-36] anatomic location of the tumor,[34-41] and any history of treatment at the same anatomic site.[34-43] Additional desirable relevant information may include the clinical size of the lesion[23,37-45] and whether the patient currently has, or in years past had, additional risk factors, such as immunosuppression,[20,23,39,43,46] radiation treatment, or solid organ transplantation.[20,41,47,48] Although not prognostically relevant, information regarding ongoing treatment that may or may not contribute to cSCC pathogenesis (eg, kinase or hedgehog pathway inhibitor) may be diagnostically useful.

Table VII. Recommendations for clinical information and pathology report for suspected cSCC

Clinical information provided to pathologist
Strongly recommended
• Age
• Sex
• Anatomic location
• Recurrent lesion
Recommended
• Size of lesion
• Immunosuppression
• History (especially radiation, burn, organ transplant)
Elements to be included in final pathology report (excision specimens)
Strongly recommended
• Degree of differentiation*
• Presence of aggressive histologic subtype†
• Depth of invasion, mm
• Clark level of invasion
• Perineural invasion
• Lymphovascular invasion
• Invasion of fascia, muscle, or bone
• Number of high-risk features‡
• Margin status
• TNM stage (AJCC)
Recommended
• Inflammation
• Infiltrative strands, single cells, small nests
• Diameter of largest involved nerve

AJCC, American Joint Committee on Cancer; *cSCC*, cutaneous squamous cell carcinoma; *TNM*, tumor, node, metastasis.
*Well differentiated, moderately differentiated, poorly differentiated, or undifferentiated.
†Acantholytic, adenosquamous, or carcinosarcomatous subtypes.
‡High-risk features include thickness greater than 2 mm, Clark level IV or V, poorly differentiated/undifferentiated, site on mucosa lip or ear, perineural invasion, and lymphovascular invasion.

The principal purpose of the biopsy pathology report is to provide the clinician with an accurate diagnosis of the presence (or absence) of cSCC. If cSCC is detected, additional features that are reported include degree of differentiation and, when possible and appropriate, any features that would classify the lesion as high risk, including aggressive histologic subtypes (acantholytic, adenosquamous, and carcinosarcomatous), depth greater than 2 mm (measured from the granular layer of the adjacent

intact epidermis), Clark level IV or greater, and presence of perineural and/or angiolymphatic invasion. The presence of prognostically favorable features, such as histopathologic subtype, including verrucous carcinoma and keratoacanthomatous SCC, may be clinically useful.

For excision specimens, the extent of the reported detail depends on whether it represents a primary excisional biopsy or re-excision of a biopsy-confirmed tumor. Any new prognostically relevant findings should be noted. It is recommended that the following items be reported, if possible and appropriate: the degree of cellular differentiation[23,35,37,39-44]; presence of any aggressive histologic subtypes[39,40]; depth of invasion in millimeters[23,33,39,42-45]; anatomic (Clark) level of invasion[40,41]; presence of any perineural invasion[23,33,37,40-45]; presence of any lymphovascular invasion[37,44]; description of any invasion of fascia, muscle, or bone[23,33,44,45]; margin status (involved or not involved by tumor) [20,34,36]; the number of high-risk features present and the relevant TNM (tumor, node, and metastasis) stage based on current AJCC criteria (Table VII) (for level of evidence/strength of recommendations, see Table V).[18,23,33] In selected cases, other elements that have been shown to have prognostic significance for clinical care may additionally be reported; they include the presence of inflammation[33,44] or infiltrative strands, single cells, or small nests of tumor.[40] When perineural invasion is observed, the diameter of the largest affected nerve (eg, when ≥ 0.1 mm) may be reported, if this is deemed to be clinically significant.[49,50] With regard to margin status, if a cSCC with aggressive features extends close to a margin, it should be reported.

Pathologic evaluation of skin biopsy specimens is ideally performed by a dermatologist or pathologist who is experienced in interpreting cutaneous neoplasms. Such a physician is most able to collectively interpret the clinical tumor findings and the histologic features (ie, clinicopathologic correlation) to provide the most precise and accurate biopsy diagnosis.

SURGICAL TREATMENT

It is generally accepted that the majority of cSCCs are successfully treated with standard treatment modalities, such as surgical excision. However, there is a subset of tumors with increased risk for local recurrence, perineural spread, and even nodal or distant metastasis, particularly in immunocompromised individuals. Unfortunately, a systematic review of the literature reveals a complete absence of RCTs and a general paucity of prospective trials assessing the effectiveness of primary surgical interventions for cSCC.[54] Treatment recommendations are generally based on retrospective data, consensus opinion, and extrapolation from data on BCC or non-cSCC of the head and neck. When the most appropriate therapy is being chosen, recurrence rate, preservation of function, patient expectations, and potential adverse effects must be taken into consideration.[55]

In this section, the available data on the most commonly used surgical treatment modalities for cSCC, including standard excision, MMS, and C&E, will be reviewed. Nonsurgical therapies will be addressed separately.

Standard excision

cSCC, similar to BCC, is characterized by asymmetric subclinical extension of the tumor beyond the clinically visible lesion. To ensure complete removal with histologically negative margins, standard excision with "bread loaf" histopathologic sectioning must include a margin of clinically normal—appearing skin around the tumor and surrounding erythema. To our knowledge, no RCT comparing different excision margins for cSCC has been performed. An extensive systematic review of observational studies on interventions for cSCC by Lansbury et al identified 12 studies addressing standard excision of cSCC, mostly retrospective case series of limited quality and with variable follow-up periods.[54] The authors reported an average local recurrence rate of 5.4% (95% confidence interval, 2.5-9.1 [n = 1144]) among all studies, with excision margins ranging from 2 to 10 mm. Incomplete excisions were reported in 8.8% of all cases, although the definitions of an incomplete excision varied widely. In 1992, Brodland and Zitelli reported that 4-mm margins were required to achieve at least 95% clearance rates when excising cSCC using MMS.[56] In the same study, for high-risk lesions larger than 2 cm in clinical diameter or with higher histologic grade, at least 6-mm margins were required to achieve 95% clearance rates. On the basis of the limited available data and consensus opinion, NCCN guidelines recommend 4- to 6-mm clinical margins for standard excision of low-risk cSCC (Table III).[3]

Given the limited available data, the work group recommends standard excision with a 4- to 6-mm margin of uninvolved skin around the tumor and/or biopsy site to a depth of the mid-subcutaneous adipose tissue with histologic margin assessment for low-risk primary cSCC (on the basis of NCCN risk stratification [Table III]). Standard excision may be considered for select high-risk tumors. However, strong caution is advised when selecting a treatment modality without complete margin assessment for high-risk cSCC. The insufficient data preclude

Table VIII. Recommendations for the surgical treatment of cSCC

A treatment plan that considers recurrence rate, preservation of function, patient expectations, and potential adverse effects is recommended.
C&E may be considered for low-risk, primary cSCC in non–terminal hair–bearing locations.
For low-risk primary cSCC, standard excision with a 4- to 6-mm margin to a depth of the mid-subcutaneous adipose tissue with histologic margin assessment is recommended.
Standard excision may be considered for select high-risk tumors. However, strong caution is advised when selecting a treatment modality for high-risk tumors without a complete margin assessment.
MMS is recommended for high-risk cSCC.

C&E, Curettage and electrodessication; *cSCC*, cutaneous squamous cell carcinoma; *MMS*, Mohs micrographic surgery.

recommendation of defined peripheral and deep margins for excision of high-risk tumors with standard excision. When standard excision is performed for high-risk tumors, a linear repair, skin graft, or healing by second intention are recommended. If a repair requiring significant tissue rearrangement is indicated, closure should be delayed until negative histologic margins are confirmed. Recommendations for standard excision of cSCC are summarized in Table VIII. The strength of these recommendations is shown in Table IX.[41,54,55,57,58]

MMS

Dr Frederic Mohs first described the use of chemosurgery for the removal of difficult or recurrent cutaneous tumors in the 1940s.[59,60] Three decades later, the concept of *en face* horizontal sectioning for complete peripheral and deep margin control pioneered by Mohs to achieve optimal cure rates and maximum tissue conservation was adapted to the "fresh tissue" technique by Tromovitch and Stegman.[61] This modification eliminated the pain from in vivo fixation with zinc chloride paste, shortened the time required to perform surgery and allowed immediate repair of a fresh surgical wound. Microscopic controlled excision, later referred to as MMS, was recommended for all recurrent or poorly defined tumors, for sclerosing BCC, and for all primary cutaneous carcinomas in areas with a predilection for recurrence.[62]

Since that time, the use of MMS has significantly increased and indications have expanded to include many other cutaneous malignancies, including cSCC. In 2012, a combined task force of the AAD, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and American Society for Mohs Surgery developed appropriate use criteria for MMS.[63] However, to date, no RCTs or prospective cohort studies comparing MMS with other treatment modalities for the treatment of cSCC have been performed. In a systematic review of the literature since 1940, Rowe et al, reported a 5-year local recurrence rate of 3.1% (n = 2065) for primary cSCC treated with MMS.[41] In comparison, the 5-year recurrence rates for C&E, standard excision, and radiation therapy were 3.7% (n = 82), 8.1% (n = 124), and 10.0% (n = 160), respectively. When high-risk factors were taken into account, MMS showed lower recurrence rates compared with standard excision and other non-MMS treatment modalities: 25.2% versus 41.7% for tumors 2 cm or larger, 32.6% versus 53.6% for poorly-differentiated cSCC, and 0% versus 47% for neurotropic cSCC. For recurrent cSCC, the meta-analysis by Rowe et al revealed a 5-year recurrence rate after MMS of 10.0% (n = 151) compared with 23.3% (n = 34) following standard excision. Similar 5-year recurrence rates for recurrent cSCC treated with MMS (ranging between 6% and 11%) were reported by others.[57,64]

In the absence of high-level data, extrapolation from a recent RCT demonstrating the benefit of MMS for primary and recurrent facial BCC may be justified to support the use of MMS for high-risk cSCC.[58] A large percentage of cSCCs are located on the head and neck, where tissue conservation is important. Similar to BCC, cSCC is characterized histologically by asymmetric subclinical extension beyond the clinically visible tumor, but it presents with perineural involvement more frequently than BCC does.[65] Both histopathologic features would support the importance of meticulous and complete margin assessment with MMS. However, aggressive histopathologic growth patterns poorly visualized with frozen sections (eg, sarcomatoid/spindle cell or single cell infiltrative cSCC) may limit the utility of MMS under certain circumstances. An additional limitation is that tissue blocks from MMS layers are not available for molecular testing or further evaluation of high-risk or unusual features by using paraffin sections.[66] To overcome this challenge, the tumor debulk specimen may be submitted for paraffin sections to document high-risk features and obtain ancillary molecular studies, if indicated, without compromising the integrity of the MMS procedure.[67] Alternatively, key pathologic high risk features can be documented in the Mohs report to facilitate prognostic assessment and guide post-operative management when indicated. Careful selection, on the basis of initial biopsy results, of

Table IX. Level of evidence and strength of recommendations for the surgical treatment of cSCC

Recommendation	Strength of recommendation	Level of evidence	References
Treatment plan	A	II	55
Standard excision with 4- to 6-mm margins for low-risk primary SCC*	B	II	54
Standard excision for high-risk SCC	B	II	54
C&E for low-risk primary SCC*	B	II, III	54
MMS for high-risk SCC*	B	II, III	41,54,57,58

C&E, Curettage and electrodessication; *cSCC*, cutaneous squamous cell carcinoma; *MMS*, Mohs micrographic surgery; *SCC*, cutaneous squamous cell carcinoma.
*As defined by the National Comprehensive Cancer Network.

Table X. Recommendations for the nonsurgical therapy of cSCC

If surgical therapy is not feasible or preferred, radiation therapy (eg, superficial radiation therapy, brachytherapy, external electron beam therapy, and other traditional radiotherapy forms) can be considered when tumors are low risk, with the understanding that the cure rate may be lower.
Cryosurgery may be considered for low-risk cSCC when more effective therapies are contraindicated or impractical.
Topical therapies (imiquimod or 5-FU) and PDT are not recommended for the treatment of cSCC on the basis of available data.
There is insufficient evidence available to make a recommendation on the use laser therapies or electronic surface brachytherapy in the treatment of cSCC.

cSCC, Cutaneous squamous cell carcinoma; *5-FU*, 5-fluorouracil; *PDT*, photodynamic therapy.

tumors appropriate for treatment with MMS and evaluation by frozen sections will minimize these limitations.

On the basis of the best available data, the work group recommends MMS for the treatment of high-risk cSCC (on the basis of NCCN risk stratification [Table VIII]; for level of evidence/strength of recommendation, see Table IX).

C&E

C&E is regularly used in daily practice for the treatment of low-risk cSCC. However, no RCTs have been performed and no prospective data are available to compare C&E with other treatment modalities. In the aforementioned systematic review by Lansbury et al, 8 retrospective series of variable follow-up periods that addressed C&E were identified.[54] A pooled analysis revealed a recurrence rate of 1.7% (95% confidence interval, 0.5-3.4 [n = 1131]). Small, individual studies suggested higher recurrence rates for lesions greater than 2 cm in diameter or located on the ear and treated with C&E.

The limited available data suggest that C&E is an effective treatment modality for properly selected tumors, although results are highly operator dependent.[68] It is the work group's opinion that C&E may be considered for small, low-risk primary cSCC (on the basis of NCCN risk stratification [Table VIII]; for level of evidence/strength of recommendation, see Table IX). Lesions on terminal hair—bearing skin (the scalp, pubic, axillary regions, and the beard area in men) should be excluded from treatment with C&E because of potential follicular extension of tumor.[3] Moreover, C&E may be associated with a longer healing time and inferior cosmetic outcome compared with standard excision and is best avoided in cosmetically sensitive areas.[69]

NONSURGICAL TREATMENT

In general, treatment of cSCC is most effectively accomplished by surgical therapy. There are relatively few exceptions to this guiding principle, especially for high-risk cSCC, because of the potential for recurrence and metastasis. If surgical therapy is not feasible or elected, nonsurgical approaches may be considered when tumors are low risk, with the understanding that the cure rate may be lower. Further research is needed to better establish the comparative safety and effectiveness of nonsurgical therapies for cSCC. The recommendations for nonsurgical treatments are shown in Table X. The level of evidence/strength of the recommendations is listed in Table XI.[54,70-79]

PDT

Photodynamic therapy (PDT) is a 2-part treatment consisting of topical application of a photosensitizer, either 5-aminolevulinic acid (ALA) or methylaminolevulinate (MAL), followed by 1 to several hours of incubation by light irradiation, typically with a blue, red, or broadband light source.[80-91] Available data for PDT and laser therapy do not currently support the

Table XI. Level of evidence and strength of recommendations for the nonsurgical treatment of cSCC

Recommendation	Strength of recommendation	Level of evidence	References
Cryosurgery	B	II	54
Radiation therapy			
• Traditional radiotherapies and modern superficial radiation therapy	B	II, III	54,70-75
• Electronic surface brachytherapy	C	III	76,77
Against topical therapy alone			
• Imiquimod	C	III	54,78,79
• 5-FU	C	III	54
Against photodynamic therapy alone	B	II	54
Laser therapy	C	III	54

cSCC, Cutaneous squamous cell carcinoma; *5-FU*, 5-fluorouracil.

efficacy of either modality in the treatment of cSCC.[54] Limited case report and case series data suggest that PDT may be used as an adjuvant modality in combination with curettage[92] and surgery[93] for invasive cSCC in high-risk patients such as solid organ transplant recipients (SOTRs) and potentially to spare tissue, but the specific contribution of PDT to observed outcomes in such combination approaches is uncertain.

When PDT is combined with surgery, multiple PDT treatments may be used. Exacerbation or induction of well-differentiated cSCC or keratoacanthoma after PDT has however been reported.[94]

Topical therapies

The available data do not currently support the use of topical modalities for the treatment of cSCC. Published studies investigating the use of topical imiquimod or 5-fluorouracil (5-FU) for cSCC (excluding SCC in situ) are limited to case reports for imiquimod and 2 small case series for 5-FU.[54,78,79] Variable lengths of follow-up and histologic clearance limit the strength of these data.[54] Because use of 5-FU typically results in marked erythema, erosions, and crust lasting for a month or longer, decreased patient compliance with treatment regimens may result in diminished effectiveness. Similarly, imiquimod dosing for cSCC is complicated by the resultant tissue effects, including erythema, edema and erosions, ulceration and crust, that are not consistent from one individual to the next. In addition, imiquimod use for larger surface areas may be associated with systemic symptoms, including fatigue, influenza-like symptoms, myalgia, and headache.

Radiation therapy

Although surgery remains the first-line, and most effective, treatment for cSCC, primary radiation therapy can be used in special situations in which surgery is not feasible, contraindicated, or not preferred by the patient after a discussion of risks and benefits. Several different types of radiotherapy can be used to treat cSCC, including superficial radiation therapy, isotope-based brachytherapy (interstitial or topical contact), or external electron beam radiation.[54,70-74,95] Primary or adjuvant radiation therapy is an effective treatment option for selected patients with cSCC, resulting in good tumor control and cosmesis,[96] with the understanding that the cure rates may be lower.[97,98] Smaller and thinner tumors may be more responsive to radiation therapy.[54,99] As with other nonsurgical approaches, the available data on radiotherapy are limited by small patient numbers and variable lengths of follow-up to detect local or regional recurrences.[54] Although there is limited evidence regarding the use of traditional variants of brachytherapy for the treatment of cSCC, such as interstitial radiotherapy and isotope-based contact brachytherapy, electronic brachytherapy, a form of superficial radiation therapy, is a newer modality for which long-term safety and effectiveness data are lacking.[76,77] Primary cSCC with concerning perineural invasion or otherwise at high risk for regional or distant metastasis may be considered for adjuvant radiation therapy to the local tumor site following surgical treatment.[100] High-level evidence about the effectiveness of this approach is lacking.

Cryosurgery

Given the lack of histologic margin control with this approach, as well as the known risk for subclinical extension of cSCC, cryosurgery should be considered only for low-risk lesions, when more effective therapies are contraindicated or impractical. The objective of cryosurgery, interchangeably

referred to as cryotherapy, in the treatment of cSCC is to cause selective destruction of the same volume of tissue that would have been removed with standard excision. Although cryosurgery is frequently used for the treatment of precursor lesions (ie, actinic keratoses), limited data are available on its use for cSCC.[54]

Laser treatment

Treatment of cSCC by a Nd:YAG laser has been reported in a single retrospective study, with this extremely limited experience precluding the recommendation of laser for this indication.[54] PDT, which includes a light source as well as a topical photosensitizer, was discussed earlier in these Guidelines.

MANAGING PATIENTS WITH METASTATIC cSCC

The risk for metastasis in cSCC is reported to be approximately 4%.[39] Among immunosuppressed individuals, particularly for SOTRs, the metastatic risk may be 2 to 3 times higher.[101] Cutaneous in-transit and regional lymph node metastases are the most common metastatic presentation, followed by distant metastases. In patients with high-risk localized tumors, successful detection of occult lymph node metastases by SLNB has been reported.[52,53] However, the effect of SLNB on management and outcome of patients with high-risk cSCC is unknown.

The available literature on management of in-transit and lymph node metastases is largely limited to retrospective reviews and case series of patients with head and neck cSCC.[51,102,103] Therapeutic recommendations are based on the extent of disease and consist primarily of surgical resection with possible lymph node dissection and consideration of adjuvant radiation therapy with or without concurrent systemic therapy. Given the rarity and complexity of metastatic cSCC, multidisciplinary consultation is recommended. For inoperable lymph node metastases, combination chemoradiation therapy should be considered. For patients with advanced disease, it is also appropriate to provide or refer to best supportive and palliative care to optimize symptom management and maximize quality of life.

Existing data on the treatment of patients with distant metastatic cSCC are sparse and limited to phase II clinical trials. Chemotherapy, including cisplatin as a single agent or combined with 5-fluorouracil (5-FU), has shown some activity, but the results have not been confirmed in larger cohorts.[104,105] In other phase II trials, epidermal growth factor receptor inhibitors, such as cetuximab and more recently panitumumab, have demonstrated efficacy in patients with advanced unresectable cSCC.[106,107] In (noncutaneous) head and neck SCC, a phase III trial demonstrated that the addition of panitumumab to combination cisplatin and 5-FU improved progression-free survival, but not overall survival.[108] The US Food and Drug Administration recently approved the immune checkpoint (programmed cell death 1) inhibitor pembrolizumab for some patients with advanced (noncutaneous) head and neck squamous cell carcinoma. Great interest currently exists in ongoing clinical trials evaluating the efficacy of immune checkpoint inhibitors for locally advanced and metastatic cSCC.

Careful consideration must be given to immunosuppressed individuals with high-risk localized or metastatic cSCC, given its more aggressive clinical behavior and poor prognosis. In SOTRs, dose reduction of the immunosuppressive agents and minimizing use of calcineurin inhibitors (eg, cyclosporine, tacrolimus) and/or antimetabolites (eg., azathioprine) in favor of mammalian target of rapamycin inhibitors (eg, sirolimus) may be considered when appropriate.[109,110] However, a recent retrospective cohort study did not demonstrate a reduction in post-transplantation risk for cSCC among SOTRs exposed to sirolimus.[111] Multidisciplinary consultation and management are strongly encouraged for SOTRs with advanced or metastatic SCC.

The recommendations for management of regional and distant metastatic SCC are shown in

Table XII. Recommendations for management of locally advanced or metastatic SCC

Surgical resection, with or without adjuvant radiation therapy and possible systemic therapy are recommended for regional lymph node metastases. Combination chemoradiation therapy should be considered for inoperable disease.
Epidermal growth factor inhibitors and cisplatin, as a single agent or in combination therapy, may be considered, as they have demonstrated efficacy for metastatic disease, albeit on the basis of limited data.
Multidisciplinary consultation and management, particularly in immunosuppressed individuals, is recommended for patients with locoregional or distant metastases. In some cases, such consultation may be appropriate for patients with locally advanced disease without known metastases.
Patients with advanced disease should be provided with or referred for best supportive and palliative care to optimize symptom management and maximize quality of life.

SCC, Squamous cell carcinoma.

Table XIII. Level of evidence and strength of recommendations for the management of locally advanced or metastatic SCC

Recommendation	Strength of recommendation	Level of evidence	References
Surgical resection with/without adjuvant radiotherapy	B	II	51,102,103
Epidermal growth factor inhibitors and cisplatin	B	I, II	104-108
Multidisciplinary consultation	A	III	Expert opinion
Palliative care	A	III	Expert opinion

SCC, Squamous cell carcinoma.

Table XII, and the level of evidence/strength of the recommendation is provided in Table XIII.[51,102-108]

FOLLOW-UP AND REDUCING RISK FOR FUTURE SKIN CANCERS

Once an cSCC has been diagnosed, in-office screening for new primary skin cancers, including BCC, cSCC, and melanoma, should be performed at least once per year, adjusting frequency on the basis of individual patient risk. Clinical assessment of regional lymph node basins may be included in the physical examination for high-risk lesions. This recommendation derives from the considerable evidence from cohort studies and registries that a patient with at least 1 cSCC is at risk for additional cSCC as well as other for skin cancers, including BCC and melanoma.

A 2010 meta-analysis by Wheless et al determined that the summary random-effects relative risk for development of a second NMSC after diagnosis of a first was 1.12 on the basis of 12 cohort studies from cancer registries versus 1.49 on the basis of 3 studies with patient-level data.[112] More recently, Wehner et al found in their prospective cohort that the 5-year probability of another NMSC after diagnosis of a first was 40.7%, and after more than 1 it was 82%.[113] At 10 years, the chances of another NMSC after the first increased to 59.6% and after diagnosis of a nonfirst NMSC the chances of another increased to 91.2%.

Initial diagnosis of NMSC, including cSCC, increases the risk for subsequent malignant melanoma (MM). Song et al found a relative risk for development of MM after diagnosis of a NMSC of 1.99 for men and 2.58 for women.[114] These data were based on 2 large prospective cohort studies with 46,237 men and 107,339 women under study. A smaller study that included 3548 people found the relative risk for MM to be 3.62 after diagnosis of an SCC.[115]

Patients who have had cSCC should be counseled regarding the risk for new primary skin cancers, the need for in-office screening, and the potential benefits of self-screening. Concurrent patient self-surveillance for cSCC and other skin cancers may be of additional utility in detecting new primary tumors while they are still small and easily treated. Family members can also help patients detect skin cancers, as they may be able to identify suspicious lesions at anatomic sites (eg, the back) that are not easily assessed by the patient.[116]

Table XIV. Recommendations for the follow-up of cSCC and reducing risk for future skin cancer

After diagnosis of a first SCC, screening for new keratinocyte cancers (BCC or cSCC) and for melanoma should be performed on at least an annual basis.
Patients with a history of cSCC should be counseled on skin self-examination and sun protection.
Topical and oral retinoids (eg, tretinoin, retinol, acitretin, and isotretinoin) should not be prescribed to reduce the incidence of keratinocyte cancers in those with a history of cSCC, unless they are SOTRs. In the situation of SOTRs, only acitretin may be beneficial.
Dietary supplementation of selenium and β-carotene is not recommended to reduce the incidence of future keratinocyte cancers in those with a history of cSCC.
There is insufficient evidence to make a recommendation on the use of oral nicotinamide, DFMO, or celecoxib in the chemoprevention of cSCC.

BCC, Basal cell carcinoma; *cSCC*, cutaneous squamous cell carcinoma; DFMO, α-difluoromethylornithine; *SCC*, squamous cell carcinoma; *SOTR*, solid organ transplant recipient.

Patients with a history of cSCC should also be counseled regarding the need for sun protection, sun avoidance, and tanning bed avoidance. Broad-spectrum chemical and physical sunscreens have been shown to reduce ultraviolet light exposure per unit time when properly applied.[117,118] Routine use of sunscreens is recommended in combination with other sun-protective behaviors, such as seeking shade and wearing broad-brimmed head coverings.

Many topical and oral agents have been recommended to reduce the risk for a new SCC or other skin cancer after an initial diagnosis of cSCC, but the evidence for these agents is mixed. Topical retinoids have not been found to reduce the incidence of keratinocyte cancers or actinic keratosis in those

Table XV. Level of evidence and strength of recommendations for the follow-up of cSCC and reducing risk for future tumors

Recommendation	Strength of recommendation	Level of evidence	References
Annual follow-up skin cancer screening	A	I	112-115,131,132
Skin self-examination and sun protection after cSCC	A	III	Expert opinion
Against the use of topical and oral retinoids*			
• Tretinoin	A	I, II	119,120,133
• Acitretin	B	I	121
• Isotretinoin	A	I	125,134
• Oral retinol	A	I	125,135
Use of acetretin for SOTR patients	B	I	123
Against chemoprevention using			
• Celecoxib	B	I	127,136
• DFMO	A	I	137,138
• Oral nicotinamide	B	I	126
Against dietary supplementation with			
• Selenium	A	I	128,129
• β-Carotene	A	I	130

cSCC, Cutaneous squamous cell carcinoma; *DFMO*, α-difluoromethylornithine; *SOTR*, solid organ transplant recipient.
*Non-SOTRs.

with a history of a keratinocyte cancer.[119] Consequently, topical retinoids are not recommended for reducing the risk for subsequent cSCC in patients with a history of cSCC. In addition, topical retinoids used for prolonged periods were associated in a single study with increased mortality, although some investigators have discounted this result as spurious.[120] Although acitretin has not been shown to be helpful in reducing the incidence of cSCC in nontransplant patients with a history of NMSC,[121] it may have a role in the management of SOTRs with a history of NMSC.[122] One small RCT demonstrated benefit to renal transplant patients with 10 or more keratotic lesions.[123] The benefits of oral retinol need more study, as 2 large RCTs have shown divergent conclusions. Isotretinoin does not appear to reduce the incidence of cSCC in those with a history of NMSC.[124,125]

Limited evidence is available to support the utility of other agents, including cyclic PDT, oral nicotinamide, and celecoxib, in reducing the risk for cSCC in patients with a history of keratinocyte carcinoma. There is early evidence from a small trial that oral nicotinamide may reduce the risk for subsequent keratinocyte carcinoma in nonimmunosuppressed individuals with a history of such carcinomas.[126] Although there is also some evidence that oral celecoxib reduces the risk for cSCC in patients with previous NMSC,[127] the potential benefits should be weighed against the significant risk for a cardiovascular event that is associated with this medication.

The dietary supplements β-carotene and selenium are not recommended for reducing risk for cSCC in patients with history of keratinocyte carcinoma. Several RCTs have shown no protective benefit against NMSC associated with either β-carotene or selenium.[128-130] Treatment-associated adverse events, notably, skin yellowing with β-carotene use and gastrointestinal upset with selenium, have been noted.

The recommendations for the follow-up and reducing risk for future tumors are shown in Table XIV, and the level of evidence/strength of the recommendations is presented in Table XV.[112-115,119-121,123,125-138]

GAPS IN RESEARCH

Much research remains to be done to elucidate the causes, natural history, and optimal management of cSCC. The relative importance of risk factors for cSCC, including the impact of immunosuppression over time, requires further elucidation. Population-based incidence, morbidity, and mortality data remain imprecise in the United States because there is no requirement for reporting these tumors to tumor registries. In the context of prevention, the long-term utility of sun protection and avoidance measures remains to be clarified. The role of SLNB in high-risk cSCC is unclear, and additional studies are warranted to determine their utility and indications. Novel therapeutic modalities are expected to continue to emerge. Results of ongoing clinical trials

with immune checkpoint inhibitors for locally advanced and metastatic cSCC are expected in near future.

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