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Target Audience: This activity is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

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Release date: December 10, 2021; Expiration date: December 10, 2022

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Squamous Cell Skin Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Squamous Cell Skin Cancer

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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Squamous Cell Skin Cancer, Version 1.2022

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Squamous Cell Skin Cancer provide recommendations for diagnostic workup, clinical stage, and treatment options for patients with cutaneous squamous cell carcinoma. The NCCN panel meets annually to discuss updates to the guidelines based on comments from panel members and the Institutional Review, as well as submissions from within NCCN and external organizations. These NCCN Guidelines Insights focus on the introduction of a new surgical recommendation terminology (peripheral and deep en face margin assessment), as well as recent updates on topical prophylaxis, immunotherapy for regional and metastatic disease, and radiation therapy.

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[*]Provided content development and/or authorship assistance.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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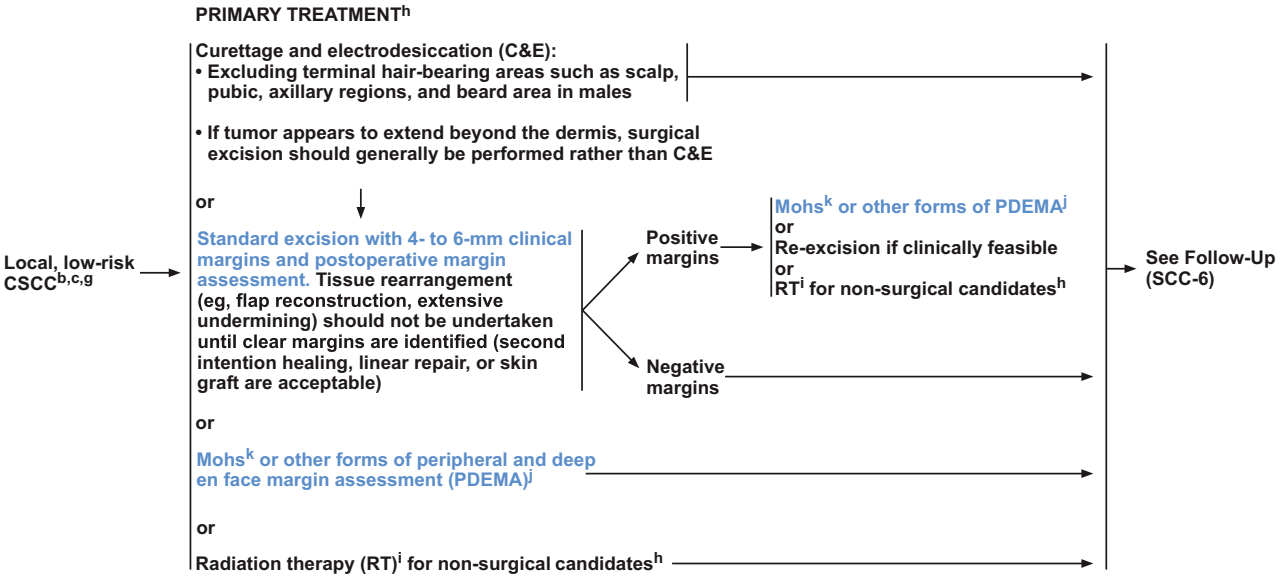

[b] See Principles of Pathology (SCC-A).
[c] See Stratification to Determine Treatment Options and Follow-up for Local CSCC Based on Risk Factors for Local Recurrence, Metastases, or Death from Disease (SCC-B) and Identification and Management of Patients at High Risk for Multiple Primary CSCCs (SCC-C).
[h] See Principles of Treatment (SCC-D).
[i] See Principles of Radiation Therapy (SCC-E).
[j] PDEMA (via permanent or frozen section) is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G).
[k] When Mohs is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.

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SCC-2

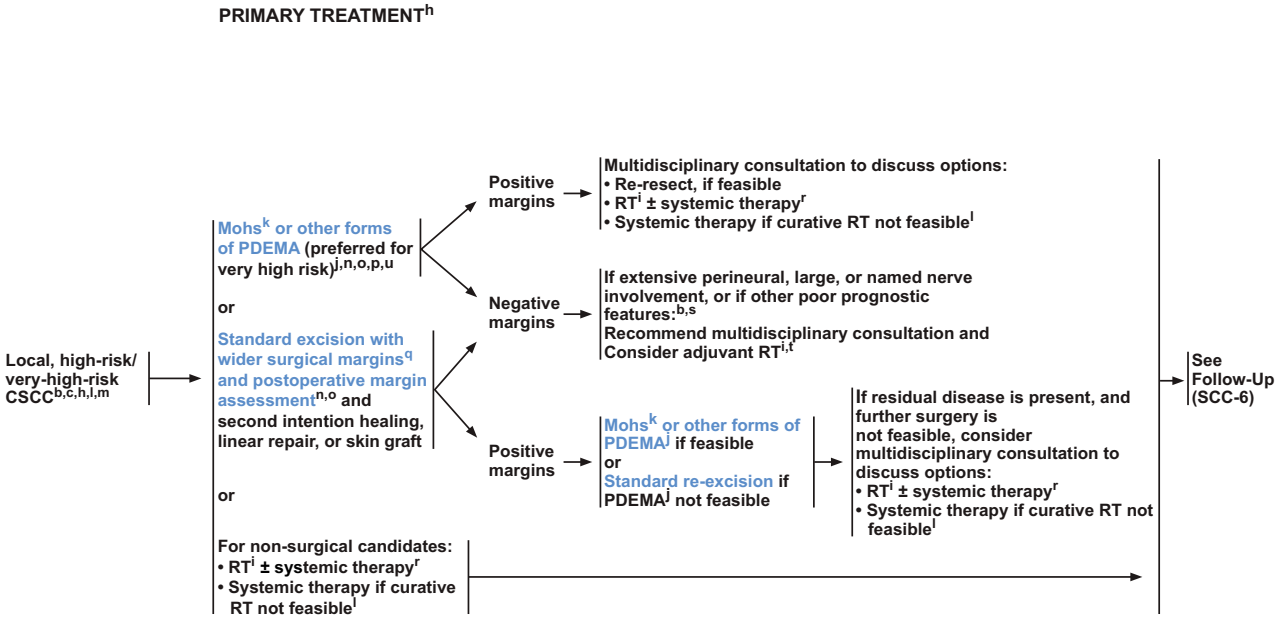
Overview

Cutaneous squamous cell carcinoma (CSCC) is the second most common skin cancer.[1–3] Numerous population-based studies have demonstrated that the incidence of CSCC is rising rapidly.[1,4–6] Some studies show that CSCC incidence rates are increasing more rapidly than basal cell carcinoma, reducing the difference in incidence between these skin cancers.[2,3,7] Although rarely metastatic, CSCC can produce substantial local destruction along with disfigurement and may involve extensive areas of soft tissue, cartilage, and bone. Patients with CSCCs generally have a good prognosis, with a 5-year survival rate of ≥90%.[1,8,9]

Peripheral and Deep En Face Margin Assessment

A major update in the 2022 version of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Squamous Cell Skin Cancer is a change of the term "complete circumferential peripheral and deep margin assessment (CCPDMA)" to "peripheral and deep en face margin assessment (PDEMA)." This change is made across all 4 NCCN Guidelines for Non-Melanoma Skin Cancer. With this change, the panel hopes to achieve broader recognition of the term by pathologists and Mohs surgeons, who are ultimately responsible for the processing of excised specimens.

The discussion was prompted by comments from the Institutional Review (IR), as well as general concern from current panel members, about a lack of understanding of the term CCPDMA term among treating physicians and pathologists around the country. The term CCPDMA was initially developed to avoid jargons that are unique to any particular specialty. It was thought that CCPDMA would enforce consistency across treatment modalities and encapsulate accurately what needs to be achieved. However, after an extensive discussion, the panel agreed that the term CCPDMA introduces significant variation in the interpretation of "complete margin assessment." Many pathologists, according to panel members, will cut vertical sections across the deep margin instead of en face or horizontal deep sections, as desired by PDEMA. Thus, the panel decided the term PDEMA has greater clarity in specifying what is meant by total margin evaluation. However, some concern remains about the lack of consensus regarding the meaning of the



See Footnotes on SCC-3A

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term "en face" among physicians from the rest of the world.

It must be reiterated that the NCCN panel strongly recommends PDEMA as the preferred surgical technique for high-risk CSCC. The 2 methods to achieve PDEMA are Mohs and Tubingen, which use rapid frozen sections and paraffin-embedded sections, respectively. It has been established in earlier versions of the guidelines that PDEMA is the preferred excision method for NCCN-designated very-high-risk CSCC because it allows intraoperative analysis of 100% of the excision margin and is associated with low recurrence rates. High-risk features, as outlined in the NCCN Guidelines, include size ≥4 cm (any location), poor differentiation, desmoplastic CSCC, >6 mm in thickness or invasion beyond subcutaneous fat, perineural involvement (PNI) with tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm, and lymphatic or vascular involvement.

An extensive meta-analysis of studies with long-term follow-up (≥5 years) reported local recurrence rates of 3.1% for primary CSCCs and 10% for recurrences treated with Mohs.[10] Results from this meta-analysis found that cure rates for Mohs depended on tumor diameter (<2 vs ≥2 cm: 98.1% vs 74.8%) and differentiation (well vs poorly differentiated: 97.0% vs 67.4%). For each of these subgroups, cure rates for Mohs were higher than for treatment with non-Mohs modalities.[10] Retrospective and prospective observational studies of localized primary CSCCs treated with Mohs reported local recurrence rates of 1.2% to 4.1% and rates of metastases between 0% and 6.3%.[11–21] Compared with primary tumors, rates of local recurrence or metastasis after Mohs are higher for recurrent tumors (previously treated with a non-Mohs modality).[13,22] For recurrent CSCCs treated with Mohs, subsequent local recurrences occurred in 5.9% to 7.7% of cases; metastasis in 0% to 10%.[11–17] Other risk factors associated with recurrence after Mohs include larger subclinical extension and more Mohs stages required for clearance.[13] CSCC with PNI is associated with elevated rates of recurrence (6.8%–32.3%) in studies that occasionally include basal cell carcinoma as well as treatment with radiation therapy (RT).[23–28] Risk factors associated with metastasis after Mohs include size >2 cm, Clark level (metastatic CSCC are more likely to be deeper, Clark level III–V), poor differentiation, location in areas of prior

Footnotes

[b] See Principles of Pathology (SCC-A).
[c] See Stratification to Determine Treatment Options and Follow-up for Local CSCC Based on Risk Factors for Local Recurrence, Metastases, or Death from Disease (SCC-B) and Identification and Management of Patients at High Risk for Multiple Primary CSCCs (SCC-C).
[h] See Principles of Treatment (SCC-D).
[i] See Principles of Radiation Therapy (SCC-E).
[j] PDEMA (via permanent or frozen section) is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G).
[k] When Mohs is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.
[l] For complicated cases, consider multidisciplinary consultation. For locally advanced disease in which curative RT and curative surgery are not feasible, consider treatment with systemic therapy or clinical trial. See Principles of Systemic Therapy (SCC-F).
[m] If patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate.
[n] In patients with very-high-risk CSCC and normal exam of nodal basin, discuss and consider radiologic imaging of nodal basin.
[o] Discuss and consider sentinel lymph node biopsy (SLNB) prior to PDEMA for patients with very-high-risk CSCCs that are recurrent or have multiple risk factors placing them in the very-high-risk group, and have normal exam of draining nodal basin (category 2B). See Stratification to Determine Treatment Options and Follow-up for Local CSCC Based on Risk Factors for Local Recurrence, Metastases, or Death from Disease (SCC-B).
[p] If invasion to parotid fascia, superficial parotidectomy may be indicated.
[q] Due to the wide variability of clinical characteristics that may define a high-risk tumor, it is not feasible to recommend a defined margin for standard excision of high-risk CSCC. Keen awareness of the subclinical extension of CSCC is advised when selecting a treatment modality without complete margin assessment for a high-risk tumor. These margins may need to be modified based on tumor or patient-specific factors.
[r] RT may be supplemented by systemic therapy in select patients. See Principles of Systemic Therapy (SCC-F).
[s] Large nerve involvement is defined by the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition for CSCC of the head and neck as ≥0.1 mm or nerve involvement deeper than the dermis. Most nerves deep to the dermis are >0.1 mm.
[t] The outcome benefit of adjuvant RT following resection of any CSCC with negative surgical margins is uncertain.
[u] For tumors in cheeks, forehead, scalp, neck, and pretibia that are <6 mm in depth and confined to the dermis, C&E may be considered as an alternative primary treatment option if comorbidities or other factors make surgical excision difficult. See Stratification to Determine Treatment Options and Follow-up for Local CSCC Based on Risk Factors for Local Recurrence, Metastases, or Death from Disease (SCC-B).

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radiation, small tumor nests and infiltrative tumor strands, single-cell infiltration, PNI, and acantholysis.[22]

Excision with PDEMA using permanent section analysis or intraoperative frozen section analysis is acceptable as an alternative to Mohs provided that it includes a complete assessment of all deep and peripheral margins (for more information, see the full version of these guidelines at NCCN.org). The descriptive term PDEMA underscores the panel's belief that complete histologic assessment of the entire marginal surface is the key to optimal tumor removal for NCCN-designated very-high-risk tumors.

Standard Excision With Incomplete Margin Assessment

As noted earlier, excision with PDEMA is the preferred surgical technique for very-high-risk CSCC. However, if standard excision with incomplete margin assessment (vertical sections) is used for treatment of a very-high-risk tumor due to unavailability of PDEMA, wider surgical margins than those recommended for low-risk lesions must be taken. Reconstruction should be delayed until clear margins have been reported, and increased recurrence rates should be expected. For the 2022 update, the IR suggested that there might need to be more guidance regarding margin sizes for very-high-risk tumors. However, the panel maintained their stance that due to the wide variability of clinical characteristics that may define a very-high-risk tumor, it is not feasible to recommend a defined margin for standard excision of very-high-risk CSCC. Keen awareness of the subclinical extension of CSCC is advised when selecting a treatment modality with incomplete margin assessment for a very-high-risk tumor. These margins may need to be modified based on tumor- or patient-specific factors.

The NCCN panel also considered a review of the literature regarding margin recommendations for high-risk CSCCs and a discussion of this topic. According to Brodland and Zitelli,[29] for CSCCs in high-risk locations (scalp, ears, eyelids, nose, lips) or with other high-risk features (histologic grade ≥2, invasion of subcutaneous tissue), lesions with a diameter <1 cm, 1 to 1.9 cm, and ≥2 cm would require margins of at least 4 mm, 6 mm, and 9 mm, respectively. Results from other retrospective analyses of CSCCs removed with Mohs further support that larger excision margins are needed to consistently achieve clear margins as tumor diameter increases and when other risk factors are present (eg, poor differentiation, high-risk location, PNI).[13,17,30,31] Compared with primary tumors, recurrent tumors have larger subclinical extension and require more Mohs stages

IDENTIFICATION AND MANAGEMENT OF PATIENTS AT HIGH RISK FOR MULTIPLE PRIMARY CSCCs

Treatment of Precancers (Diffuse Actinic Keratoses, Field Cancerization, and CSCC Prophylaxis)

- Use of nicotinamide may be effective in reducing the development of CSCCs.
- Actinic keratoses should be treated at first development.
  - Accepted treatment modalities include cryotherapy, topical 5-fluorouracil (5-FU)[2,3,4,5] (preferred) with or without calcipotriol (calcipotriene), topical imiquimod, topical tirbanibulin, photodynamic therapy (eg, aminolevulinic acid [ALA], porfimer sodium), and C&E. For hyperkeratotic actinic keratoses, pretreatment with topical tazarotene, curettage, or topical keratolytics (topical urea, lactic acid, and salicylic acid) prior to above therapies may be considered.
  - Other modalities that may be considered include topical diclofenac (category 2B), chemical peel (trichloroacetic acid), and ablative skin resurfacing (eg, laser, dermabrasion).
- Actinic keratoses that have an atypical clinical appearance or do not respond to appropriate therapy should be biopsied for histologic evaluation.
- Ablative laser vermilionectomy may be of value in the treatment of extensive actinic cheilitis.

Treatment of Skin Cancers

- Because patients in high-risk groups may develop multiple lesions in short periods of time, destructive therapy (eg, C&E, cryotherapy) may be a preferred treatment for clinically low-risk tumors because of the ability to treat multiple lesions at a single patient visit. If C&E has been performed based solely on the clinical appearance of a low-risk tumor, the pathology from the biopsy taken at the time of C&E should be reviewed to make sure there are no high-risk pathologic features that would suggest the need for further therapy beyond C&E.
- In patients who develop multiple adjacent tumors in close proximity, surgical excision of invasive disease sometimes does not include surrounding in situ disease, and tissue rearrangement should be minimized. In situ disease may then be treated with topical approaches similar to actinic keratoses/field cancerization.
- Compared to the low-risk population, RT is used more frequently as an adjuvant therapy in high-risk patients and for perineural disease.
- Satellite lesions and in-transit cutaneous metastases may occur more frequently in this population. They must be treated aggressively with multidisciplinary consultation.
- In organ transplant recipients and other patients undergoing immunosuppressive therapy, decreasing the level of immunosuppressive therapy and/or incorporating mTOR inhibitors may be considered in cases of life-threatening skin cancer or the rapid development of multiple tumors.

Follow-Up

- Follow-up schedules should be titrated to the frequency of tumor development.

[2] The longest duration of prophylaxis against SCC has been demonstrated with 5-FU plus calcipotriol.
[3] Cunningham TJ, Tabacchi M, Eliane JP, et al. Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. J Clin Invest 2017;127:106-116.
[4] Rosenberg AR, Tabacchi M, Ngo KH, et al. Skin cancer precursor immunotherapy for squamous cell carcinoma prevention. JCI Insight 2019;4:e125476.
[5] Jansen MHE, Kessels JPHM, Nelemans PJ, et al. Randomized trial of four treatment approaches for actinic keratosis. N Engl J Med 2019;380:935-946.

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for complete removal.[13,31] Currently, the European Dermatology Forum recommends standard excisions with 6- to 10-mm peripheral clinical margins for high-risk CSCCs based on criteria defined by Stratigos et al.[32,33] The British Association of Dermatologists recommend at least 6-mm peripheral clinical margins for high-risk CSCC tumors and ≥10 mm margins for very-high-risk tumors (refer to Keohane et al[34] for risk stratification). The United Kingdom National Multidisciplinary Guidelines also concur with a minimum of 6-mm clinical margins for high-risk CSCC as defined by Newlands et al.[35] Thus, there seems to be consensus among the European guidelines, which should provide additional points of guidance for treating physicians. However, the NCCN panel, at this point in time, does not recommend a defined margin for standard excision of high-risk CSCC due to lack of data regarding optimal margins for various risk profiles.

Management of Patients at High Risk of Developing Multiple CSCCs

Treatment of Precancers

Actinic keratoses are a premalignant skin condition that should be treated at first development, particularly in patients with diffuse actinic keratosis/field cancerization, because these patients are at high risk of developing multiple primary CSCCs. Cryotherapy has been used to treat actinic keratosis for many decades, despite lack of prospective randomized trials comparing it with nontreatment. In more recent years, large prospective randomized trials in patients with actinic keratoses (n>100) have shown that each of the following therapies provides better complete clearance rates compared with placebo: topical 5-FU ± calcipotriol,[36–41] topical imiquimod,[42–45] topical tirbanibulin,[46] and photodynamic therapy.[47–54]

In this update of the NCCN Guidelines, the panel voted to include a preference for 5-FU based on data from a randomized trial testing 4 treatment approaches for actinic keratosis. In this study, the cumulative probability of remaining free from treatment failure was significantly higher among patients who received 5-FU (74.7%; 95% CI, 66.8%–81.0%) than among those who received imiquimod (53.9%; 95% CI, 45.4%–61.6%), MAL-PDT (37.7%; 95% CI, 30.0%–45.3%), or ingenol mebutate (28.9%; 95% CI, 21.8%–36.3%).[55] Additionally, the hazard ratio for treatment failure was significantly higher with

IDENTIFICATION AND MANAGEMENT OF PATIENTS AT HIGH RISK FOR MULTIPLE PRIMARY CSCCs

Patient Education
- **Individual risk assessment is necessary and should be discussed.**
- **Both extensive and repetitive patient education regarding sun avoidance and protection is required.**
- **Sun avoidance and protection methods must be stringent.**
- **Monthly self examination of all skin surfaces is recommended. If a patient has a history of invasive skin cancer, self examination of the lymph nodes should be taught and performed.**
- **Rapid entrance into the health care delivery system at the onset of tumor development is critical.**
- **Patient education should begin, in the case of organ transplant recipients, at transplantation and in the case of xeroderma pigmentosum, at birth or diagnosis.**

Prevention
- **Use of oral retinoids (eg, acitretin,[6] isotretinoin) has been effective in reducing the development of actinic keratoses and CSCC in some high-risk patients. Side effects of oral retinoids may be significant. Therapeutic effects disappear shortly after cessation of the drug. Oral retinoids are teratogenic and must be used with extreme caution in women of childbearing potential. Topical retinoids have been shown not to reduce development of actinic keratosis or CSCC.**
- **Use of nicotinamide may be effective in reducing the development of CSCCs. Therapeutic effects disappear shortly after cessation of the drug.**
- **Aggressive treatment of precancers can prevent the development of subsequent invasive tumors.**

[6] Badri O, Schmults CD, Karia PS, Ruiz ES. Efficacy and cost analysis for acitretin for basal and squamous cell carcinoma prophylaxis in renal transplant recipients. Dermatol Surg 2021;47:125-126.

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imiquimod (2.03; 95% CI, 1.36%–3.04%), MAL-PDT (2.73; 95% CI, 1.87%–3.99%), and ingenol mebutate (3.33; 95% CI, 2.29%–4.85%) than with 5-FU ($P \leq .001$ for all).[55] The panel emphasized that the longest duration for CSCC prophylaxis has been demonstrated with the combination of 5-FU and calcipotriol. As a follow-up to the original study by Cunningham et al,[41] it was recently demonstrated that more participants who received topical calcipotriol + 5-FU for actinic keratosis remained disease-free over the >1,500-day period ($P = .0765$) compared with those receiving petroleum jelly–based skin product + 5-FU.[56] Moreover, significantly fewer participants in the test cohort developed CSCC on the treated face and scalp within 3 years (2/30 [7%] vs 11/40 [28%] in the control group; hazard ratio, 0.215; 95% CI, 0.048–0.972; $P = .032$).[56]

In this version of the NCCN Guidelines, the panel voted to include topical tirbanibulin for the treatment of actinic keratosis. In recently published results from 2 identically designed double-blind phase III trials, patients received either tirbanibulin or vehicle (placebo) ointment for the treatment of actinic keratoses on the face or scalp. In both trials, complete clearance by day 57 occurred in significantly more patients in the tirbanibulin group compared with the vehicle group (trial 1: 44% vs 5% [95% CI, 32–47; $P < .001$]; trial 2: 54% vs 13% [95% CI, 33–51; $P < .001$]).[46] Besides adding topical tirbanibulin, the panel removed topical ingenol mebutate because it was taken off the market pending further review of its association with higher skin cancer occurrence.

Prevention in High-Risk Patients

Treatment of precancerous lesions at first development can help prevent the development of subsequent invasive tumors, but prophylactic treatment may be needed for patients who have a history of multiple lesions and/or extensive diffuse actinic keratosis/field cancerization. Oral synthetic retinoids (eg, acitretin, isotretinoin) have been tested in prospective studies in patients at high risk for multiple actinic keratoses or CSCCs, including transplant recipients,[57–62] patients with xeroderma pigmentosa,[63] or those with psoriasis and PUVA (psoralen + UVA) exposure.[64] By comparison with placebo or with CSCC incident rates during treatment-free periods, data from these studies support that oral synthetic retinoids significantly reduce the incidence of new CSCCs.[58–61,63,64]

PRINCIPLES OF RADIATION THERAPY

General Principles

- Protracted fractionation is associated with improved cosmetic results and should be utilized for poorly vascularized or cartilaginous areas.
- For extensive perineural invasion, clinically evident perineural involvement, or involvement of named nerves (particularly in the head and neck region), consider including the course of the local nerves proximally.
- RT is contraindicated for genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome) and relatively contraindicated for patients with connective tissue diseases (eg, scleroderma).
- Given higher complication rates, re-irradiation should not be routinely utilized for recurrent disease within a prior radiation field.
- Isotope-based brachytherapy can be an effective treatment for certain sites of disease, particularly on the head and neck.
- There are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy.

General Treatment Information

Primary Tumor	Examples of Dose Fractionation and Treatment Duration
Definitive RT	
Tumor diameter <2 cm	60–64 Gy over 6 to 7 weeks 50–55 Gy over 3 to 4 weeks 40 Gy over 2 weeks 30 Gy in 5 fractions over 2 to 3 weeks
Tumor diameter ≥2 cm, T3/T4, or those with invasion of bone or deep tissue	60–70 Gy over 6 to 7 weeks 45–55 Gy over 3 to 4 weeks
Postoperative Adjuvant RT	60–64 Gy over 6 to 7 weeks 50 Gy over 4 weeks
Regional Disease	
• Lymph node regions, after lymph node dissection	
▸ Negative margins, no ECE	50–60 Gy over 5 to 6 weeks
▸ Positive margins or ECE	60–66 Gy over 6 to 7 weeks
• Lymph node regions, without lymph node dissection	
▸ Clinically negative, at risk	50 Gy over 5 weeks
▸ Clinically positive	60–70 Gy over 6 to 7 weeks
• Clinically at-risk nerves	50–60 Gy over 5 to 6 weeks

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SCC-E

Because of the inconsistency of data demonstrating acitretin efficacy, the panel decided to include a recently published review to further support the recommendation of acitretin for high-risk patients.[65] It was calculated across 4 independently published articles that acitretin led to a 54% reduction in CSCC (mean, 0.57 per patient per year) and 56% reduction in keratinocyte carcinomas (mean, 0.68 per patient per year).[65] Despite its efficacy, it was postulated that the drug is still underused due to its relatively high cost, the need for frequent laboratory studies, adverse effects, and rebound after cessation of efficacious therapy.[65]

Systemic Therapy for Squamous Cell Skin Cancer

A wide variety of cytotoxic therapies have been tested in patients with regional or distant metastatic CSCC. Those most commonly used are cisplatin, carboplatin, and 5-FU, either as monotherapy or combination regimens.[66–76] For the 2022 update, the panel voted to include carboplatin ± paclitaxel under options useful in certain circumstances for use with RT. A prospective study by Suntharalingam et al[77] demonstrated that among patients with head and neck mucosal SCC, weekly carboplatin and paclitaxel given concurrently with definitive once-daily external-beam RT was well tolerated with a complete response (CR) at the primary site of 82%. The total (primary site and neck) CR was 75% and the 3-year overall survival was 48%. Two recent albeit retrospective studies confirmed the efficacy of this regimen. Vlacich et al[78] reported that the 30-year locoregional control rate with intensity-modulated RT and concurrent carboplatin + paclitaxel was 83.2%, with disease-free survival and overall survival rates of 78.8% and 76.5%, respectively. Maring et al[79] reported a recurrence rate of 30% for patients treated with RT plus carboplatin + paclitaxel, compared with 38% of those treated with RT + cisplatin (P=.6). Event-free survival and overall survival were reported to be 30 and 28 months, respectively, for the RT plus carboplatin + paclitaxel group, versus 37 and 35 months, respectively, for the RT + cisplatin group. However, significantly higher grade 3/4 acute toxicity was observed for the cisplatin group (P=.002). Even though all 3 studies reported treatment completion by most participants (>90%), Agulnik et al[80] deemed the regimen infeasible due to a high occurrence of adverse events. Nevertheless, their study enrolled a very small number of

PRINCIPLES OF SYSTEMIC THERAPY

Local Disease (Including Multiple Primaries) Amenable to Curative Surgery
- Systemic therapy is not recommended.

Primary and Recurrent Locally Advanced Disease in Non-Surgical Candidates (See SCC-3)
- For patients who have residual disease and further surgery is not feasible, recommend RT, and multidisciplinary teams can consider concurrent systemic therapy in select cases (Table 1).
- For patients who have complicated cases of locally advanced disease in which curative surgery and curative RT are not feasible,[1] recommend multidisciplinary consultation to consider systemic therapy alone (Table 2).

New Regional Disease (See SCC-4 and SCC-5)
- For most cases of fully resected regional disease, adjuvant systemic therapy is not recommended, unless within a clinical trial.
- For patients with resected high-risk regional disease, consider RT ± systemic therapy (Table 1).
- For patients with unresectable, inoperable, or incompletely resected disease, multidisciplinary consultation is needed to consider:
  - RT ± systemic therapy (Table 1)
  - Systemic therapy alone if curative RT not feasible[1] (Table 2)

Regional Recurrence or Distant Metastatic Disease (See SCC-6)
- For regional recurrence or distant metastases, multidisciplinary team can consider systemic therapy alone (Table 2) or in combination with RT (Table 1).

Table 1: Systemic Therapy Options for Use with RT

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cisplatin[2] • Clinical trial[3,4]	• None	• EGFR inhibitors (eg, cetuximab)[2] • Cisplatin + 5-FU[2] • Carboplatin ± paclitaxel[2,5,6]

Table 2: Options for Systemic Therapy Alone

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cemiplimab-rwlc[3,4] (if curative RT or surgery is not feasible[1] for locally advanced, recurrent, or metastatic disease) • Pembrolizumab[3,4] (if curative RT or surgery is not feasible[1] for locally advanced, recurrent, or metastatic disease) • Clinical trial[3,4]	• If ineligible for or progressed on immune checkpoint inhibitors and clinical trials, consider: ▸ Carboplatin + paclitaxel	• If ineligible for or progressed on immune checkpoint inhibitors and clinical trials, consider: ▸ EGFR inhibitors (eg, cetuximab)[2] ▸ Capecitabine ▸ Cisplatin[2] ▸ Cisplatin + 5-FU[2] ▸ Carboplatin[2]

See Footnotes and References on SCC-F (2 of 2)

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participants (n=6) and therefore the results should be considered with caution. It should be noted that these studies were conducted in patients with head and neck mucosal SCC; data were extrapolated to CSCC.

In addition to several trials testing new approaches to treating locally advanced unresectable or metastatic CSCC with targeted agents,[81–84] immune checkpoint inhibitors have been tested in this setting[85,86] (ClinicalTrials.gov identifiers: NCT02721732, NCT02760498, NCT02978625, NCT03108131), In the Version 2.2021 update of the NCCN Guidelines, the panel modified their recommendations for pembrolizumab and cemiplimab-rwlc. Both immune checkpoint inhibitors are now recommended for locally advanced, recurrent, or metastatic disease if curative RT or surgery is not feasible. Recent published data reported an objective response rate (ORR) of 44% to 54%, a CR of 0% to 13%, and a partial response (PR) of 31% to 50% to cemiplimab-rwlc in patients with locally advanced, recurrent, or metastatic CSCC.[87–90] Data from the phase II KEYNOTE-629 trial, which included patients with locally advanced, recurrent, or metastatic CSCC, reported an ORR of 34% to 50%, a CR of 4% to 17%, and a PR of 25% to 33% for patients treated with pembrolizumab.[91,92] Preliminary data and the clinical experience of NCCN panel members suggest that other anti–PD-1 inhibitors may also be effective in this setting.

RT for Squamous Cell Skin Cancer

Although surgery is the mainstay of local treatment for CSCC, patient preference and other factors may lead to the choice of RT as primary therapy for local disease without lymph node involvement. A large meta-analysis reported 5-year recurrence risks of 6.7% and 10% after RT of primary and recurrent CSCC, respectively.[10] Subsequent retrospective analyses on smaller samples of patients with primary CSCCs treated with first-line RT (37–233 patients) have reported a large range of recurrence rates—from 2.8% to 30%, with higher rates for patients with locally advanced disease (size >2 cm or deeply invasive).[93–98] The risk of recurrence appears to increase with increasing lesion size and T stage.[96,98,99] A few small studies (n<20) have reported that for CSCCs that were previously treated and recurred, treatment with RT results in recurrence in 16.7% of cases.[95,98]

In this update of the NCCN Guidelines, the panel removed their recommendation that RT is usually

FOOTNOTES AND REFERENCES

[1] Assessment of feasibility of RT should be made by a radiation oncologist.
[2] These options have occasionally produced useful responses, but data supporting efficacy are limited.
[3] Recent published phase II trial data support the efficacy and safety of cemiplimab-rwlc and pembrolizumab in patients with locally advanced, recurrent, and metastatic CSCC. Preliminary data and the clinical experience of NCCN Panel Members suggest that other anti–PD-1 inhibitors may also be effective in this setting. Migden MR, Khushalani N, Chang ALS, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. Lancet Oncol 2020;21:294-305. Rischin D, Migden MR, Lim AM, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. J Immunother Cancer 2020;8:e000775. Hughes BGM, Munoz-Couselo E, Mortier L, et al. Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): an open-label, nonrandomized, multicenter, phase II trial. Ann Oncol 2021;32:1276-1285.
[4] In solid organ transplant recipients, potential benefit from immune checkpoint inhibitor therapy has to be weighed against a significant risk of organ rejection. For patients receiving immunosuppressive therapy, in consultation with their treating physician, consider dose reduction of the immunosuppressive agent(s) and/or minimizing the doses of calcineurin inhibitors and/or antimetabolites in favor of mTOR inhibitors where appropriate. Patients with underlying immunodeficiencies, including CLL, were excluded from the phase I–II cemiplimab-rwlc trial, so the efficacy of cemiplimab-rwlc in this population is unclear.
[5] Maring S, Elsayad K, Stenner M, et al. Efficacy of carboplatin/paclitaxel-based radiochemotherapy in locally advanced squamous cell carcinoma of head and neck. Oncol Res Treat 2018;41:736-743.
[6] Vlacich G, Diaz R, Thorpe SW, et al. Intensity-modulated radiation therapy with concurrent carboplatin and paclitaxel for locally advanced head and neck cancer: toxicities and efficacy. Oncologist 2012;17:673-681.

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reserved for patients aged >60 years because of concerns about long-term sequelae in younger patients. It was generally agreed among panel members that age is not the primary consideration for RT and that patients aged <60 years can receive RT for multiple reasons, including personal preferences. Additionally, there was concern from the IR that the statement regarding insufficient long-term efficacy and safety data for the routine use of radioisotope or electronic surface brachytherapy was inaccurate. The panel revised this statement to say "isotope-based brachytherapy can be an effective treatment for certain sites of disease, particularly on the head and neck" and maintained their stance that "there are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy." The revision in the isotope-based brachytherapy recommendation is based on results from multiple studies acknowledging the efficacy of this technique.[100–106] Of note, a retrospective multicentric analysis of 1,676 carcinomas of the skin of the nose and nasal vestibule yielded a local control rate of 93% with a minimum follow-up of 2 years. It was determined in this study that local control depended on tumor size (diameter <2 cm: 96%; diameter 2–3.9 cm: 88%; diameter ≥4 cm: 81%) and tumor site (external surface of the nose: 94%; vestibule: 75%).[105] Thus, isotope-based brachytherapy can be considered for appropriate patients with CSCC.

Summary

For the NCCN Guidelines for Squamous Cell Skin Cancer, Version 1.2022, the panel spent a substantial amount of time deliberating and finalizing the new terminology "PDEMA: peripheral and deep en face margin assessment," which is now used in all 4 NCCN Guidelines for Non-melanoma Skin Cancer. The change is deemed important for broader understanding and application of desirable surgical and histologic techniques, which will ideally reduce disease recurrence. New data from recent clinical trials and current news were also discussed extensively, and are now reflected in the updated recommendations for CSCC prophylaxis (5-FU and 5-FU plus calcipotriol, topical tirbanibulin, and the removal of topical ingenol mebutate) and regional disease treatment (carboplatin ± paclitaxel in combination with RT, cemiplimab-rwlc, and pembrolizumab). Some

PRINCIPLES OF PDEMA TECHNIQUE

- **Peripheral and deep en face margin assessment (PDEMA), also known as complete margin assessment, is a descriptive term for surgical techniques that allow high-quality histologic visualization and interpretation of the entire marginal surface of surgically excised tissue. The NCCN Guidelines Panel recognizes that a variety of surgical methods may achieve complete margin assessment. This NCCN appendix is intended to be inclusive of this diversity, while defining the features that are essential to the superior cure rates achieved by these techniques.[1]**
- **The most commonly used form of PDEMA is Mohs. When anatomic structures at the deep margin (eg, major vessels, nerves, bone) preclude complete histologic evaluation of the marginal surface via Mohs or other forms of PDEMA, Mohs or other forms of PDEMA should be used to evaluate as much of the marginal surface as feasible. Treatment considerations for non-visualized areas may be the subject of multidisciplinary discussion.**
- **A surgical procedure can be described as PDEMA if and only if all of the following criteria are met:**
  1. **The entire marginal surface of the surgical specimen is microscopically visualized and histopathologically analyzed for the presence of cancer. The marginal surface includes the complete deep and peripheral margin.**
  2. **The surgical specimen is oriented with respect to the surgical site and marked in a manner such that any positive margin identified in histopathologic analysis can be accurately located and re-excised.**
  3. **The surgical margin of any re-excised tissue is again entirely visualized and oriented as above. This process is repeated until no further cancer is identified at the surgical margin or until further excision is not anatomically possible or not in the best interest of the patient.**
  4. **The time interval between the steps of this process is rapid enough to prevent significant size or shape changes in the wound bed (ie, granulation, contraction) that would decrease the accuracy of orientation.**

[1] Gloster HM, Harris KR, Roenigk RK. A comparison between Mohs micrographic surgery and wide surgical excision for the treatment of dermatofibrosarcoma protuberans. J Am Acad Dermatol 1996;35:82-87.

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recommendations for RT were also revised, with the removal of the 60-year age cutoff for RT and the updated language for isotope-based brachytherapy. The panel hopes these recommendations will be incorporated into professional practice, with the ultimate goal of improving outcomes for patients with squamous cell skin cancer.

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