GUIDELINES OF CARE FOR THE MANAGEMENT
OF CUTANEOUS SQUAMOUS CELL CARCINOMA

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ABSTRACT

Cutaneous squamous cell carcinoma (cSCC) is the second most common form of human cancer and has an increasing annual incidence. While most cSCC is cured with office-based therapy, advanced cSCC poses a significant risk of morbidity, quality of life impact, 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, however where relevant, applicability to recurrent cSCC is noted, as is general information on the management of patients with metastatic disease.

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 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 biological 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.

ABBREVIATIONS

AAD = American Academy of Dermatology
AJCC = American Joint Committee on Cancer
BCC = Basal Cell Carcinoma
BWH = Alternative/Brigham and Women’s Hospital
C&E = curettage and electrodesiccation
MM = malignant melanoma
MMS = Mohs micrographic surgery
NCCN = National Comprehensive Cancer Network
RCT = randomized controlled trial
cSCC = cutaneous Squamous Cell carcinoma
SLNB = sentinel lymph node biopsy
SOTR = solid organ transplant recipients
5-FU = 5-fluorouracil

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 (i.e., mucosal) SCC are outside the scope of this document, as
is a discussion of cSCC in situ (Bowen’s 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 also includes recommendations on appropriate biopsy
techniques, staging, follow-up, and prevention of cSCC. A detailed discussion of
specific chemo- or radiotherapeutic approaches for distant metastatic SCC falls outside
the scope of this guideline. However, general recommendations on 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.

METHOD

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, which 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 him 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 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 non-melanoma skin cancer (NMSC), searches were collectively undertaken for literature on cSCC and basal cell carcinoma (BCC) simultaneously using a set of search terms applicable to both cSCC and/or BCC. A parallel AAD guideline on BCC has also been developed.\textsuperscript{1} MeSH 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, electrodessication, excision, incomplete, cryosurgery, Mohs (micrographic) surgery, topical, fluorouracil, imiquimod, laser, radiotherapy, radiation, photochemotherapy, phototherapy, metastasis, vismodegib, sonidegib, prevention, prevention and control, and recurrence.

A total of 1120 articles were reviewed for possible inclusion; 188 were retained based on 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 available guidelines on cSCC were also evaluated.\textsuperscript{2-4}

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

I. Good-quality patient-oriented evidence (i.e. 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 (i.e. evidence measuring intermediate, physiologic, or surrogate end points that may or may not reflect improvements in patient outcomes).

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

A. 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.

Where published evidence-based data was not available, expert opinion was utilized to generate clinical recommendations.

This guideline has been developed in accordance with the American Academy of Dermatology (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. 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 five years from the date of publication, unless reaffirmed, updated, or retired at or before that time.

INTRODUCTION

Cutaneous SCC 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 US, lifetime risk of developing an cSCC is estimated at 9-14% for men and 4-9% for women. Each year in the US, at least 200,000-400,000 new cases of cSCC are expected, and disease-related death occurs in more than 3,000 people with cSCC. A Canadian study also detected an increase in annual incidence in cSCC over 200% in both men and women from the period 1960 to 2000. According to a study of US healthcare workers that analyzed data from prospective questionnaires obtained during 1976-2008 from over 250,000 participants enrolled in 3 large cohort studies, 18-year follow-up of these cohorts showed an increasing incidence of invasive cSCC over time.

While 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, has emerged as an increasingly important contributor to tumorigenesis.

Cutaneous SCC 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.\textsuperscript{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.\textsuperscript{13}

The treatment of cSCC has long been a substantial component of the clinical practice of dermatologists, who are well aware of 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 electrodessication (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 based on 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.\textsuperscript{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 healthcare 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
upon which each treatment recommendation is based is critical to selecting and providing care optimally tailored to individual patients.

While 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 US continues to increase\textsuperscript{16}, a thorough understanding of the management of cSCC and the evidence upon 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.\textsuperscript{17} In the 7\textsuperscript{th} Edition of the Staging Manual, published in 2010, cSCC was specifically addressed in the chapter Cutaneous Squamous Cell Carcinoma and Other Cutaneous Carcinomas.\textsuperscript{18} In the recently published 8\textsuperscript{th} Edition, cSCC is included in the chapter Cutaneous Squamous Cell Carcinoma of the Head and Neck.\textsuperscript{19} Although the chapter focuses primarily on cSCC, the staging system applies to all histologic subtypes of carcinoma in the head and neck, with the exception of Merkel cell carcinoma.

Several studies have evaluated various aspects of the 7\textsuperscript{th} Edition AJCC staging system for cSCC and consistently identified unsatisfactory prognostication among stage groups.\textsuperscript{20} In 2013, Brunner et al. noted the heterogeneous nature of stage group IV, and in 2014 pointed out that nodal (N) classification demonstrated less prognostic
significance in cSCC compared to mucosal SCC. In 2013, Jambusaria-Pahlajani et al proposed an alternative tumor (T) classification system for cSCC based on a retrospective cohort study. This alternative Brigham and Women’s Hospital (BWH) system classifies T categories based on the presence of several clinical and pathological risk factors, as summarized in Table 2. The BWH system was validated by an expanded retrospective cohort from the same group, as well as an independent systematic literature review. Although the BWH system does not address N and M classifications and advanced stage groups as the AJCC staging system, 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 a stratification to differentiate between high and low risk tumors, similar to BCC. This stratification, summarized in Table 3, takes both clinical and pathological 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 how to treat cSCC, rather than to provide accurate prognostication and assess outcome as the BWH system. For this reason, treatment recommendations throughout the currently presented guidelines are based on the NCCN risk stratification (recommendation Table 4; level of evidence/strength of recommendation Table 5).

Cross-sectional imaging for cSCC is rarely indicated to stage for metastatic disease, but may be considered in high-risk tumors (e.g. BWH category ≥ T2b). A
thorough clinical exam of the regional lymph node basins should always be performed. Imaging may also be considered to assess for deep structural involvement with extensive localized disease. The value of sentinel lymph node biopsy (SLNB) in cSCC is currently unknown. Retrospective and prospective case series have demonstrated successful detection of occult nodal metastases and suggested a prognostic role in patients with high-risk tumors. However, the effect of SLNB on management and outcome of patients with cSCC is unknown; enrollment of high-risk patients in clinical trials is encouraged, when available.

**BIOPSY**

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 (e.g., by tangential technique) biopsy\(^1\); 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, while 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 one is 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 6, and the level of evidence/strength of the recommendation in Table 5.

\(^1\) 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.
The 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, as well as patient preference and physician judgment. Most investigations that have compared biopsy method for detection of NMSC have studied BCC rather than cSCC. 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 in certain cases 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, and loss of function, particularly on the head, neck, and other vital, functional, sensory, or cosmetically sensitive sites.

CLINICAL AND PATHOLOGICAL INFORMATION

Presumptive diagnosis of cSCC is based on the physician’s interpretation of clinical information, including clinical appearance and morphology, anatomic location, and patient-reported history. Clinical diagnosis is routinely confirmed by biopsy findings prior to treatment. When the clinician is submitting biopsy tissue for
histopathologic diagnosis, when possible and appropriate, key elements of the patient
demographics, clinical presentation, and clinical history should be provided to the
pathologist (Table 7; level of evidence/strength of recommendations in Table 5). These
include patient age and gender, anatomic location, and if it is known that a
tumor was previously treated at the same anatomic site. Additional desirable
relevant information may include the clinical size of the lesion, and whether the
patient currently, or in years past, had additional risk factors, such as
immunosuppression, radiation treatment, or solid organ
transplantation. While not prognostically relevant, information regarding ongoing
treatment with a kinase (e.g. vemurafenib) or hedgehog pathway (vismodegib) inhibitor
may be diagnostically useful.

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 poor
cellular differentiation, aggressive histologic subtypes (acantholytic, adenosquamous,
carcinosarcomatous), depth >2 mm (measured from the granular layer of the adjacent
intact epidermis), Clark level IV or greater, and presence of perineural and/or
angiolympathic invasion. The presence of prognostically favorable features, such as
histopathologic subtypes, 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 to report, if possible and appropriate, the degree of cellular differentiation\textsuperscript{23,38,40,42-47}; presence of any aggressive histologic subtypes\textsuperscript{42,43}; depth of invasion in millimeters\textsuperscript{23,36,42,45-48}; anatomic (Clark) level of invasion\textsuperscript{43,44}; presence of any perineural invasion\textsuperscript{23,36,40,43-48}; presence of any lymphovascular invasion\textsuperscript{40,47}; description of any invasion of fascia, muscle, or bone\textsuperscript{23,36,47,48}; margin status (involved or not involved by tumor)\textsuperscript{20,37,39}; the number of high risk features present and the relevant TNM stage based on current AJCC criteria (Table 7; level of evidence/strength of recommendations in Table 5).\textsuperscript{18,23,36} In selected cases, other elements that have been shown to have prognostic significance for clinical care may additionally be reported, including the presence of inflammation\textsuperscript{36,47} or of infiltrative strands, single cells, or small nests of tumor.\textsuperscript{43} When perineural extension is observed, the diameter of the largest affected nerve may be reported, if this is deemed to be clinically significant.\textsuperscript{52,53} With regard to margin status, it should be reported if a cSCC with aggressive features extends close to a margin.

Pathologic evaluation of skin biopsies 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 (i.e., clinicopathologic correlation) to provide the most precise and accurate biopsy diagnosis.

SURGICAL TREATMENT

It is generally accepted that the majority of cSCC are successfully treated with standard treatment modalities, such as surgical excision, or C&E. 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 RCT and a general paucity of prospective trials assessing the effectiveness of primary surgical interventions for cSCC. Treatment recommendations are generally based on retrospective data, consensus opinion, and extrapolation from data on BCC or non-cutaneous SCC of the head and neck. When choosing the most appropriate therapy, recurrence rate, preservation of function, patient expectations and potential adverse effects must be taken in thorough consideration.

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

**Standard excision**

Cutaneous SCC, similar to BCC, is characterized by asymmetrical subclinical extension of tumor beyond the clinically visible lesion. To ensure complete removal with histologically negative margins, standard excision with “bread loaf” histopathological sectioning must include a margin of clinically normal appearing skin around the tumor and surrounding erythema. To date, no RCT have been performed comparing different excision margins for cSCC. 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. The authors reported an average local recurrence rate of 5.4% (95% CI 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 Mohs micrographic surgery. In the same study, for high-risk lesions >2 cm in clinical diameter or with higher histological grade, at least 6 mm margins were required to achieve 95% clearance rates. Based on the limited available data and consensus opinion, NCCN guidelines recommend 4-6 mm clinical margins for standard excision of low-risk cSCC (Table 3).

Given the limited available data, the workgroup recommends standard excision with 4-6 mm margin of uninvolved skin around the tumor and/or biopsy site to a depth of the mid subcutaneous adipose tissue with histological margin assessment for low-risk primary cSCC (based on NCCN risk stratification, Table 3). 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. Insufficient data precludes 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 8. The strength of these recommendations is shown in Table 9.

Mohs Micrographic Surgery

Dr. Frederic Mohs first described the use of chemosurgery for the removal of difficult or recurrent cutaneous tumors in the 1940s. Three decades later, the
concept of *en face* horizontal sectioning for complete peripheral and deep margin control pioneered by Mohs to achieve optimal cure rate and maximum tissue conservation, was adapted to the “fresh tissue” technique by Tromovitch and Stegman.\(^59\) 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 Mohs micrographic surgery (MMS), was recommended for all recurrent or poorly defined tumors, sclerosing BCC, and for all primary cutaneous carcinomas in areas with a predilection for recurrence.\(^60\)

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.\(^61\) However, to date, no RCT or prospective cohort studies have been performed comparing MMS to other treatment modalities for the treatment of cSCC. 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.\(^44\) In comparison, 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 taking high-risk factors into account, MMS showed lower recurrence rates compared to standard excision and other non-MMS treatment modalities: 25.2% versus 41.7% for tumors \(\geq\) 2 cm in size, 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 to 23.3% (n=34) following standard excision. Similar 5-year recurrence rates for recurrent cSCC treated with MMS were reported by others ranging between 6-11%.\textsuperscript{62,63} 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.\textsuperscript{64} A large percentage of cSCC are located on the head and neck where tissue conservation is important. Similar to BCC, cSCC is characterized histologically by asymmetrical subclinical extension beyond the clinically visible tumor and more frequently than BCC presents with perineural involvement.\textsuperscript{65} Both histopathological features would support the importance of meticulous and complete margin assessment with MMS. However, aggressive histopathological growth patterns poorly visualized with frozen sections (e.g. sarcomatoid/spindle cell or single cell infiltrative cSCC) may limit the utility for 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 using paraffin sections.\textsuperscript{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.\textsuperscript{67} Alternatively, key pathologic high risk features can be documented in the Mohs report, to facilitate prognostic assessment and guide postoperative management when indicated. Careful selection, based on initial biopsy results, of tumors appropriate for treatment with MMS and evaluation by frozen sections will minimize these limitations.
Based on the best available data, the workgroup recommends MMS for the treatment of high-risk cSCC (based on NCCN risk stratification, Table 8; level of evidence/strength of recommendation Table 9).

Curettage and electrodesiccation

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

The limited available data suggest that C&E is an effective treatment modality for properly selected tumors, though results are highly operator dependent. It is the workgroup opinion that C&E may be considered for small, low-risk primary cSCC (based on NCCN risk stratification, Table 8; level of evidence/strength of recommendation Table 9). Lesions on terminal hair-bearing skin (scalp, pubic, axillary regions, and beard area in men) should be excluded from treatment with C&E due to potential follicular extension of tumor. Moreover, C&E may be associated with a longer healing time and inferior cosmetic outcome compared to standard excision and is best avoided in cosmetically sensitive areas.

NON-SURGICAL 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 due to 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 non-surgical therapies for cSCC. The recommendations for non-surgical treatments are shown in Table 10. The level of evidence/strength of the recommendations is listed in Table 11.

**Photodynamic Therapy**

Photodynamic therapy is a two-part treatment consisting of topical application of a photosensitizer, either 5-aminolevulinic acid (ALA) or methylaminolevulinate (MAL), followed by one to several hours of incubation by light irradiation, typically with a blue, red, or broadband light source.\(^{70-81}\) Available data for PDT and laser therapy does not currently support their efficacy in the treatment of cSCC.\(^{54}\) Limited case report and case series data suggests PDT may be used as an adjuvant modality in combination with curettage\(^{82}\) and surgery\(^{83}\) for invasive cSCC, potentially to spare tissue and in high risk patients like solid organ transplant recipients (SOTR), but the specific contribution of PDT to observed outcomes in such combination approaches is uncertain.

When PDT is combined with surgery, multiple treatments of PDT may be employed. Exacerbation or induction of well-differentiated cSCC or keratoacanthoma after PDT has been reported.\(^{84}\)

**Topical Therapies**
Available data does 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 of typically one to two patients for imiquimod, and two small case series for 5-FU.\textsuperscript{54,85,86} Variable lengths of follow-up and histologic clearance limit the strength of these data.\textsuperscript{54}

Since 5-FU use 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 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**

While surgery remains the first line, and most effective treatment for cSCC, primary radiation therapy can be used in special situations when 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, brachytherapy (interstitial, or topical contact), or external electron beam radiation.\textsuperscript{54} Primary or adjuvant radiation therapy is an effective treatment option for selected patients with cSCC resulting in good tumor control and cosmesis\textsuperscript{87}, with the understanding that the cure rate may be lower.\textsuperscript{88,89} Smaller and thinner tumors may be more responsive to radiation therapy.\textsuperscript{54,90} As with other non-surgical approaches, available data on radiotherapy is limited by small patient numbers and variable lengths
of follow-up to detect local or regional recurrences.\textsuperscript{54} While there is limited evidence regarding the use of traditional variants of brachytherapy, such as interstitial radiotherapy and isotope-based contact brachytherapy for the treatment of cSCC, electronic brachytherapy is a newer modality for which long-term safety and effectiveness data are lacking.\textsuperscript{91} Primary cSCC with concerning perineural invasion or otherwise at high risk for regional or distant metastasis may also be treated with adjuvant radiation following surgical treatment of the local basin.\textsuperscript{92} High level evidence is lacking about the effectiveness of this approach.

\textit{Cryosurgery}

Given the lack of histological margin control with this approach and known subclinical extension of cSCC, cryosurgery should only be considered for low-risk lesions under select clinical circumstances, 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. While frequently used for the treatment of precursor lesions (i.e. actinic keratoses), limited data is available on the use of cryosurgery for cSCC.\textsuperscript{54}

\textit{Laser Treatment}

Treatment of cSCC by Nd:YAG laser has been reported in a single retrospective study, with this extremely limited experience precluding the recommendation of laser for this indication.\textsuperscript{54} Photodynamic therapy, which includes a light source as well as a topical photosensitizer, is discussed above.
MANAGING PATIENTS WITH METASTATIC cSCC

The risk of metastasis in cSCC is reported to be approximately 4%\(^\text{42}\). Among immunosuppressed individuals, particularly for SOTR, the metastatic risk may be two to three times higher.\(^\text{93}\) 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.\(^\text{27,28}\) However, the effect of SLNB on management and outcome of patients with high-risk cSCC is unknown.

The available literature on the management of in-transit and lymph node metastases is largely limited to retrospective reviews and case series of patients with head and neck cSCC.\(^\text{26,94,95}\) 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.\(^\text{26}\) 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 is sparse and limited to phase II clinical trials. Chemotherapy, including cisplatin as a single agent or combined with 5-fluorouracil (5-FU), has shown occasional activity, but results have not been confirmed.\(^\text{96,97}\) 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. In (non-cutaneous) 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.

Careful consideration must be given to immunosuppressed individuals with high-risk localized or metastatic cSCC, given the more aggressive clinical behavior and poor prognosis. In SOTR, dose reduction of the immunosuppressive agents and minimizing of calcineurin inhibitors (e.g. cyclosporine, tacrolimus) and/or antimetabolites (e.g. azathioprine) in favor of mTOR inhibitors (e.g. sirolimus) may be considered when appropriate. However, a recent retrospective cohort study did not demonstrate a reduction in post-transplantation risk of cSCC among SOTRs exposed to sirolimus.

Multidisciplinary consultation and management are strongly encouraged for SOTR with advanced or metastatic SCC.

The recommendations for management of regional and distant metastatic SCC is shown in Table 12, and the level of evidence/strength of the recommendation in Table 13.

FOLLOW-UP AND REDUCING RISK OF FUTURE SKIN CANCERS

Once a patient has been diagnosed with an cSCC, in-office screening for new primary skin cancers, including BCC, cSCC, and melanoma, should be performed at least once a year. Clinical assessment of regional lymph node basins may be included in the physical exam for high-risk lesions. This recommendation derives from the considerable evidence from cohort studies and registries that a patient with at least one cSCC is at risk for additional cSCC as well as other skin cancers, including BCC and melanoma.
A 2010 meta-analysis by Wheless and colleagues determined that the summary random-effects relative risk (SRR) of developing a second NMSC after diagnosis of a first was 1.12 (based on 12 cohort studies from cancer registries) and 1.49 based upon 3 studies with patient level data. 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 82% after more than one. At 10 years the chances increased to 59.6% of another NMSC after the first and 91.2% after diagnosis of a non-first NMSC.

Initial diagnosis of NMSC, including cSCC, increases the risk of subsequent malignant melanoma (MM). Song and colleagues found a relative risk of 1.99 for men and 2.58 for women of developing MM after diagnosis of a NMSC. This data was based upon two large prospective cohort studies with 46,237 men and 107,339 women under study. A smaller study including 3548 people found the relative risk for MM to be 3.62 after diagnosis of an SCC.

Patients who have had cSCC should be counseled regarding the risk of 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 (e.g., the back) that are not easily assessed by the patient. 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. Routinely 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 of 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 with a history of a keratinocyte
cancer. Consequently, topical retinoids are not recommended for reducing the risk of
subsequent cSCC in patients with a prior 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. Acitretin has
not been shown to be helpful in reducing the incidence of cSCC in non-transplant
patients with a history of NMSC. However, one small RCT demonstrated benefit to
renal transplant patients with 10 or more keratotic lesions. The benefits of oral retinol
need more study as two large RCTs have shown divergent conclusions. Isotretinoin
does not appear to reduce the incidence of cSCC in those with a history of NMSC.

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

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

The recommendations for the follow-up and reducing risk of future tumors are
shown in Table 14, and the level of evidence/strength of the recommendations in Table
15.

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 US
since 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 sentinel lymph node biopsies 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.
REFERENCES


American Academy of Dermatology. Position Statement on Electronic Surface Brachytherapy for Basal Cell Carcinoma (BCC) and Squamous Cell Carcinomas (SCC). 


Publishable Conflict of Interest Statement

The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies’ Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

The below information represents the authors disclosed relationships with industry during guideline development. Relevant relationships requiring recusal for drafting of guideline recommendations and content by Work Group members were not noted for this guideline.

April Armstrong, MD, MPH served as an advisory board member for Abbvie, Amgen, Janssen-Ortho, Merck, Novartis, Pfizer and UCB receiving honoraria; as a consultant for Celgene, Eli Lily, Jannsen-Ortho, and Modernizing Medicine receiving honoraria; as a speaker for Abbvie receiving honoraria; and as a PI for Eli Lily, Janssen-Ortho, Novartis, and Regeneron receiving grants/research funding.

Jeremy S. Bordeaux, MD, MPH served as an advisor board member for Lubax receiving honoraria; as an employpee of Massachusetts General Hospital receiving salary; and in other role with Journal Watch Dermatology receiving honoraria.
Marc Brown, MD served as an advisory board member for DUSA Pharmaceuticals receiving no compensation.

David J. Margolis, MD, PhD served as an advisory board member for Astellas, Celleration, and Kerecis receiving fees; as a PI for Valeant receiving grants/research funding; and as a Data Safety Monitoring Board member for DermaSciences, Macrocure, and Sanofi/Regeneron receiving fees.

Stanley Miller, MD served as an employee of UpToDate, Inc. receiving patent royalties/other compensation.

Eliot Mostow, MD, MPH served as a consultant for Elsevier receiving salary; as a speaker and PI for Healthpoint receiving honoraria and grants/research funding; as an advisory board member for Vivacare receiving honoraria.

Christen Mowad, MD served on the Board of Directors for Elsevier receiving honoraria, in other roles with UpToDate, Inc. receiving patient royalties/other compensation, and as a PI for Amgen receiving fees. Dr. Mowad also had a relative serving as an employee of Takeda Pharmaceuticals receiving salary.

Aleksander Sekulic, MD, PhD served as an advisory board member for Roche and as a PI for Genentech receiving fees.

Conway Huang, MD served as a consultant for Castle Biosciences, Inc. receiving honoraria.

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Christopher Bichakjian, MD, Christian Baum, MD, Klaus J. Busam, MD; Daniel B. Eisen, MD, Vivek Iyengar, MD; Clifford Lober, MD, JD, Jane Messina, MD; Alexander Miller, MD; Kishwer Nehal, MD, Kristi Schmitt-Burr, Paul Storrs, MD, Joyce Teng, MD, PhD, Siegrid Yu, MD, John YS Kim, MD; Jeffrey H. Kozlow, MD, MS, Bharat Mittal, MD; Jeffrey Moyer, MD, Phillip Rodgers, MD; Kevin Boyer, MPH; and Wendy Smith Begolka, MBS have no relationships to disclose.
Table 1. 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, harms, 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
  - Beta-carotene

* BCC only
Table 2. Brigham and Women’s Hospital tumor classification system\textsuperscript{23}

<table>
<thead>
<tr>
<th>Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>In situ SCC</td>
</tr>
<tr>
<td>T1</td>
<td>0 Risk factors\textsuperscript{1}</td>
</tr>
<tr>
<td>T2a</td>
<td>1 Risk factor</td>
</tr>
<tr>
<td>T2b</td>
<td>2-3 Risk factors</td>
</tr>
<tr>
<td>T3</td>
<td>4 Risk factors or bone invasion</td>
</tr>
</tbody>
</table>

\textsuperscript{1}Risk factors include tumor diameter $\geq$ 2 cm, poorly differentiated histology, perineural invasion, and tumor invasion beyond the subcutaneous fat (excluding bone, which automatically upgrades to T3).
Table 3. National Comprehensive Cancer Network stratification of low versus high risk cSCC³

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location³/Size²</td>
<td>Area L &lt; 20 mm</td>
<td>Area L ≥ 20 mm</td>
</tr>
<tr>
<td></td>
<td>Area M³ &lt; 10 mm</td>
<td>Area M ≥ 10 mm</td>
</tr>
<tr>
<td></td>
<td>Area H⁴</td>
<td></td>
</tr>
<tr>
<td>Borders</td>
<td>Well defined</td>
<td>Poorly defined</td>
</tr>
<tr>
<td>Primary vs Recurrent</td>
<td>Primary</td>
<td>Recurrent</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Site of prior radiation therapy or chronic inflammatory process</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Rapidly growing tumor</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Neurological symptoms</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Pathological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree of differentiation</td>
<td>Well to moderately differentiated</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>High-risk histological subtype⁵</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Depth (thickness or Clark level)⁶</td>
<td>&lt;2 mm, or I, II, III</td>
<td>≥2 mm or IV, V</td>
</tr>
<tr>
<td>Perineural, lymphatic, or vascular involvement</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

¹Area L = trunk and extremities (excluding hands, feet, nail units, pretibia and ankles).
²Area M = cheeks, forehead, scalp, neck, and pretibia.
³Area H = central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, pre- and postauricular skin/sulci, temple, ear, genitalia, hands, and feet.
⁴Including peripheral rim of erythema.
⁵Location independent of size may constitute high risk.
⁶Area H constitutes high risk based on location, independent of size.
⁷Adenoid (acantholytic), adenosquamous (showing mucin production), desmoplastic or metaplastic (carcinosarcomatous) subtypes.
⁸A modified Breslow measurement should exclude parakeratosis or scale/crust, and should be made from base of ulcer is present. If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.
Table 4. Recommendations for grading and staging of cSCC

Stratification of localized SCC using the NCCN guideline framework is recommended for clinical practice. Clinicians should refer to the Brigham and Women’s Hospital (BWH) tumor classification system to obtain the most accurate prognostication of patients with localized cSCC.

Table 5. Level of evidence and strength of recommendations for grading and staging, biopsy, clinical information and pathology report for the treatment of cSCC

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grading and Staging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• AJCC</td>
<td>B</td>
<td>II</td>
<td>20-25</td>
</tr>
<tr>
<td>• BWH</td>
<td>B</td>
<td>II</td>
<td>23-25</td>
</tr>
<tr>
<td>• NCCN</td>
<td>C</td>
<td>III</td>
<td>2,3</td>
</tr>
<tr>
<td>Biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Information Provided to Pathologist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Age</td>
<td>A</td>
<td>I, II</td>
<td>36-38</td>
</tr>
<tr>
<td>• Gender</td>
<td>B</td>
<td>II</td>
<td>37,39</td>
</tr>
<tr>
<td>• Anatomic location</td>
<td>B</td>
<td>I, II</td>
<td>37-46</td>
</tr>
<tr>
<td>• Recurrent lesion</td>
<td>A</td>
<td>I, II</td>
<td>44,47,48</td>
</tr>
<tr>
<td>• Size of lesion</td>
<td>A</td>
<td>I, II</td>
<td>23-40-48</td>
</tr>
<tr>
<td>• Immunosuppression</td>
<td>B</td>
<td>I, II</td>
<td>20,23,42,46,49</td>
</tr>
<tr>
<td>• Prior history, esp radiation, burn, organ transplant</td>
<td>B</td>
<td>II</td>
<td>20,44,50,51</td>
</tr>
<tr>
<td>Pathology Report Elements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Degree of differentiation*</td>
<td>B</td>
<td>I, II</td>
<td>23,38,40,42-47</td>
</tr>
<tr>
<td>• Presence of aggressive histologic subtype**</td>
<td>B</td>
<td>I, II</td>
<td>42,43</td>
</tr>
<tr>
<td>• Depth of invasion (mm)</td>
<td>A</td>
<td>I, II</td>
<td>23,36,42,45-48</td>
</tr>
<tr>
<td>• Clark level of invasion</td>
<td>B</td>
<td>II</td>
<td>43,44</td>
</tr>
</tbody>
</table>
- Perineural invasion
- Lymphovascular invasion
- Invasion of fascia, muscle, or bone
- Number of high-risk features***
- Margin status
- TNM Stage (AJCC)
- Inflammation
- Infiltrative strands, single cells, small nests
- Diameter of largest involved nerve

<table>
<thead>
<tr>
<th>Feature</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>I, II</th>
<th>23, 36, 40, 43-48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perineural invasion</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>I, II</td>
<td>23, 36, 47, 48</td>
</tr>
<tr>
<td>Lymphovascular invasion</td>
<td>A</td>
<td></td>
<td></td>
<td>I, II</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Invasion of fascia, muscle, or bone</td>
<td>A</td>
<td></td>
<td></td>
<td>I, II</td>
<td></td>
</tr>
<tr>
<td>Number of high-risk features***</td>
<td></td>
<td>C</td>
<td></td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Margin status</td>
<td></td>
<td>B</td>
<td></td>
<td>II</td>
<td>20, 37, 39</td>
</tr>
<tr>
<td>TNM Stage (AJCC)</td>
<td></td>
<td>A</td>
<td></td>
<td>I</td>
<td>23, 36</td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td>A</td>
<td></td>
<td>I</td>
<td>36, 47</td>
</tr>
<tr>
<td>Infiltrative strands, single cells, small nests</td>
<td></td>
<td>B</td>
<td></td>
<td>II</td>
<td>43</td>
</tr>
<tr>
<td>Diameter of largest involved nerve</td>
<td></td>
<td>B</td>
<td></td>
<td>II</td>
<td>52, 53</td>
</tr>
</tbody>
</table>

*well, moderately, poorly or un-differentiated

**acantholytic, adenosquamous, or carcinosarcomatous subtypes

***high-risk features include thickness >2 mm, Clark level IV or V, poorly-differentiated/undifferentiated, site on mucosa lip or ear, perineural invasion, lymphovascular invasion

**Table 6:** 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 upon 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 initial biopsy specimen is inadequate for accurate diagnosis.
**Table 7:** Recommendations for clinical information and pathology report for suspected cSCC

<table>
<thead>
<tr>
<th>Clinical information provided to pathologist:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strongly recommended</strong></td>
</tr>
<tr>
<td>- Age</td>
</tr>
<tr>
<td>- Gender</td>
</tr>
<tr>
<td>- Anatomic location</td>
</tr>
<tr>
<td>- Recurrent lesion</td>
</tr>
<tr>
<td><strong>Recommended</strong></td>
</tr>
<tr>
<td>- Size of lesion</td>
</tr>
<tr>
<td>- Immunosuppression</td>
</tr>
<tr>
<td>- Prior history (esp radiation, burn, organ transplant)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Elements to be included in final pathology report (excision specimens):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strongly recommended</strong></td>
</tr>
<tr>
<td>- Degree of differentiation*</td>
</tr>
<tr>
<td>- Presence of aggressive histologic subtype**</td>
</tr>
<tr>
<td>- Depth of invasion (mm)</td>
</tr>
<tr>
<td>- Clark level of invasion</td>
</tr>
<tr>
<td>- Perineural invasion</td>
</tr>
<tr>
<td>- Lymphovascular invasion</td>
</tr>
<tr>
<td>- Invasion of fascia, muscle, or bone</td>
</tr>
<tr>
<td>- Number of high-risk features***</td>
</tr>
<tr>
<td>- Margin status</td>
</tr>
<tr>
<td>- TNM Stage (AJCC)</td>
</tr>
<tr>
<td><strong>Recommended</strong></td>
</tr>
<tr>
<td>- Inflammation</td>
</tr>
<tr>
<td>- Infiltrative strands, single cells, small nests</td>
</tr>
<tr>
<td>- Diameter of largest involved nerve</td>
</tr>
</tbody>
</table>

*well, moderately, poorly or un-differentiated
**acantholytic, adenosquamous, or carcinosarcomatous subtypes
***high-risk features include thickness >2 mm, Clark level IV or V, poorly-differentiated/undifferentiated, site on mucosa lip or ear, perineural invasion, lymphovascular invasion
Table 8. Recommendations for the surgical treatment of cSCC

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment plan</td>
<td>A</td>
<td>II</td>
<td>55</td>
</tr>
<tr>
<td>Standard excision w/ 4-6mm margins for low-risk primary SCC*</td>
<td>B</td>
<td>II</td>
<td>54</td>
</tr>
<tr>
<td>Standard excision for high-risk SCC</td>
<td>B</td>
<td>II</td>
<td>54</td>
</tr>
<tr>
<td>C&amp;E for low risk primary SCC*</td>
<td>B</td>
<td>II, III</td>
<td>54</td>
</tr>
<tr>
<td>Mohs Micrographic Surgery for high-risk SCC*</td>
<td>B</td>
<td>II, III</td>
<td>44, 54, 63, 64</td>
</tr>
</tbody>
</table>

*as defined by NCCN
Table 10. Recommendations for the non-surgical therapy of cSCC

If surgical therapy is not feasible or preferred, radiation therapy (e.g. superficial radiation therapy, brachytherapy, external electron beam 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 based on 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.

Table 11. Level of evidence and strength of recommendations for the non-surgical treatment of cSCC

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryosurgery</td>
<td>B</td>
<td>II</td>
<td>54</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Traditional radiotherapies and modern superficial radiation therapy</td>
<td>B</td>
<td>II, III</td>
<td>54,122</td>
</tr>
<tr>
<td>- Electronic surface brachytherapy</td>
<td>C</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>Against topical therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Imiquimod</td>
<td>C</td>
<td>III</td>
<td>54,85,86</td>
</tr>
<tr>
<td>- 5-FU</td>
<td>C</td>
<td>III</td>
<td>54</td>
</tr>
<tr>
<td>Against photodynamic therapy</td>
<td>B</td>
<td>II</td>
<td>54</td>
</tr>
<tr>
<td>Laser therapy</td>
<td>C</td>
<td>III</td>
<td>54</td>
</tr>
</tbody>
</table>
Table 12. Recommendations for management of locally advanced or metastatic SCC

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>B</td>
<td>II</td>
<td>26,94,95</td>
</tr>
<tr>
<td>Epidermal growth factor inhibitors and cisplatin, as single agent or in combination therapy, may be considered as they have demonstrated efficacy for metastatic disease, albeit based on limited data.</td>
<td>B</td>
<td>I, II</td>
<td>96-100</td>
</tr>
<tr>
<td>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.</td>
<td>A</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Patients with advanced disease should be provided or referred for best supportive and palliative care, to optimize symptom management and maximize quality of life.</td>
<td>A</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

Table 13: Level of evidence and strength of recommendations for the management of locally advanced or metastatic SCC

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical resection with/without adjuvant radiotherapy</td>
<td>B</td>
<td>II</td>
<td>26,94,95</td>
</tr>
<tr>
<td>Epidermal growth factor inhibitors and cisplatin</td>
<td>B</td>
<td>I, II</td>
<td>96-100</td>
</tr>
<tr>
<td>Multidisciplinary consultation</td>
<td>A</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Palliative care</td>
<td>A</td>
<td>III</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>
Table 14: Recommendations for the follow-up of cSCC and reducing risk of 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-exam and sun protection.

Topical and oral retinoids (e.g. 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 SOTR patients. In the situation of SOTR, only acitretin may be beneficial.

Dietary supplementation of selenium and Beta-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.

Table 15: Level of evidence and strength of recommendations for the follow-up of cSCC and reducing risk of future tumors

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of Recommendation</th>
<th>Level of Evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual follow-up skin cancer screening</td>
<td>A</td>
<td>I</td>
<td>104-107,123,124</td>
</tr>
<tr>
<td>Against the use of topical and oral retinoids*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Tretinoin</td>
<td>A</td>
<td>I, II</td>
<td>111,112,125</td>
</tr>
<tr>
<td>- Acitretin</td>
<td>B</td>
<td>I</td>
<td>113</td>
</tr>
<tr>
<td>- Isotretinoin</td>
<td>A</td>
<td>I</td>
<td>116,126</td>
</tr>
<tr>
<td>- Oral retinol</td>
<td>A</td>
<td>I</td>
<td>116,127</td>
</tr>
<tr>
<td>*non-SOTR patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of acetretin for SOTR patients</td>
<td>B</td>
<td>I</td>
<td>114</td>
</tr>
<tr>
<td>Against chemoprevention using:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Celecoxib</td>
<td>B</td>
<td>I</td>
<td>118,128</td>
</tr>
<tr>
<td>- DFMO</td>
<td>A</td>
<td>I</td>
<td>129,130</td>
</tr>
<tr>
<td>- Oral nicotinamide</td>
<td>B</td>
<td>I</td>
<td>117</td>
</tr>
<tr>
<td>Against dietary supplementation with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Selenium</td>
<td>A</td>
<td>I</td>
<td>119,120</td>
</tr>
<tr>
<td>- Beta-carotene</td>
<td>A</td>
<td>I</td>
<td>121</td>
</tr>
</tbody>
</table>