National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Squamous Cell Skin Cancer

Version 2.2022 — May 2, 2022

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[NCCN Guidelines Panel Disclosures]

Continue

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Þ Internal medicine
† Medical oncology
ζ Otolaryngology
≠ Pathology/Dermatopathology
Ÿ Reconstructive surgery
§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
* Discussion Section Writing Committee

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

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 2.2022 of the NCCN Guidelines for Squamous Cell Skin Cancer from Version 1.2022 include:

MS-1
- **The Discussion section has been updated to reflect the changes in the algorithm.**

Updates in Version 1.2022 of the NCCN Guidelines for Squamous Cell Skin Cancer from Version 1.2021 include:

Global changes:
- **Changed "Mohs micrographic surgery (MMS) or other forms of CCPDMA" to "Mohs or other forms of PDEMA."**
- **Changed "Complete circumferential peripheral and deep margin assessment (CCPDMA)" to "Peripheral and deep en face margin assessment (PDEMA)."**
- **Changed "CCPDMA" to "PDEMA."**
- **Changed "MMS" to "Mohs."**

SCC-1
- **Workup**
  - **Second sub-bullet under H&P revised: Regional lymph node exam *as indicated for suspicion of nodal disease.***
- **Footnote e revised: For rare cases that present with distant metastatic disease at diagnosis, treat as distant metastases pathway on SCC-6. ~~Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic).~~**
- **Footnote g added: Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is often sufficient to diagnose local recurrence, but MRI can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or other imaging modalities can be employed for confirmation and to gauge extent of disease.**

SCC-2
- **Primary Treatment**
  - **Curettage and electrodesiccation (C&E), second bullet revised: If tumor appears to ~~be not confined to skin (penetrates beyond the skin)~~ *extend beyond the dermis*, surgical excision should generally be performed *rather than C&E.***
  - **Second option revised: Standard excision with 4- to 6-mm clinical margins and postoperative margin assessment. *Tissue rearrangement (eg, flap reconstruction, extensive undermining) should not be undertaken until clear margins are identified* ~~and~~ *(*second intention healing, linear repair, or skin graft *are acceptable)*.**
  - **Option added: Mohs or other forms of peripheral and deep en face margin assessment (PDEMA).**

Continued

Updates in Version 1.2022 of the NCCN Guidelines for Squamous Cell Skin Cancer from Version 1.2021 include:

SCC-2 (continued)
- **Footnotes removed:**
  - **Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified. (Also page SCC-3A)**
  - **RT is often reserved for patients older than 60 years because of concerns about long-term sequelae. (Also page SCC-3A)**
- **Footnote j revised: ~~Excision with complete circumferential peripheral and deep margin assessment (CCPDMA)~~ *PDEMA* ~~with~~ *(via* permanent ~~section analysis~~ or ~~intraoperative~~ frozen section ~~analysis~~*)* is an alternative to ~~MMS~~ *Mohs*. See Principles of ~~CCPDMA~~ *PDEMA* Technique (SCC-G). (Also page SCC-3A)**
- **Footnote k added: 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.**

SCC-3
- **Primary Treatment**
  - **Second option revised: Standard excision with wider surgical margins and postoperative margin assessment and *second intention healing,* linear *repair*, or ~~delayed repair~~ *skin graft*.**
  - **Pathway following Mohs or other forms of PDEMA, Negative margins revised: If extensive perineural, large, or named nerve involvement, or if other ~~high-risk features~~ *poor prognostic features*: Recommend multidisciplinary consultation and Consider adjuvant RT.**

SCC-3-A
- **Footnotes revised:**
  - **Footnote k: When ~~MMS~~ *Mohs* ~~with margin assessment~~ 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.**
  - **Footnote l: For complicated cases, consider multidisciplinary consultation. For locally advanced disease in which curative RT and curative surgery are not feasible, consider treatment with ~~immunotherapy~~ *systemic therapy* ~~(cemiplimab-rwlc~~ or clinical trial~~)~~. See Principles of Systemic Therapy (SCC-F).**
  - **Footnote o: Discuss and consider sentinel lymph node biopsy (SLNB) *prior to PDEMA* for patients with the very-high-risk CSCCs that are recurrent or have multiple risk factors placing them in 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).**
  - **Footnote p: If invasion to parotid fascia, superficial parotidectomy ~~is~~ *may be* indicated.**
  - **Footnote 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.*~~; m~~*M*ost nerves deep to the dermis are >0.1 mm.**
  - **Footnote u: For tumors in cheeks, forehead, scalp, neck, and pretibia that are <6 mm *in depth* and confined to the dermis...**

Continued

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Updates in Version 1.2022 of the NCCN Guidelines for Squamous Cell Skin Cancer from Version 1.2021 include:

SCC-4

- **Clinical Staging and Preoperative Assessment**
  - **Option following FNA or core biopsy, Negative revised: Consider re-evaluation: clinical exam, CT with contrast of the nodal basin, repeat FNA, core biopsy, or ~~open lymph node~~ excision*al biopsy*.**
- **Primary Treatment**
  - **Option following Surgical evaluation revised: *Unresectable*, inoperable, or ~~not fully~~ incompletely ~~resectable~~ *resected* disease.**
- **Footnote x added: An open biopsy may be considered to confirm a negative initial FNA or core lymph node biopsy if clinical suspicion remains high.**

SCC-6

- **Footnotes revised:**
  - **Footnote g revised: Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is often sufficient to diagnose local recurrence, but MRI can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or ~~CT~~ *other* imaging *modalities* can be employed for confirmation and to gauge extent of disease.**
  - **Footnote ff revised: Surveillance ~~CT with contrast~~ *imaging* of regional nodal basin and to evaluate for distant metastatic disease, ideally based on multidisciplinary board recommendation, or as clinically indicated.**
- **Footnote gg added: Under highly selective circumstances, in the context of multidisciplinary consultation, resection of limited metastases can be considered.**

SCC-A

- **Second header revised: Principles of Excision Reporting (including Mohs ~~micrographic~~ excisions)**
  - **Third bullet revised: Immunohistochemistry may be utilized as needed to help identify lymphovascular or nerve invasion, or to identify single *tumor cells* or *small aggregates* ~~few-cell tumor foci~~.**
- **Third header revised: Recommended Elements for Pathology Reporting of Excisional Specimens (including Mohs ~~micrographic~~ excisions).**

SCC-B 2 of 2

- **Footnote 1 revised: Risk ~~stratification~~ *category assignment* should be based on the highest risk factor present. The high-risk group has elevated risk of local recurrence; the very-high-risk group has elevated risk of local recurrence and elevated risk of metastasis.**

SCC-C 2 of 3

- **First header revised: Treatment of Precancers (Diffuse Actinic Keratoses, Field Cancerization, *and CSCC Prophylaxis*).**
  - **Bullet added: Use of nicotinamide may be effective in reducing the development of CSCCs.**
  - **Second bullet, first sub-bullet revised: Accepted treatment modalities include cryotherapy, topical 5-fluorouracil (5-FU) (*preferred)* with or without calcipotriol (calcipotriene), topical imiquimod, ~~topical ingenol mebutate~~ *topical tirbanibulin*, photodynamic therapy (eg, aminolevulinic acid [ALA], porfimer sodium), and C&E...**

Continued

Updates in Version 1.2022 of the NCCN Guidelines for Squamous Cell Skin Cancer from Version 1.2021 include:

SCC-C 2 of 3 (continued)
- **Treatment of Skin Cancers**
  - **Second bullet revised: 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.* ~~secondary approaches.~~**
- **Footnote 2 added: The longest duration of prophylaxis against SCC has been demonstrated with 5-FU plus calcipotriol.**
- **References updated.**

SCC-C 3 of 3
- **References updated.**

SCC-D
- **Bullet removed: Use of nicotinamide may be effective in reducing the development of CSCCs.**

SCC-E
- **Bullet added: Isotope-based brachytherapy can be an effective treatment for certain sites of disease, particularly on the head and neck.**
- **Last bullet revised: There are insufficient long-term efficacy and safety data to support the routine use of ~~radioisotope or~~ electronic surface brachytherapy.**

SCC-F 1 of 2
- **Second header revised: *Primary and Recurrent* Locally Advanced Disease in Non-Surgical Candidates (See SCC-3)**
- **New Regional Disease**
  - **Third bullet revised: For patients with *unresectable*, inoperable, or ~~not fully~~ *incompletely* ~~resectable~~ *resected* disease ~~inoperable or incompletely resected regional disease~~, multidisciplinary consultation to consider.**
- **Table 1: Systemic Therapy Options for Use with RT**
  - **Useful in Certain Circumstances, option revised: Carboplatin ± *paclitaxel***

SCC-F 2 of 2
- **Reference 3 revised: Recent published phase II trial data ~~reported an objective response (OPR) of 44% (95% CI, 32-55), partial response rate (PR) of 31% and complete response rate (CR) of 13% to cemiplimab-rwlc in patients with locally advanced or recurrent CSCC. Data from the phase II KEYNOTE-629 trial, which included patients with recurrent or metastatic CSCC or locally advanced CSCC, reported an OPR of 50% (95% CI, 36-64), a PR of 33%, and a CR of 17%, for patients treated with pembrolizumab.~~ *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.**
- **References updated.**

SCC-G
- **Header revised: Principles of ~~CCPDMA~~ *PDEMA* Technique**
- **New bullet added: 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.~~not fully~~ *incompletely* ~~resectable~~ *resected* disease ~~inoperable or incompletely resected regional disease~~, multidisciplinary consultation to consider.**
- **Table 1: Systemic Therapy Options for Use with RT**
  - **Useful in Certain Circumstances, option revised: Carboplatin ± *paclitaxel***

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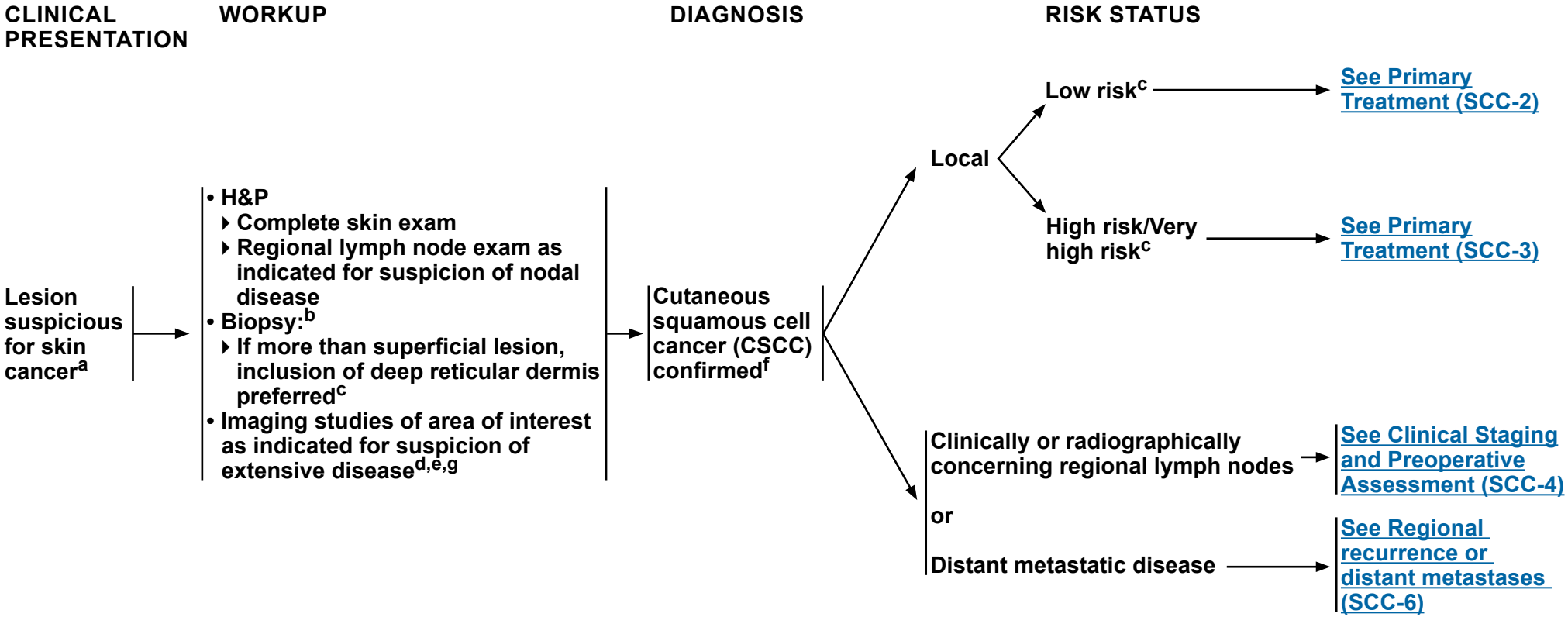
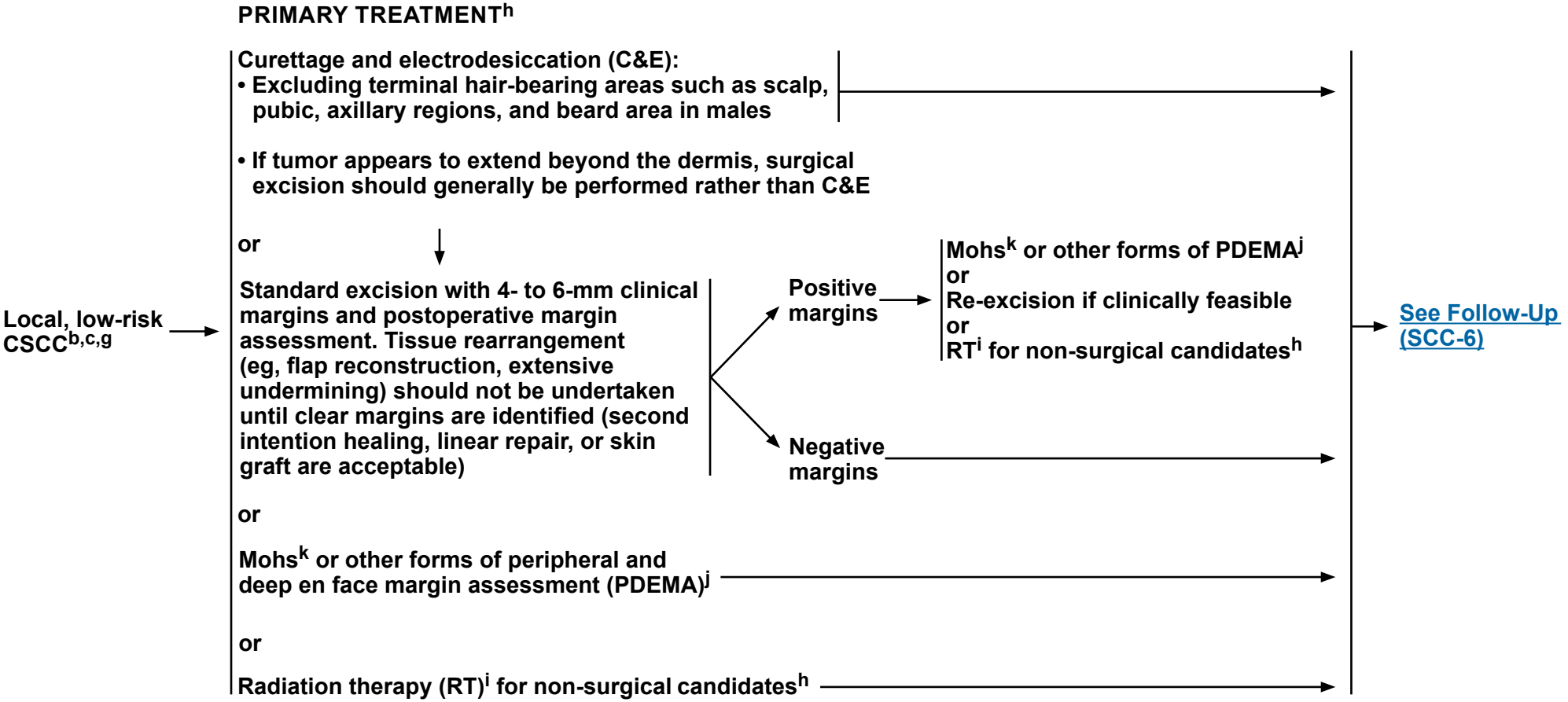


[a] For more information, see American Academy of Dermatology Association: https://www.aad.org/public/diseases/skin-cancer/squamous-cell-carcinoma.
[b] See Principles of Pathology (SCC-A).
[c] See Stratification to Determine Treatment Options and Follow-up for Local CSCC Based on Risk Factors for Local Recurrence, Metastases, or Death from Disease (SCC-B) and Identification and Management of Patients at High Risk for Multiple Primary CSCCs (SCC-C).
[d] Extensive disease includes deep structural involvement such as bone, perineural disease, and deep soft tissue. If perineural disease or deep soft tissue involvement is suspected, MRI with contrast is preferred. If bone disease is suspected, CT with contrast is preferred unless contraindicated.
[e] For rare cases that present with distant metastatic disease at diagnosis, treat as distant metastases pathway on SCC-6.
[f] Including CSCC in situ (showing full-thickness epidermal atypia, excluding actinic keratoses).
[g] Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is often sufficient to diagnose local recurrence, but MRI can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or other imaging modalities can be employed for confirmation and to gauge extent of disease.

Note: All recommendations are category 2A unless otherwise indicated.
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.



[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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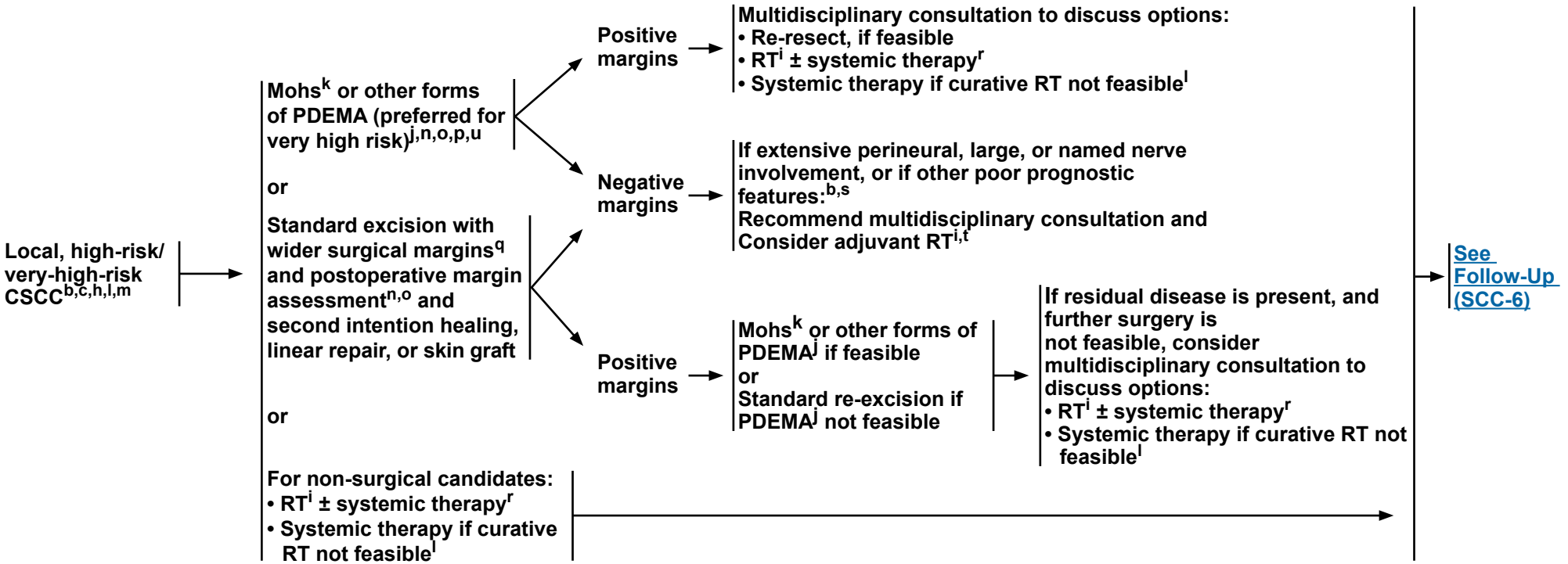
PRIMARY TREATMENT[h]



See Footnotes on SCC-3A

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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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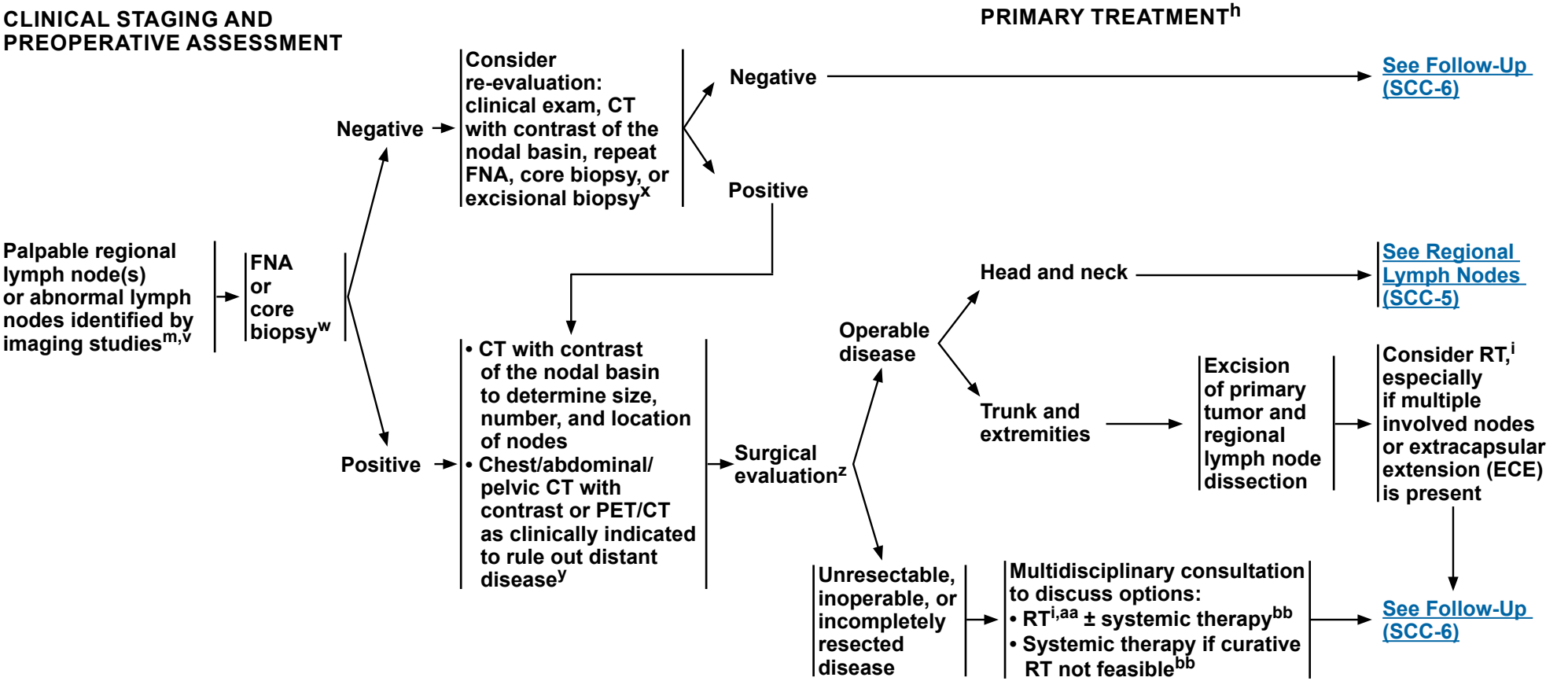

[h] See Principles of Treatment (SCC-D).
[i] See Principles of Radiation Therapy (SCC-E).
[m] If patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate.
[v] See Identification and Management of Patients at High Risk for Multiple Primary CSCCs (SCC-C).
[w] Ultrasound-guided biopsy by a center or physician with expertise is recommended. Core biopsy may be preferred over FNA in cases where primary tumor histology is uncertain or if a larger tissue sample is required for further genetic or other testing.
[x] An open biopsy may be considered to confirm a negative initial FNA or core lymph node biopsy if clinical suspicion remains high.
[y] MRI of the brain may be considered to rule out subclinical cortical involvement in cases with bone invasion.
[z] Regional lymph node dissection is preferred unless the patient is not a surgical candidate.
[aa] Consider palliative RT/surgery for symptomatic sites. Stereotactic body RT (SBRT) may also be considered in select patients.
[bb] See Principles of Systemic Therapy (SCC-F).

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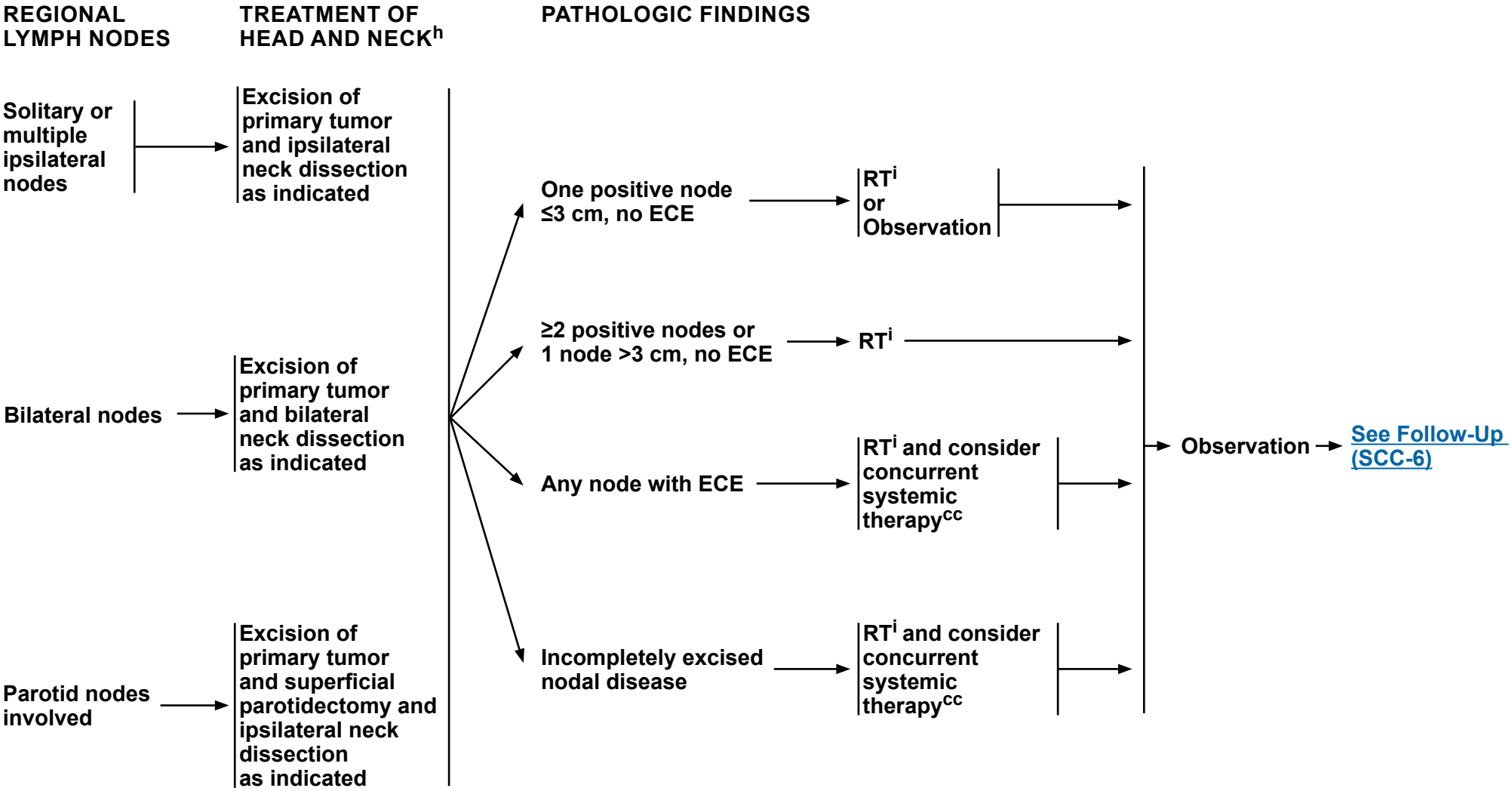

[h] See Principles of Treatment (SCC-D).
[i] See Principles of Radiation Therapy (SCC-E).
[cc] Multidisciplinary consultation recommended. See Principles of Systemic Therapy (SCC-F).

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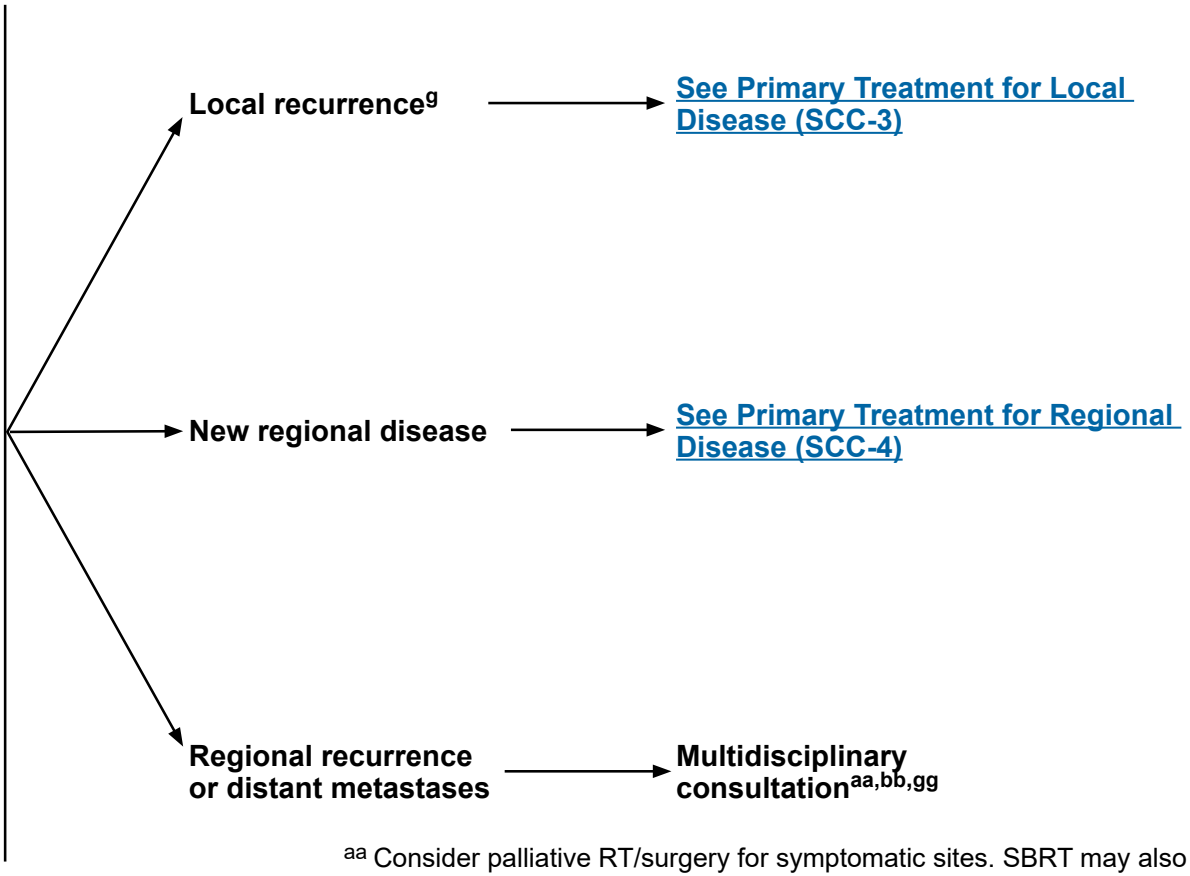
FOLLOW-UP

Local disease:

- **H&P[dd,ee]**
  - **For low-risk patients: Every 3–12 mo for 2 y, then every 6–12 mo for 3 y, then annually for life[c]**
  - **For high-risk patients: Every 3–6 mo for 2 y, then every 6–12 mo for 3 y, then annually for life[c]**
  - **For very-high-risk patients: Every 3–6 mo for 2 y, then every 6 mo for 3 y, then every 6–12 mo for life[c]**
- **Consider imaging if clinical exam insufficient for following disease[g]**
- **Patient education**
  - **Sun protection**
  - **Self examination of skin**

Regional disease:

- **H&P[dd,ee]**
  - **Every 2–3 mo for 1 y, then every 2–4 mo for 1 y, then every 4–6 mo for 3 y, then every 6–12 mo for life**
- **Consider imaging if clinical exam insufficient for following disease[g,ff]**
- **Patient education**
  - **Sun protection**
  - **Self examination of skin and lymph nodes**



[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).

[g] Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is often sufficient to diagnose local recurrence, but MRI can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or other imaging modalities can be employed for confirmation and to gauge extent of disease.

[aa] Consider palliative RT/surgery for symptomatic sites. SBRT may also be considered in select patients.

[bb] See Principles of Systemic Therapy (SCC-F).

[dd] Including complete skin and regional lymph node exam.

[ee] Frequency of follow-up should be adjusted based on risk.

[ff] Surveillance imaging of regional nodal basin and to evaluate for distant metastatic disease, ideally based on multidisciplinary board recommendation, or as clinically indicated.

[gg] Under highly selective circumstances, in the context of multidisciplinary consultation, resection of limited metastases can be considered.

Note: All recommendations are category 2A unless otherwise indicated.
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.

PRINCIPLES OF PATHOLOGY

Principles of Biopsy Reporting

- Pathologic evaluation of skin biopsies is ideally performed by a dermatologist, pathologist, or dermatopathologist experienced in interpreting cutaneous neoplasms. Reporting of margins and the elements below is not required for biopsy specimens.

Principles of Excision Reporting (including Mohs excisions)

- Specimens from intended complete surgical removal (eg, shave excisions) should be labeled as such so that margin status is reported.
- Since depth of invasion (in mm) may not be ascertained on tangentially cut Mohs specimens, anatomic level of invasion should be reported. Frozen or permanent section analysis of the clinical tumor specimen may be undertaken if needed for complete reporting of the features below to enable American Joint Committee on Cancer (AJCC) tumor staging.[1,2]
- Immunohistochemistry may be utilized as needed to help identify lymphovascular or nerve invasion, or to identify single tumor cells or small aggregates.

Recommended Elements for Pathology Reporting of Excisional Specimens (including Mohs excisions)

- NOTE: Tumors less than 2 cm in diameter without perineural invasion (as defined below) that are superficial (<6 mm in depth or confined to skin and fat) are AJCC T1 and do not require specific reporting of the histologic findings below with the exception of grade. However, reporting the presence of any of the prognostic features below is strongly encouraged.
- Elements reported (on requisition form) by the clinician submitting the tissue:
  - Anatomic location
  - Clinical pre-excision diameter in cm
  - Primary or recurrent tumor
  - Clinical or radiologic nerve invasion, including name of nerve
  - Other risk factors (optional) eg, immunosuppression, prior radiation at site
- Elements reported by the physician reporting the histologic findings:
  - Margin status (whether or not tumor is present at margins)
  - Well, moderate, or poor differentiation
  - Depth of invasion (either Breslow depth [in mm] measured from granular layer of adjacent normal epidermis to the base of the tumor OR tissue plane of deepest invasion eg, dermis, fat, fascia, muscle, perichondrium/periosteum, cartilage bone, other)
  - Perineural invasion defined as tumor cells within the nerve sheath of a nerve deep to dermis or with a caliber 0.1 mm or larger
  - Lymphovascular invasion
  - High-risk histology eg, desmoplasia, adenomatous, sarcomatous, or spindle cell
  - Low-risk histology (optional) eg, verrucous, keratoacanthomatous

[1] Alam M, Armstrong A, Baum C, et al. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018;78:560-578.
[2] Califano JA, Lydiatt WM, Nehal KS, et al. Cutaneous squamous cell carcinoma of the head and neck. In: Amin MB, Edge S, Greene F, et al., eds. AJCC Cancer Staging Manual (Eighth Edition). New York: Springer International Publishing;2017:171-181.

Note: All recommendations are category 2A unless otherwise indicated.
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.

STRATIFICATION TO DETERMINE TREATMENT OPTIONS AND FOLLOW-UP FOR LOCAL CSCC BASED ON RISK FACTORS FOR LOCAL RECURRENCE, METASTASES, OR DEATH FROM DISEASE

Risk Group[1]	Low Risk	High Risk	Very High Risk
Treatment options	See SCC-2	See SCC-3	See SCC-3
H&P			
Location/size[2]	Trunk, extremities ≤2 cm	Trunk, extremities >2 cm – ≤4 cm	>4 cm (any location)
		Head, neck, hands, feet, pretibia, and anogenital (any size)[5]	
Borders	Well-defined	Poorly defined	
Primary vs. recurrent	Primary	Recurrent	
Immunosuppression	(-)	(+)	
Site of prior RT or chronic inflammatory process	(-)	(+)	
Rapidly growing tumor	(-)	(+)	
Neurologic symptoms	(-)	(+)	
Pathology (See SCC-A)			
Degree of differentiation	Well or moderately differentiated		Poor differentiation
Histologic features: Acantholytic (adenoid), adenosquamous (showing mucin production), or metaplastic (carcinosarcomatous) subtypes	(-)	(+)	Desmoplastic SCC
Depth[3,4]: Thickness or level of invasion	≤6 mm and no invasion beyond subcutaneous fat		>6 mm or invasion beyond subcutaneous fat
Perineural involvement	(-)	(+)	Tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm
Lymphatic or vascular involvement	(-)	(-)	(+)

See footnotes on SCC-B (2 of 2)

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FOOTNOTES

[1] Risk category assignment should be based on the highest risk factor present. The high-risk group has elevated risk of local recurrence; the very-high-risk group has elevated risk of local recurrence and elevated risk of metastasis.
[2] Preoperative clinical tumor diameter.
[3] If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.
[4] Deep invasion is defined as invasion beyond the subcutaneous fat OR >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor, consistent with the AJCC Cancer Staging Manual, 8th Edition).
[5] Location on the head, neck, hands, feet, pretibia, or anogenital area constitutes high risk based on location, independent of size. Narrow excision margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment such as with Mohs/PDEMA is recommended for optimal tumor clearance and maximal tissue conservation. For tumors <6 mm in size, without other high-risk or very-high-risk features, other treatment modalities may be considered if at least 4-mm clinically tumor-free margins can be obtained without significant anatomic or functional distortions.

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

Definition

- **Certain patient groups are at high risk for developing multiple CSCCs and tumors that can behave aggressively. These include:**
  - **Organ transplant recipients**
  - **Other settings of immunosuppression (eg, lymphoma, chronic lymphocytic leukemia [CLL], drug-induced, HIV)**
  - **Genetic syndromes predisposing to CSCC formation[1]**
- **Within these high-risk groups, individual high-risk patients should be identified for closer follow-up.**
- **Important individual risk factors include:**
  - **Total number of tumors**
  - **Frequency of development**
  - **Occurrence of aggressive tumors (eg, extension beyond cutaneous structures, perineural involvement, large and poorly differentiated, having ≥3 risk factors for recurrence) (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]).**

Diagnosis

- **Skin lesions in these high-risk populations may be difficult to assess clinically. Therefore, a low threshold for performing skin biopsies of suspect lesions is necessary.**
- **In these patients, urgent diagnosis and treatment of lesions are important, and nodal staging (CT with contrast and/or ultrasound or pathologic evaluation) may be considered in those with significant risk of nodal metastases.**

[1] Examples include xeroderma pigmentosum, generalized eruptive keratoacanthoma of Grzybowski, Rothmund-Thomson syndrome, dyskeratosis congenita, epidermodysplasia verruciformis, recessive dystrophic epidermolysis bullosa, severe generalized junctional epidermolysis bullosa, and Ferguson-Smith disease.

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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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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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PRINCIPLES OF TREATMENT

- **The primary goals of treatment of CSCCs are the complete removal of the tumor and the maximal preservation of function and cosmesis. All treatment decisions should be customized to account for the particular factors present in the individual case and for the patient's preference.**
- **Surgical approaches often offer the most effective and efficient means for accomplishing cure, but considerations of function, cosmesis, and patient preference may lead to choosing RT as primary treatment in order to achieve optimal overall results.**
- **In certain patients at high risk for multiple primary tumors, increased surveillance and consideration of prophylactic measures may be indicated. (See Identification and Management of Patients at High Risk for Multiple Primary CSCCs [SCC-C]).**
- **In patients with CSCC in situ (Bowen disease), alternative therapies such as topical 5-FU, topical imiquimod, photodynamic therapy (eg, ALA, porfimer sodium), or vigorous cryotherapy may be considered even though cure rates may be lower than with surgical treatment modalities.**
- **When Mohs with margin assessment 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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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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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)

Note: All recommendations are category 2A unless otherwise indicated.
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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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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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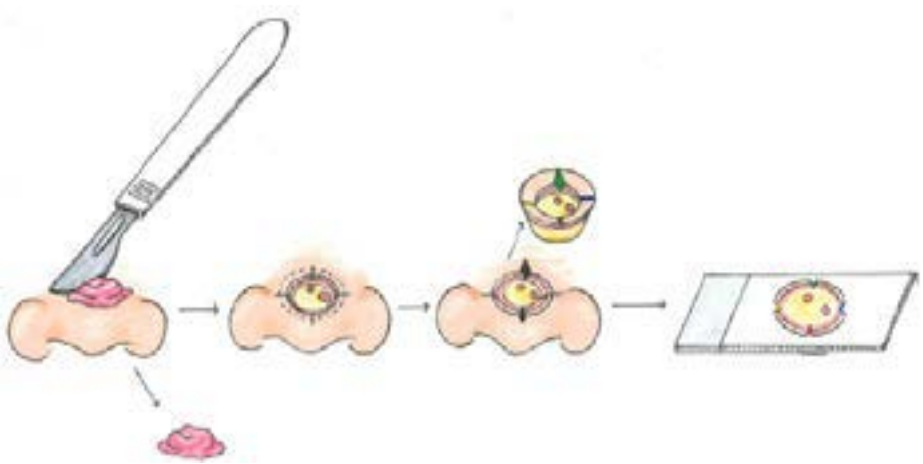
PRINCIPLES OF PDEMA TECHNIQUE

- **Visualization of the entire marginal surface of an irregular surgical specimen may be challenging, but is critical to the success of PDEMA methods. Typically, this visualization is achieved by flattening topographically complex surfaces onto a single plane and sectioning the specimen *parallel* to this plane (see Figure 1). Sampling methods such as perpendicular sectioning, also known as "breadloafing," *do not* achieve direct visualization of the entire surgical margin and would prevent a procedure from achieving PDEMA.**
- **PDEMA can be achieved with either frozen sections or formalin fixation and paraffin embedding. Although it is often helpful for the surgeon to examine the specimen histologically, the surgeon is not required to examine the specimen histopathologically to achieve PDEMA; a trained pathologist or dermatopathologist may communicate results to the surgeon. If a pathologist or dermatopathologist analyzes the specimen, a consistent communication system must be in place to designate the marginal surfaces for examination and to ensure that the three-dimensional orientation of marginal surfaces and of tissue blocks relative to the wound bed are maintained and communicated to the surgeon to enable accurate localization of residual tumor within the wound bed. The use of multiple operating settings and surgeons is also consistent with PDEMA as long as the orientation of the tissue and wound bed are accurately communicated and complete margin assessment is maintained.[2]**

Figure 1

Courtesy of Dr. Brooke Walls, DO, FAAD, Aspen Center for Cosmetic Medicine & Dermatology

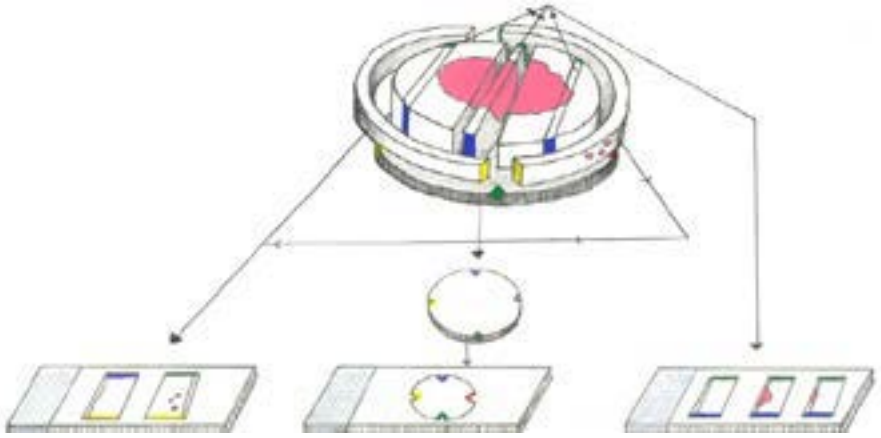
Tubingen muffin technique



Processed or discarded

OR

Tubingen torte technique



[2] Leigheb M, Zavattaro E, Bellinzona F, et al. Micrographic surgery (Tubingen torte technique) for the treatment of an invasive dermatofibrosarcoma protuberans with muscular involvement. G Ital Dermatol Venereol 2010;145:309-311.

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PRINCIPLES OF PDEMA TECHNIQUE

- **Published examples of PDEMA include:**
  - **Mohs[3,4]**
  - **Tubingen muffin technique[5,6]**
  - **Tubingen torte technique (see https//ems-mohs.eu/fileadmin/user_upload/ESMS_Position_Paper_-_WEB.pdf)**
- **Examples of techniques that do not achieve PDEMA include:**
  - **Wide local excision with "breadloafing" (perpendicular section prevents visualization of the entire margin)**
  - **Square procedure,[7] quadrant technique, moat technique, and perimeter technique[8] (wherein the deep margin is assessed with vertical sections so complete visualization of the deep margin is absent). As compared to "breadloafing," these techniques provide more complete peripheral margin evaluation for superficial tumors (eg, melanoma in situ and extramammary Paget disease) that do not involve subcutaneous tissues. However, these techniques do not provide complete deep margin evaluation so are not PDEMA.**

PDEMA Checklist	Yes	No
Is the entire peripheral margin of the surgical specimen microscopically visualized?		
Is the entire deep margin of the surgical specimen microscopically visualized?		
Is the surgical specimen oriented to the wound bed and marked such that any positive margin identified in histopathologic analysis can be accurately located and re-excised?		
Is the process of excision and complete histologic examination repeated until no further cancer is identified or until further excision is no longer in the best interest of the patient?		
Is the process rapid enough to prevent distortion of the wound bed that would decrease accuracy of tissue orientation?		

All of the above categories must be marked Yes to achieve PDEMA. If any of the above are marked No, the procedure does not achieve PDEMA.

[3] Tromovitch TA. Microscopically controlled excision of skin tumors. Arch Dermatol 1974;110:231-232.
[4] Behshad R. Mohs Micrographic Surgery. In: Kantor J, ed. Dermatologic Surgery. McGraw-Hill Education; 2018:388-413.
[5] Möhrle M, Breuninger H. [The Muffin technique--an alternative to Mohs' micrographic surgery]. J Dtsch Dermatol Ges 2006;4:1080-1084.
[6] Farma JM, Ammori JB, Zager JS, et al. Dermatofibrosarcoma protuberans: How wide should we resect? Ann Surg Oncol 2010;17:2112-2118.
[7] Johnson TM, Headington JT, Baker SR, Lowe L. Usefulness of the staged excision for lentigo maligna and lentigo maligna melanoma: The "square" procedure. J Am Acad Dermatol 1997;37:758-764.
[8] Moehrle M, Breuninger H, Röcken M. A confusing world: what to call histology of three-dimensional tumour margins? J Eur Acad Dermatol Venereol 2007;21:591-595.

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American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Cutaneous Carcinoma of the Head and Neck (8th ed., 2017)[1,2]

Table 1. **Definitions for T, N, M**

T	Primary Tumor
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor smaller than or equal to 2 cm in greatest dimension
T2	Tumor larger than 2 cm, but smaller than or equal to 4 cm in greatest dimension
T3	Tumor larger than 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion*
T4	Tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement

*Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

Clinical N (cN)

cN	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in any node(s) and clinically overt ENE [ENE(+)]
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and ENE (+)

Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological extranodal extension (ENE) should be recorded as ENE(−) or ENE(+).

[1] These staging tables are for cutaneous squamous cell carcinoma, cutaneous carcinoma, basal cell carcinoma of the head and neck, and all other nonmelanoma skin carcinomas of the head and neck (except Merkel cell carcinoma). Anatomic site of external vermilion lip is included because it has a more similar embryologic origin to skin, and its etiology—which is often based on ultraviolet exposure—is more similar to other nonmelanoma skin cancers. The AJCC Staging Manual, Eighth Edition does not include staging for cutaneous carcinoma outside the head and neck.

[2] Used with the permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing

Continued

American Joint Committee on Cancer (AJCC)
TNM Staging Classification for Cutaneous Carcinoma of the Head and Neck (8th ed., 2017)[1,2]

Pathological N (pN)

pN	Regional Lymph Nodes
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension, ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)

Note: A designation of “U” or “L” may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological extranodal extension (ENE) should be recorded as ENE(−) or ENE(+).

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

G	Histologic Grade
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Table 2. **AJCC Prognostic Stage Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IV	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	Any T	N3	M0
	T4	Any N	M0
	Any T	Any N	M1

[1] These staging tables are for cutaneous squamous cell carcinoma, cutaneous carcinoma, basal cell carcinoma of the head and neck, and all other nonmelanoma skin carcinomas of the head and neck (except Merkel cell carcinoma). Anatomic site of external vermilion lip is included because it has a more similar embryologic origin to skin, and its etiology—which is often based on ultraviolet exposure—is more similar to other nonmelanoma skin cancers. The AJCC Staging Manual, Eighth Edition does not include staging for cutaneous carcinoma outside the head and neck.

[2] Used with the permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Squamous Cell Skin Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Squamous Cell Skin Cancer. Last updated April 25th, 2022.

Table of Contents

Overview

Cutaneous squamous cell carcinoma (SCC or CSCC) is the second most common skin cancer.[1-3] Numerous population-based studies have demonstrated that the incidence of SCC is rising.[1,4-8] Some studies show that SCC incidence rates are rising more rapidly than basal cell carcinoma (BCC), reducing the difference in incidence between these two skin cancers.[2,3,9] Although rarely metastatic, SCC can produce substantial local destruction along with disfigurement and may involve extensive areas of soft tissue, cartilage, and bone. SCCs generally have a good prognosis, with 5-year survival of about 98%.[1,10-12]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Squamous Cell Skin Cancer, an electronic search of the PubMed database was performed to obtain key literature using the following search term: squamous cell carcinoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[13]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Risk Factors for SCC

A number of risk factors are associated with the development of SCC. The most recognized environmental carcinogen is sunlight. Evidence reveals that chronic sun exposure, total site-specific exposure, and number of site-specific sunburns are strongly correlated with development of SCC.[14-18] Due to the link with chronic and cumulative sun exposure, SCC rates are higher in occupations involving outdoor work[19-21] and increase with age, particularly in sun-exposed sites.[2,5,9,16,17,22] Indoor tanning is also significantly associated with SCC. According to two large meta-analyses, any exposure to indoor tanning increases the risk of SCC by 67%,[23] with the prevalence of indoor tanning much higher than previously thought among US adults and college students.[24] Individuals with light skin, hair, and eye color who have received too much sun exposure are at the greatest risk for SCC.[14,15,25-29] The incidence of ultraviolet (UV)-induced SCCs is very low in non-white populations and has been poorly quantified in people of mixed ethnicities. Most of SCCs develop on sun-exposed skin sites, especially the head and neck area.[5,16,22,30,31] Actinic keratoses (AKs) and Bowen's disease, if left untreated, can also progress to invasive SCC with the potential for metastasis.[20,32-37]

Furthermore, SCCs are also known to develop in association with scars or chronic wounds (Marjolin's ulcer).[38-44] These types of SCCs occur at similar rates in all races and ethnicities. Such SCC lesions tend to be difficult to treat and have higher risk of recurrence.[45-47]

Lastly, certain genetic syndromes greatly predispose affected individuals to SCC formation, such as albinism[43,48-52] and xeroderma pigmentosum.[53-57] Certain settings of immunosuppression (eg, organ transplantation, lymphoma, chronic lymphocytic leukemia, drug-induced

immunosuppression, and HIV) also predispose affected individuals to UV-induced SCC.[58-72] Most notably, analyses of transplant registries have reported a 5-fold to 113-fold increase in incidence of SCC in transplant recipients compared to the general population.[60,61,68,72] These patient groups are also at high risk of developing multiple CSCCs and tumors that can behave aggressively.[45,53-57,73-86] Within these high-risk groups, individual patients should be identified for closer follow-up (See *Identification and Management of Patients at High Risk for Multiple Primary CSCCs* in the Algorithm).

Clinical Presentation and Workup

On clinical presentation of a suspicious lesion, workup for SCC begins with a history and physical examination, with an emphasis on a complete skin and regional lymph node (LN) examination. A full skin examination is recommended because individuals with a skin cancer often have additional, concurrent precancers or cancers located at other, usually sun-exposed skin sites. These individuals are also at increased risk of developing cutaneous melanoma.[81,87,88]

A skin biopsy is then performed on any suspicious lesion. The biopsy should include deep reticular dermis if the lesion is suspected to be more than a superficial process. This procedure is preferred because an infiltrative histology may sometimes be present only at the deeper, advancing margins of a tumor and superficial biopsies will frequently miss this component.[89,90] Skin lesions in high-risk populations may be difficult to assess clinically; therefore, a low threshold for performing skin biopsies in these patients is necessary. Basosquamous carcinoma may behave as aggressively as CSCC.[91-93]

Imaging studies of the area of interest should be done when extensive disease is suspected, which includes deep structural involvement such as bone, perineural disease, and deep soft tissue.[94,95] Due to its higher sensitivity, MRI with contrast is preferred for perineural disease or deep soft tissue involvement.[96-98] If bone disease is suspected, CT with contrast is preferred unless contraindicated. Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is often sufficient to diagnose local recurrence, but MRI can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or other imaging modalities can be employed for confirmation and to gauge extent of disease. For rare cases that present with distant metastatic disease at diagnosis, the distant metastases pathway should be followed. (see Guidelines sections *SCC-4 Clinical Staging and Preoperative Assessment* and *SCC-6 Regional Recurrence or Distant Metastases*).

Risk Stratification of Local CSCC Based on Risk Factors for Local Recurrence, Metastases, or Death

After biopsy, a risk assessment of the primary tumor should be performed (See Stratification to Determine Treatment Options and Follow-up for Local CSCC Based on Risk Factors for Local Recurrence, Metastases, or Death from Disease in the algorithm). Risk category assignment should be based on the highest risk factor present. The high-risk group has elevated risk of local recurrence while the very-high-risk group has elevated risks of local recurrence and metastasis. Other staging systems, including the AJCC 8th edition staging system of CSCC, have been formulated and independently tested to define high-risk groups among patients with localized disease, and can act as additional sources of reference.[10,73-75,81,99-105]

History & Physical

Location and Size

Anatomic location has been known to be a risk factor for SCC recurrence and metastasis for many years.[45,74,106] In general, SCCs that develop in

the head and neck area, particularly the ears and vermillion lips, are more likely to recur and metastasize than those developing on the trunk and extremities.[10,45,73,74,99,106-109] Besides the head and neck, SCCs that develop on the hands, feet, pretibial, and anogenital areas are also at greater risk of local recurrence and nodal metastasis, independent of size.[10,110,111]

Size has also been shown to be a risk factor for SCC recurrence and metastasis.[45,74,109,112,113] Although different divisions have been used, the most recent and robust data support that tumors >2 cm are at higher risk of recurrence, metastasis, and poor disease-specific survival (DSS).[10,45-47,73-75,114,115] Taken together, the NCCN Panel recommends that low-risk location (trunk, extremities) and size ≤ 2 cm constitute low-risk CSCC. Low-risk location (trunk, extremities) and size > 2 cm (but ≤ 4 cm), or high-risk locations outlined above, constitute high-risk CSCC.

Regardless of location, the NCCN Panel recommends that a tumor diameter of > 4 cm warrants the very-high risk designation. This is based on data from a large, prospective study, which demonstrate that lesion sizes of < 4 cm and ≥ 4 cm are associated with 3-year DSS of 93% and 67% (P = 0.0003), respectively.[112] Studies have also reported that mean lesion size of 4.2 cm (± 3.4)[116] and > 5 cm[109] as significantly associated with LN metastases.

Borders

The risk factor of well-defined versus ill-defined clinical tumor borders has been reported in the context of BCC and extrapolated to the SCC population based on clinical experience of the NCCN panel.[117-119]

Primary Versus Recurrent Disease

The higher risk of recurrence and metastasis for recurrent versus primary disease has been extensively documented in the literature.[45,112,114,116,120,121]

Immunosuppression

In addition to increasing the risk of SCC development, immunosuppression has been shown to be associated with recurrence, metastasis, and death in multiple reports.[45,73-75,78-81,122] Studies from the organ transplant literature have further elucidated features linked with SCCs in this unique population of immunocompromised patients.[79,101,123,124] A retrospective review confirmed that organ transplant recipients with CSCC had more primary tumors and were more likely to have deep tissue spread and perineural and lymphatic invasion.[79] Other studies found diffuse/focal spindle cell morphology, evidence of human papillomavirus (HPV) infection, and aggressive subclinical extension to be more likely in SCCs from transplant patients.[123,125] Two large retrospective studies reported high rates of SCC recurrence and metastasis among transplant patients despite the fact that most SCCs were stage I/II at presentation.[101,124]

Site of Prior Radiotherapy or Chronic Inflammatory Process

Tumors developing in sites of prior radiotherapy (RT) refer to primary CSCCs arising in areas previously irradiated for unrelated conditions. All recurrent tumors are defined as high risk irrespective of prior therapy. Data support that prior RT for unrelated (frequently benign) conditions is a risk factor for SCC recurrence or metastasis.[114,126] Retrospective studies and meta-analyses have also documented increased rates of metastasis for SCC arising from sites of chronic scarring or inflammation.[45,46,116,120,127-129]

Rapidly Growing Tumor

The evidence for growth rate and prognosis is lacking in CSCC. Based on clinical experience, the NCCN Panel included rapid growth rate as a high-risk factor. A Japanese study reported a pair of tumor size and rapid growth as prognostic factor for SCC.[130] In a small retrospective series, tumor growth rate of > 4 mm/month exhibits a higher risk of nodal progression and a shorter progression time to LN metastasis.[131] There is

also evidence that CSCC in immunosuppressed individuals are often characterized by aggressive behavior and rapid growth.[132,133]

Neurologic Symptoms

In tumors with perineural involvement (PNI), clinical symptoms suggesting possible involvement of sensory or motor nerves are commonly absent but may occur. Symptoms include pain, burning, stinging, anesthesia, paresthesia, facial paralysis, diplopia, and blurred vision.[134,135] Any suggestion of neurologic involvement in the region of a CSCC should place that tumor in a high-risk category, as PNI is associated with recurrence, metastasis, and poor outcomes.[10,45,73,75,106,112,114,129,136-138] Poorer outcomes are associated with the presence of clinical symptoms and extent of neuronal involvement.[75,139-142]

Pathology

Degree of Differentiation

Although Broders originally divided CSCC histologically into four grades in 1920, the NCCN Panel has adopted the current trend to reduce the divisions to two groups: 1) well or moderately differentiated; and 2) poorly differentiated.[99,143] Many studies, including some very large retrospective studies (N > 1000) provide evidence that poor differentiation is correlated with CSCC recurrence, metastasis, DSS, and overall survival (OS).[10,45,46,73,75,106,109,114,116,121,129,130,144]

Histology

The histologic subtypes of acantholytic (adenoid), adenosquamous (or mucin-producing), and metaplastic (carcinosarcomatous) SCC are rare.[145] Only case reports and case series document the outcomes of patients with these subtypes, and thus their prognostic significance is debated.[146-151] Since these tumors may have a high risk of recurrence and likely would not be included in the high-risk category on the basis of their degree of differentiation, the panel decided to list them as separate risk factors.

Another histologic feature associated with greatly increased risks of recurrence and metastasis is desmoplasia.[74,152] A retrospective study using the PALGA national registry of the Netherlands reported significantly higher rates of metastasis for desmoplastic versus non-desmoplastic CSCCs: 89% versus 21% (P < .001).[113] A more recent review of 72 patients with desmoplastic SCC reported a rate of recurrence of 80%.[153]

Depth

Data from many large studies support that risk of recurrence and metastasis increases with increasing lesion depth.[10,45,73,75,99,109,113-115,121,154] CSCC lesion depth can be quantified as thickness in mm[155] or by anatomic layer(s) invaded, both of which have been included in the T classification of the AJCC 7th and 8th Edition staging for CSCC.[143,156]

Prospective data from Brantsch and colleagues reported metastasis rates of 0% of tumors ≤ 2.0 mm in thickness, 4% of tumors 2.1-6.0 mm in thickness, and 16% of tumors thicker than 6.0 mm, with depth measured as the greatest vertical distance from the top to the bottom of the tumor.[74] Other studies show that the risk of recurrence and metastasis is significantly higher for lesions with thickness >2 mm.[73,109,115] Meta-analyses have shown that 4-mm and 6-mm thickness cutoffs are prognostic for recurrence and metastasis,[45,73] and one retrospective study showed that risk for recurrence and metastasis increases significantly for every 1-mm increase in tumor depth.[102] Regarding anatomic level of invasion, some studies showed significantly higher risk of recurrence or metastasis for CSCC lesions with Clark levels IV-V, corresponding to invasion of the deep reticular dermis or subcutaneous fat, respectively.[45,113] Other studies have shown that lesions with invasion into the subcutaneous fat significantly increases rates of recurrence and metastasis.[10,73,75,99,112,114,115]

The NCCN Panel has chosen thickness > 6 mm or invasion beyond subcutaneous fat to be considered high risk. If clinical evaluation of

incisional biopsy suggests that microstaging is inadequate, the Panel recommends considering narrow margin excisional biopsy to obtain accurate measurement of thickness and anatomic level of invasion.

Perineural Involvement

PNI is uncommon in any non-melanoma skin cancer (NMSC), but develops more frequently and is more aggressive in CSCC versus BCC.[140,141,157,158] PNI poses increased risks of recurrence, metastasis (nodal and distant), and death, is more common in recurrent versus primary tumors, and is associated with other risk factors, including larger lesion size, poor differentiation, and adenosquamous, desmoplastic, and metaplastic subtypes.[10,45,73,75,99,106,112,114,129,136-138,153,159-162] Specifically, PNI with tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥ 0.1 mm has been associated with metastasis and DSS.[99,103,156] If large nerve involvement is suspected, MRI should be considered to evaluate extent and/or rule out skull involvement in those with head and neck tumors.[96,97,135,142,163]

Lymphatic or Vascular Involvement

Significant association between lymphovascular invasion (LVI) and LN metastasis has been reported in prospective[116,138] and retrospective studies[137]. One retrospective study showed that in high-risk CSCC populations with PNI or neurotropism, LVI was significantly associated with DSS and all-cause death.[103]

Treatment Modalities for Local SCC

Curettage and Electrodesiccation (C&E)

C&E is a fast and cost-effective technique for superficial lesions; however, it does not allow histologic margin assessment. Retrospective and observational data with long-term follow-up (>5 year) indicate that cure rates are between 95-100% for patients with primary CSCC lesions treated with C&E.[45,164-166] These estimates are largely based on low-risk cases, and there is evidence to suggest that the cure rate is lower for tumors with risk factors. One study reported recurrence rates of 0.4% versus 11% for CSCCs with diameter less than versus greater than 2 cm, and another reported a recurrence rate of 19% for SCCs on the skin of the pinna that were treated with C&E.[167,168]

The NCCN panel recommends this technique as a primary treatment option for ***local, low-risk CSCCs*** with three caveats. First, this technique should not be used to treat areas with terminal hair growth such as the scalp, pubic or axillary regions, or beard area in males due to the risk that a tumor extending down follicular structures might not be adequately removed. Second, if the subcutaneous layer is reached during the course of C&E, then surgical excision should generally be performed instead. This change in therapy is necessary as the effectiveness of the C&E technique rests on the ability of the clinician to distinguish between firm, normal dermis, and soft tumor tissue when using a sharp curette. Since subcutaneous adipose is even softer than tumor tissue, the ability of the curette to distinguish, and therefore to selectively and completely remove tumor cells, diminishes. Third, if C&E has been performed based only on the appearance of a low-risk tumor, biopsy results of the tissue taken at the time of C&E should be reviewed to make sure that there are no high-risk pathologic features that would require additional therapy. For ***local, high-risk/very-high-risk CSCC*** tumors in the cheeks, forehead, scalp, neck, and pretibial that are < 6mm 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.

Mohs Micrographic Surgery or Excision with Peripheral and Deep En Face Margin Assessment (PDEMA)

Mohs is a primary treatment option for ***local, low-risk CSCC*** and ***local, high-risk CSCC***, as well as the preferred surgical technique for ***local, very-high-risk CSCC*** because it allows intraoperative analysis of 100% of the excision margin. 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.[45] Moreover, local recurrence rates have been reported to be significantly less likely with Mohs compared to standard excision.[169,170] 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.[45]

Retrospective and prospective observational studies of localized primary SCCs treated with Mohs reported local recurrence rates of 1.2% to 4.1% and rates of metastases between 0% and 6.3%.[164,165,171-184] Compared with primary tumors, rates of local recurrence or metastasis after Mohs are higher for recurrent tumors (previously treated with a non-Mohs modality).[114,173] For recurrent CSCCs treated with Mohs, subsequent local recurrences occurred in 5.9% to 7.7% of cases; metastasis in 0% to 10%.[171-177] Other risk factors associated with recurrence after Mohs include larger subclinical extension and more Mohs stages required for clearance.[173] CSCC with PNI is associated with elevated rates of recurrence (6.8%-32.3%) in studies that occasionally include BCC as well as treatment by RT.[140,159,161,185-187] Risk factors associated with metastasis after Mohs include: size >2 cm, Clark's level (metastatic CSCC are more likely to be deeper – Clark level III-V), poor differentiation, location in areas of prior radiation, small tumor nests and infiltrative tumor strands, single-cell infiltration, PNI, and acantholysis.[114]

It is not uncommon to find discrepancies between pathology results from preoperative biopsy or initial debulking compared with frozen sections taken during Mohs.[188-190] When Mohs with marginal assessment 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 pathologic evaluation with paraffin sections is recommended. If invasion to the parotid fascia is noted, superficial parotidectomy may be indicated.

Excision with PDEMA using permanent section analysis or intraoperative frozen section analysis (IOFSA) is acceptable as an alternative to Mohs provided that it includes a complete assessment of en face peripheral and horizontal deep margins coupled with close communication between pathologists and surgeons regarding where within the tumor bed further resection is needed. These subsequent specimens must also be processed and results communicated via the PDEMA method. Low recurrence rates (0%–1%), and specifically lower recurrence rates when compared directly to standard excision,[191] have been reported where histologically clear margins are achieved.[192] It is important to note that truly histologically negative margins are not necessarily achieved by IOFSA alone, without PDEMA. Studies have reported that for CSCC tumors with negative margins upon IOFSA, permanent paraffin section analysis indicates positive margins in 10% to 20%.[189,190,193-195] These discrepancies may be due to unrepresentative sampling of the margins, and IOFSA cases in which permanent section showed positive margins have reported much higher recurrence rates.[195] Overall, the descriptive term PDEMA underscores the Panel's belief that complete assessment of all tissue margins is the key to optimal tumor removal for high-risk tumors. Such effort at local control is particularly important in SCC because one third of

deaths occur from local disease alone. Mohs or other forms of PDEMA are also recommended in case of positive margins after standard excision for both ***local, low-risk CSCC*** and ***local, high-risk/very-high-risk CSCC***.

Standard Excision with Postoperative Margin Assessment

A common therapeutic option for CSCC is standard surgical excision followed by postoperative pathologic evaluation of margins. Retrospective analyses and prospective observational studies have reported rates of recurrence or metastasis ranging from 0% and 14%, with most studies reporting rates of 6% or lower.[45,115,144,154,164,165,176,181,196-200] Distant metastasis was rarely observed, and rates of regional metastasis were highly variable across studies, ranging from 0% to 13%.[144,154,181,196,200,201] One large meta-analysis found that recurrence rates were lower for primary versus recurrent tumors, both with follow-up of less than 5 years (5.7% vs. 17.3%) and with longer follow-up (8.1% vs. 23.3%).[45] Incomplete excisions can depend on lesion location, thickness, PNI, invasion into the deep fascia, differentiation, surgeons' skills, and primary versus recurrent tumors,[173,202-204] among other factors.[181,196,205-212]

The clinical margins chosen by the NCCN Panel for the primary treatment of ***local, low-risk CSCC*** are based on the work of Brodland and colleagues.[213] Their analysis indicated that for well-circumscribed CSCC lesions less than 2 cm in diameter, excision with 4-mm clinical margins should result in complete removal in more than 95% of cases. For low-risk lesions >2 cm in diameter, results indicated that 6-mm margins would be needed to achieve histologically clear margins in 95% cases.

The NCCN Panel also recommends standard excision as the primary treatment for ***local, high-risk/very-high-risk CSCC*** when Mohs micrographic surgery (Mohs) and other forms of PDEMA is not available, however, wider surgical margins than those recommended for low-risk lesions must be taken and increased recurrence rates should be expected. According to Brodland et al., 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.[213] 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.[173,177,202,214] Currently, European Guidelines recommend standard excisions with 6 to 10 mm peripheral clinical margins for high-risk to very-high-risk CSCCs.[215-218] 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.

Whenever standard excision is utilized, any peripheral rim of erythema around a SCC must be included in what is assumed to be the tumor. For patients with positive margins from surgical excision and postoperative margin assessment, re-excision often yields clean margins, and in many cases, the re-excision specimen contains no tumor cells.[144,154,197,219-221] Re-excision with postoperative margin assessment is therefore among the recommended treatment options for positive margins after standard excision of both ***local, low-risk CSCC*** and ***local, high-risk/very-high-risk CSCC***. In any case, tissue rearrangement should not be undertaken until clear margins are identified.

Radiation Therapy

Radiation as Primary Therapy

Although surgery is the mainstay of local treatment for SCC, patient preference and other factors may lead to the choice of RT as primary

therapy for ***local, low-risk*** and ***local, high-risk/very-high-risk CSCC***. A large meta-analysis reported 5-year recurrence rates of 6.7% and 10% after RT of primary and recurrent SCC, respectively.[45] Subsequent retrospective analyses of patients with primary CSCCs have reported a large range of recurrence rates, from 2.8% to 42%, the latter for patients with locally advanced disease (size >2 cm or deeply invasive).[164,222-228] The risk of recurrence appears to increase with increasing lesion size and T-stage.[225,227,229] A few small studies (n < 20) have reported that for CSCCs that have been previously treated and recurred, treatment with RT results in recurrence in 16.7% of cases.[224,227]

Retrospective analyses have reported recurrence rates ranging from 0% to 10.5% in situ SCC lesions treated with RT as primary therapy, with most studies reporting local control rates near 100%.[226,227,230-233]

Adjuvant Radiation

For ***local, low-risk*** and ***local, high-risk/very-high-risk CSCC***, the NCCN panel recommends adjuvant RT for non-surgical candidates in case of positive margins after definitive surgery. It has been shown that adjuvant RT improved locoregional control and survival outcomes for patients with positive margins after surgery or other high-risk features for recurrence.[234-239] However, RT in the salvage setting is usually not curative so every effort should be taken to obtain a clear surgical margin prior to RT initiation.[186] For any CSCC that shows evidence of extensive perineural, large, or named nerve involvement, or if other poor prognostic features are present, adjuvant RT can be considered even if negative margins are achieved after surgery.[239] The outcome benefit of adjuvant RT following resection of CSCC with negative margins has recently been estimated to be approximately 50% reduction in local and nodal recurrence risks,[240] despite older inconclusive data.[238,241,242] Other retrospective studies combined results for patients treated with other modalities (eg, Mohs/standard excision alone, RT alone, chemotherapy), patients with other types of skin cancer (BCC and metatypical BCC), patients with LN metastases, and a mix of patients with primary and recurrent skin lesions, with and without positive margins.[139,161,237,243-245] These studies suggest that postoperative RT for patients with high-staged CSCC may improve local and regional control and disease-free survival (DFS), but a survival benefit has not been demonstrated.

Radiotherapy Safety & Administration

The NCCN Panel previously cautioned that RT is often reserved for patients older than 60 years because of concerns about long-term sequelae, including secondary malignancies; however, this statement has been retracted. This is because age is no longer a major factor in determining treatment modality.

Large cohort and population-based studies (N > 1000) have shown that rates of NMSCs are significantly higher in those who received prior RT (either for a benign condition or for cancer) compared with those who have no history of therapeutic RT exposure.[246-249] In patients who developed NMSC after prior RT, most NMSC lesions occurred within the radiation field, with elevated risk of NMSC confined to the site of RT exposure. The risk of NMSC was particularly high in patients who received therapeutic RT early in life.

RT can result in poor cosmetic outcomes, including telangiectasia, changes in skin pigmentation, and fibrosis. More serious long-term complications include non-healing ulcers (especially for SCC in situ[230-232]); soft tissue, cartilage, bone, or brain necrosis; decreased sensation; and cataracts (for lesions in the periorbital region).[227,229,231,233,250-252]

Specifics about the application of RT, including total doses, treatment duration, and contraindications, are described under *Principles of Radiation Therapy* in the Algorithm. RT is contraindicated in patients with genetic conditions predisposing to irradiation-related skin cancer (eg,

basal cell nevus syndrome[253-257] and DNA-repair disorders such as Fanconi's anemia, xeroderma pigmentosum), and relatively contraindicated in patients with connective tissue diseases (eg, lupus, scleroderma).[258-260] Given higher rates of poor cosmesis and complications with increasing cumulative radiation dose,[229,250,261] reirradiation should not be routinely utilized for recurrent disease within a prior radiation field. Protracted fractionation is associated with improved cosmetic results,[250,252,262] and should be utilized for poorly vascularized or cartilaginous areas. Retrospective studies have found that for patients with CSCC and PNI, treatment failures tend to occur along involved nerves.[139,263,264] The NCCN Panel recommends including the course of the local nerves proximally for extensive PNI, clinically evident PNI, or involvement of named nerves (particularly in the head and neck region).

A variety of external beam options have been shown to be effective for treating CSCC and have similar cosmetic/safety results.[229,250,262,265-267] Isotope-based brachytherapy can be an effective treatment for certain sites of disease, particularly on the head and neck.[268-274] A retrospective multicentric analysis of 1676 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%, 2-3.9 cm: 88%, ≥ 4 cm: 81%) and tumor site (external surface of the nose: 94%, vestibule: 75%).[273] On the other hand, there are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy.

Sentinel Lymph Node Biopsy

The NCCN Panel recommends a discussion and consideration of sentinel lymph node biopsy (SLNB) prior to PDEMA for 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 the draining nodal basin. Studies have reported sub-clinical nodal metastases in 7% to 21% of patients with high-risk non-anogenital CSCC who underwent SLNB.[100,110,137,138,275-281] Although small sample sizes and low rates of SLN positivity limit assessment of prognostic factors, a few studies suggest that risk factors for SLNB positivity include tumor diameter and thickness, LVI, PNI, and the presence of multiple high-risk factors.[100,137,138,279,282]

Several studies reported that among patients with localized SCC and a negative SLNB, nodal metastases were later detected in 2% to 15% of patients.[100,110,137,138,276-278,280,283] In addition to false negatives, some studies documented patients with a negative SLNB who developed local recurrences or metastases outside of the previously biopsied LN basin.[110,138,276] It has been shown that despite receiving completion lymph node dissection, patients with a positive SLN had higher rates of postoperative recurrence/metastases, ranging from 33% to 45%,[137,138,276,279] and were also more likely to die from SCC, with significantly lower 3-year DSS rates compared with SLN-negative patients.[110,138,279] Therefore, although SLNB may have prognostic value, it is unclear whether SLNB followed by completion lymph node dissection or adjuvant RT improve patient outcomes.

Systemic Therapy for Local High-Risk SCC

The NCCN Panel recommends systemic therapy with or without RT for ***local, high-risk/very-high-risk CSCC*** in case of positive margins after Mohs or other forms of PDEMA, residual disease after definite surgery, and for non-surgical candidates. For patients who have complicated cases of locally advanced disease in which curative surgery and curative RT are not feasible, multidisciplinary consultation is recommended to consider systemic therapy alone (Refer to *Principles of Systemic Therapy* in the algorithm and Discussion section *Systemic Therapy Options*). In the absence of data from prospective comparative studies, it is unclear which systemic therapies are appropriate for localized disease in the context of concomitant RT. In contrast, large randomized trials have tested systemic

therapy options for head and neck mucosal SCCs.[284-286] Therefore, for the rare cases of localized high-risk SCC in which chemoradiation is considered, the NCCN panel recommends referring to the systemic therapy options for mucosal SCC in the NCCN Guidelines for Head and Neck Cancers.

Regional Lymph Node Involvement in SCC

Regional nodal involvement significantly increases the risk of recurrence and mortality.[47,109,121] Nodal metastasis also commonly coincides with other adverse histopathologic findings such as LVI, poor differentiation, and PNI.[10,75,99,106,109,114,116,121,287] About 60-82% of patients with nodal disease show involvement in the parotid gland, while cervical neck node disease without parotid invasion is observed in 18-41% of cases.[288]

Workup for Suspicion of Regional Lymph Node Involvement

The presence of palpable regional LNs or suspicious LNs identified by imaging studies should prompt a fine-needle aspiration (FNA) or core biopsy of suspicious node(s). If initial pathology results are negative, the NCCN Panel recommends considering re-evaluation by clinical exam, CT with contrast imaging of the nodal basin, and/or pathology on additional LN specimens taken by repeat FNA, core biopsy, or open biopsy of the suspicious node(s). For patients with pathologic evidence of LN disease, preoperative imaging of the nodal basin by CT with contrast is recommended to determine the size, number, and location of involved nodes. PET/CT of the nodal basin can be useful for RT planning. In addition, chest/abdominal/pelvic CT with contrast or PET/CT are recommended as clinically indicated to rule out distant metastatic disease.

Treatment of SCC with Regional Lymph Node Involvement

The NCCN Panel recommends resection of regional disease over RT or chemotherapy. RT with or without concurrent systemic therapy is reserved for patients who are not surgical candidates. Most studies of CSCC patients with regional involvement focus on treatment of parotid and/or cervical nodes either with surgery alone (parotidectomy and/or neck dissection) or surgery plus adjuvant RT. Some studies included patients receiving concomitant chemotherapy[76,289-295] or patients who received RT alone[120,294,296-298]. For studies where the majority of patients receive surgery plus adjuvant RT, recurrence rates are 20-35% and estimates of

5-year DFS and DSS are 59-83% and 63-83%, respectively.[76,77,289,290,292-294,296,298-303] Many studies support that adjuvant RT improved local regional control, DFS, and OS compared with surgery or RT alone.[289,290,293,294,296,298-300,303] In contrast, other studies found no significant association between adjuvant RT and improved disease outcomes.[76,289,301,302] There may be subsets of patients who derive more clinical benefit from adjuvant RT than other patients; however, it is difficult to identify such patients. Results vary for all of the prognostic factors frequently considered such as immunosuppression, primary tumor size, LVI, PNI, differentiation, and features of the regional disease such extracapsular extension (ECE) and number of involved nodes.[76,77,289,290,292,293,296,298,300,303,304]

Several staging systems have been proposed for regional CSCC, as shown in Table 1. O'Brien proposed a staging system that separates parotid involvement from neck LN involvement based on multivariate analysis showing improved local control for P1 compared with P2/P3.[305] Multivariate analyses of survival and locoregional control have yielded favorable[291,296,298,303] as well as discordant results[77,291,300] regarding the prognostic value of O'Brien P-stage. O'Brien also showed that survival was significantly better for patients with N0/N1 compared with N2.[305] Two studies supported this result,[77,303] but several others did not.[296,298,300] According to the AJCC 7th edition, N1 disease with no ECE had a 5-year cure rate of 92%.[139] N2 disease with immunosuppression, in particular transplant patients or those with hematologic malignancies, on the other hand, had a 5-year survival of 52%, in contrast to 72% for immunocompetent patients.[306] The AJCC 7th edition staging does not separate parotid from cervical lymph node involvement and includes both 3-cm and 6-cm cutoffs for largest lymph node dimension.[307] Forest et al. found that lymph node size was related to ECE, and that 6-cm cutoff and 3-cm cutoff groups performed similarly.[289] Risk stratification per the NCCN Guidelines takes into account both ECE[300,308,309] and margin status after resection[291,298,300,305,308] as prognostic factors for recurrence and survival. The recent update of the AJCC staging system also includes ECE as a criterion for determining N-stage.[156] It should be noted that there are studies that showed no significant association between outcomes and ECE or margin status.[291,293]

The NCCN-recommended and preferred treatment for CSCC with lymph node involvement is excision of the primary tumor and regional lymph node dissection for all surgical candidates. Patients treated with dissection of nodes in the trunk and extremities should consider adjuvant RT of the nodal bed, especially if multiple nodes are involved or if ECE is present. For patients with nodal metastasis to the head and neck, the extent of surgery should depend on the number, location, and size of effected nodes. Postoperative adjuvant treatment should depend on the pathologic findings after surgery—namely the extent of resection, number of positive nodes, and presence or absence of ECE. Patients with ECE or incompletely excised nodes should receive adjuvant RT and also consider concurrent systemic therapy depending on individual toxicity tolerance. Patients with inoperable nodal disease should be treated with RT of the nodal bed and consider concurrent systemic therapy. Multidisciplinary consultation is recommended for these cases and should consider the systemic therapies used to treat head and neck squamous cell carcinomas as indicated in the NCCN Guidelines for Head and Neck Cancers. For symptomatic sites, palliative RT or surgery should be considered. Stereotactic body radiation (SBRT) may be appropriate in select patients.

Systemic Therapy for Regional Disease

The NCCN Panel recommends systemic therapy with or without RT for ***regional CSCC*** in case of unresectable, inoperable, or incompletely resected nodal disease and concurrently with RT as outlined in *Principles of Systemic Therapy* in the algorithm and Discussion section *Systemic Therapy Options*.

Table 1. Staging Systems for Regional Cutaneous SCC of the Head and Neck

O'Brien 2002 Staging System[305]	
Parotid Stage	
Stage	Criteria
P1	1 LN+ ≤3 cm
P2	1 LN+ >3 and ≤6 cm or ≥2 LN+
P3	1 LN+ >6 cm or Involves VII nerve or skull base
Neck Stage	
Stage	Criteria
N0	No clinical neck disease
N1	1 LN+ ≤3 cm ipsilateral
N2	1 LN+ >3 cm or ≥2 LN+ or ≥1 LN+ contralateral

AJCC 7th Edition (2009) Regional LN Staging[307]	
Stage	Criteria
N1	1 LN+ ≤3 cm ipsilateral
N2a	1 LN+ >3 and ≤6 cm ipsilateral
N2b	≥2 LN+ all ≤6 cm ipsilateral
N2c	≥1 LN+ ≤6 cm bilateral/contralateral
N3	≥1 LN+ >6 cm

AJCC 8th Edition (2017) Regional LN Pathological Staging[156]	
Stage	Criteria[a]
N1	1 LN+ ≤3 cm ENE(-)
N2a	1 LN+, >3 and ≤6 cm ipsilateral ENE(-) or 1 LN+ ≤3 cm ipsilateral ENE(+)
N2b	≥2 LN+ all ≤6 cm ipsilateral ENE(-)
N2c	≥1 LN+ all ≤6 cm bilateral/ contralateral ENE(-)_
N3a	≥1 LN+ >6 cm ENE(-)
N3b	1 LN+ ≤3 cm ENE(+) contralateral, or ≥1 LN+ >3 cm ipsilateral ENE(+) or ≥2 LN+, any ENE(+)

Forest 2010 N1S3 Staging System[289]	
Stage	Criteria
I	1 LN+ ≤3 cm
II	1 LN+ >3 cm or ≥2 LN+ ≤3 cm
III	≥2 LN+ >3 cm

NCCN Guidelines	
Risk Level	Criteria
Low	1 LN+ ≤3 cm, no ECE
Medium	1 LN+ >3 cm no ECE or ≥2 LN+ no ECE
High	≥1 LN+ with ECE or Incompletely excised disease

ECE, extracapsular extension; ENE(+), with extranodal extension; ENE(-), without extranodal extension; LN+, positive lymph node(s)
[a]Pathologic criteria

Recurrence and Metastasis

Metastatic CSCC is rare, estimated at 1.9-2.7% of all CSCC, with nodal metastases and distant metastatic disease estimated at 3.7% and 0.4%, respectively.[10,106] For the management of local tumor recurrence or new regional disease, the Algorithm directs clinicians to follow the appropriate pathways for primary treatment. Complicated high-risk tumors, regional recurrence, or the development of distant metastases should be managed by a multidisciplinary tumor board. The NCCN Panel encourages participation in a clinical trial for patients with metastatic CSCC. Unfortunately, such trials are scarce. For symptomatic sites, palliative RT or surgery should be considered. SBRT may be appropriate in select patients. Under highly selective circumstances and in the context of multidisciplinary consultation, resection of limited metastases can be considered.

Systemic Therapy for Distant Metastatic Disease

Unfortunately, evidence regarding systemic therapy for distant metastatic CSCC is limited, except for in the case of the recently established immunotherapy paradigm. Whereas a number of small studies have reported responses to cytotoxic therapy in patients with local or regional CSCC (Refer to *Principles of Systemic Therapy* in the algorithm and Discussion section *Systemic Therapy Options*), few of these studies included patients with distant metastatic CSCC.

Systemic Therapy Options

Systemic therapy with or without RT is recommended for primary and recurrent locally advanced disease in non-surgical candidates, for patients with resected high-risk regional disease, patients with unresectable, inoperable, or incompletely resected disease, and in patients with regional recurrence or distant metastatic disease. For locoregional disease for which surgery or RT are unlikely to be curative, both cytotoxic and EFGR inhibitor systemic therapy (monotherapy or combination) have been successfully used to reduce tumor load, which in some cases enabled complete resection or complete response with or without concurrent/subsequent RT.[310-314] In the absence of prospective comparative trial data, it is unclear whether systemic therapy provides additional clinical benefit when used postoperatively with RT. Small retrospective studies were unable to establish definitely that the addition of chemotherapy to postoperative RT significantly improved any disease-related outcome in patients with regional disease,[292,309,315-317] except for one study.[318] The emergence of anti-PD-1 inhibitors and robust clinical trial data have recently opened up novel treatment venues for patients with both locally advanced and metastatic CSCC not amenable to surgery and RT. It must be noted that the preferred recommendation for all of these settings is enrolment in a clinical trial.

The systemic therapy options for use with RT recommended by the NCCN Panel are cisplatin (preferred)[319-322] or epidermal growth factor receptor (EGFR) inhibitors (eg, cetuximab[321-329], erlotinib[330], gefitinib[314], panitumumab[331]), cisplatin + 5-fluorouracil (5-FU)[320,328,329,332], and carboplatin ± paclitaxel[286,319,321] (useful in certain circumstances). Evidence supporting the efficacy of any of these regimens is mostly limited to case reports and small retrospective studies. In a small (N = 0) prospective phase II study in patients with locally advanced primary or nodal disease who received definitive RT with concurrent cisplatin or carboplatin, the overall complete response (CR) was reported to be 63%.[319] Efficacy and

safety data for cisplatin, cetuximab, or carboplatin + paclitaxel in combination with RT can also be extrapolated from large randomized trials in patients with non-cutaneous head and neck cancers.[284-286] On the other hand, data from a rare, large (N = 321) randomized trial in patients with CSCC of the head and neck testing RT ± carboplatin did not find an added benefit with carboplatin.[315]

The systemic therapy options for use alone without RT recommended by the NCCN Panel are cemiplimab-rwlc[333-336] and pembrolizumab[337,338] (preferred if curative RT or surgery is not feasible for locally advanced, recurrent, or metastatic disease), or carboplatin + paclitaxel[339] (other recommended regimen), and EGFR inhibitors (eg, cetuximab[312,313,322,323,325,327,329,339,340], panitumumab[331,341], gefinitib[342], dacomitinib[343], erlotinib[344]), capecitabine[312,322], cisplatin ± 5-FU[310,312,320,322,329], and carboplatin (useful in certain circumstances) if the patients are ineligible for or progressed on checkpoint inhibitors and clinical trials.

Published data reported an objective response rate (ORR) of 44-54%, CR of 0-13%, and partial response (PR) of 31-50% to cemiplimab-rwlc in patients with locally advanced, recurrent, or metastatic CSCC.[333-336] Data from the phase II KEYNOTE-629 trial, which included patients with locally advanced, recurrent, or metastatic CSCC, reported an ORR of 34-50%, a CR of 4-17%, and a PR of 25-33% for patients treated with pembrolizumab.[337,338] Preliminary data and the clinical experience of NCCN Panel members suggest that other anti–PD-1 inhibitors may also be effective in this setting. It was recently demonstrated in a retrospective study that patients receiving immunotherapy showed a statistically significant better survival compared to those treated with other systemic therapies (P = 0.034);[322] the validity of this finding remains to be tested in prospective randomized studies. The use of immune checkpoint inhibitors might perhaps be extended to other indications, with early reports advocating its safety and efficacy in the neoadjuvant setting,[345] as well as concurrently with RT.[346]

In the case of EGFR inhibitors, all recommended regimens have been tested in small, single-arm phase II clinical trials among patients with CSCC nonamenable to surgery and RT. However, low rates of response were documented. Among 25 patients who received cetuximab, 8 PR's and 2 CR's were documented, with a disease control rate of 69%.[313] As for gefitinib, among 40 patients treated, the ORR was reported to be 16%, with an additional 35% achieving stable disease at 8 weeks.[342] In a smaller study of 16 CSCC patients testing panitumumab, the best ORR (PR and CR) was 31%, with a further 6 patients achieving stable disease.[341] The response rates reported for 42 patients treated with dacomitinib were 2% CR, 26% PR, with a disease control rate of 86%.[343] The ORR for 39 patients treated with erlotinib was 10%, with a disease control rate of 71%.[344] Efficacy data for chemotherapeutic agents are not much better. In a systemic review of 60 patients with metastatic CSCC treated with cisplatin, the CR was reported to be 2%, with an ORR of 45% and median DFS of 14.6 months.[329] Data supporting carboplatin utility are even more limited, with most studies examining carboplatin combinations and not carboplatin monotherapy.[322,339]

Follow-Up

It has been well-established that 13-50% of these patients will develop another SCC within 5 years.[347-349] This represents at least a 10-fold increase in risk compared to the general population.[348,349] Patients with a prior SCC are also at increased risk of developing cutaneous melanoma and BCC, and patients with multiple prior SCCs are at even higher risk.[88,348] Therefore, continued long-term surveillance of these patients is essential, as is patient education about sun protection and regular self-examination of the skin. Additionally, 70-80% of cutaneous SCC recurrences develop within 2 years of the initial therapy.[10,45,81,99,102] Therefore, close follow-up of these patients during this time period is critical.

Patient education is a key component of follow-up for patients who have had cutaneous SCC. All patients should be made aware of the various resources that discuss skin cancer prevention. Patients should be educated in strict sun protection and taught how to perform a comprehensive self-examination of the skin. For those who had regional SCC, training in self-examination of lymph nodes is also recommended.

Patients should also be monitored with regular physical exams including complete skin and regional lymph node examination. The frequency of follow-up should be adjusted based on risk (Refer to *SCC-6 Follow-up* in the Algorithm). For following disease, the imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is often sufficient to diagnose local recurrence, but MRI can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or other imaging modalities can be employed for confirmation and to gauge extent of disease. In certain patients at high risk for multiple primary tumors, increased surveillance and consideration of prophylactic measures may be indicated.

Superficial Therapies for SCC *In Situ*

Given the limited penetration beyond the epidermis and lower cure rates than with surgical techniques, superficial therapies should be reserved for those patients with SCC in situ.[350-353] The NCCN Panel's experience indicates that they may be effective for anatomically challenging locations, and recurrences are often small and manageable. Recommended superficial therapies include topical fluorouracil (5-FU), topical imiquimod, photodynamic therapy (PDT), and cryotherapy.

Retrospective studies, meta-analyses, and a small open-label phase II trial have shown that imiquimod was effective for treating patients with SCC in situ, with high rates of initial clearance (70%–100%) and low rates of recurrence.[354-358] One small double-blind randomized trial showed that imiquimod led to the resolution of 73% of lesions compared to 0% with vehicle control ($P < .001$).[359] Clearance rates with 5-FU tend to be lower than those for topical imiquimod and vary widely, ranging from 27% to 92%.[355,358,360-362] Toxicities are similar between imiquimod and 5-FU, being primarily inflammatory skin reactions such as severe eczematous reactions, ulceration, and erosions.[355,361,362]

PDT with photosensitizing agents including methyl aminolevulinate (MAL) and 5-aminolevulinic acid (ALA) is another option for superficial SCC. MAL is no longer produced in the United States. For SCC in situ, rates of initial complete clearance following PDT range between 52% and 98%.[361,363-374] Durable complete response rates range from 48% to 89%.[361-366,368-372,374,375] It has been shown that differences in PDT techniques can cause significant differences in clearance rate for SCC in situ.[364,372] Furthermore, results from randomized trials showed fewer treatments required for complete clearance and higher durable complete response rates with PDT versus cryotherapy.[362,376] Compared to 5-FU, PDT was also associated with higher rates of initial complete clearance and higher durable complete response rates.[361,362] Data suggest that 5-FU may be associated with

lower risk of adverse events compared with PDT or cryotherapy, but it is unclear whether risk of toxicity differs between cryotherapy and PDT.[361,362,376]

Cryotherapy has been used for many years as a fast and cost-effective means for removal of SCCs. Prospective and retrospective studies, including large meta-analyses, have shown recurrence rates of 0% to 4% for invasive SCCs treated with cryotherapy.[45,377-380] For SCC in situ, recurrence rates range from 1% to 13% in retrospective studies[230,351,352,380] and 0% to 50% in prospective studies.[350,362,376,379,381] One prospective study reported that patients were much more likely to experience pain with cryotherapy compared with C&E, and time to complete healing was also significantly longer with cryotherapy.[350] Cryotherapy may also be associated with poorer cosmetic outcomes compared with topical 5-FU.[362]

Management of Patients at High Risk of Developing Multiple SCCs

Treatment of Precancers in High-risk Patients

AKs are a premalignant skin condition that should be treated at first development, particularly in patients with diffuse AKs and/or field cancerization, as these patients are at high risk of developing multiple primary CSCCs.[382] Cryotherapy has been used to treat AK for many decades, despite lack of prospective randomized trials comparing them with non-treatment. In more recent years, large prospective randomized trials in patients with AKs (N > 100) have shown that each of the following therapies provides better complete clearance rates compared with placebo: topical 5-FU with or without calcipotriol,[383-388] topical imiquimod,[389-392], topical tirbanibulin,[393] and PDT.[394-402]

Prospective randomized trials have reported pair-wise comparisons of the above treatments, but results are not consistent. These comparisons include PDT versus cryotherapy,[394,396,399,403-405] imiquimod,[406,407] 5-FU,[408-410] or ingenol mebutate;[411-413] cryotherapy versus 5-FU or imiquimod;[414-416] and 5-FU versus imiquimod[417] or ingenol mebutate.[418,419] Meta-analyses of randomized trials have attempted to determine an order of preference for these treatments.[420-423] The NCCN panel currently assigns a preference for 5-FU based on data from a randomized trial which reported the cumulative probability of remaining free from treatment failure was significantly higher for 5-FU (74.7%) than imiquimod (53.9%), MAL-PDT (37.7%), or ingenol mebutate (28.9%).[424] The longest duration for CSCC prophylaxis has been demonstrated with the combination of 5-FU and calcipotriol.[388] It was demonstrated that more participants who received topical calcipotriol plus 5-FU for AK remained disease-free over the > 1,500-day period compared to those receiving petroleum jelly-based skin product plus 5-FU.[425] Moreover, significantly fewer participants in the test cohort developed CSCC on the treated face and scalp within 3 years (7% vs. 28% in control group, hazard ratio 0.215, $P = 0.032$).[425]

Topical tirbanibulin was added to the list of recommended treatment for AK based on results from two identically designed double-blind phase III trials in which patients received either tirbanibulin or vehicle ointment for the treatment of AKs on the face or scalp. In both trials, complete clearance by day 57 occurred in significantly more patients in the tirbanibulin group compared to the vehicle group (trial 1: 44% versus 5%, P<0.001; trial 2: 54% versus 13%, P<0.001).[393]

The utility of topical diclofenac is less clear, as efficacy results vary across large randomized trials, with some studies reporting no significant difference between diclofenac/hyaluronan and hyaluronan alone.[387,426-428] Diclofenac/hyaluronan has also been shown to be inferior to MAL-PDT and to 5-FU for the treatment of AKs.[429,430] The Panel therefore assigns category 2B for diclofenac in this setting.

Fewer high-quality data are available regarding the efficacy and safety of other treatments that are sometimes used and may be considered for treating AKs: chemical peels (trichloroacetic acid) and ablative skin resurfacing (eg, dermabrasion, laser).[431-438] These studies have all confirmed that chemical peel or laser resurfacing significantly reduced AKs, although in some studies they were less effective than PDT or 5-FU. The use of chemical peels and ablative skin resurfacing varies widely across NCCN institutions.

AKs that have an atypical clinical appearance or do not respond to appropriate therapy should be biopsied for histologic evaluation. AK on the lip, known as actinic cheilitis, may require a different approach. Prospective studies on the treatment of actinic cheilitis are limited. Therapies tested include surgical vermilionectomy, lip shave, electrodessication, laser vermilion ablation, laser resurfacing, 5-FU, laser + 5-FU, trichloroacetic acid (TCA) chemical peel, PDT, PDT + imiquimod, and diclofenac.[439-450] The NCCN panel considers ablative laser vermilionectomy to be of value for treating some cases of extensive actinic cheilitis.

Treatment of SCC in High-Risk Patients

For individuals who rapidly develop multiple CSCC lesions, destructive techniques such as C&E and cryotherapy may be employed. Some NCCN panel members use a combination of shave excision to remove the bulk of the tumor and ensure sufficient material for pathology, and then destructive techniques for margin control. The details of the techniques used to remove CSCC lesions in high-risk patients with multiple lesions vary widely between NCCN Member Institutions and between practitioners at these institutions, and there is no standard language for describing these methods. Compared to the low-risk population, RT is used more frequently as an adjuvant therapy in high-risk patients and for PNI.[451] Satellite lesions and in-transit cutaneous metastases may occur more frequently and are more likely to progress in this population.[452,453]

One strategy for cases of life-threatening skin cancer or rapid development of multiple tumors in organ transplant recipients is dose reduction of immunosuppressive therapy and/or the use of mTOR inhibitors. Analyses of large populations of organ transplant patients have found that the incidence of new skin cancers is linked to the duration and dose of immunosuppression.[454-456] Prospective randomized trials have shown that switching from other immunosuppressants to mTOR inhibitors reduces the risk of developing new CSCC lesions, particularly in patients with a history of one or more CSCCs.[457-465] In the case where surgery is impractical due to high CSCC burden, oral capecitabine has been suggested in the transplantation setting, although toxicity is a concern.[466]

Prevention in High-Risk Patients

Treatment of precancers at first development can help prevent the development of subsequent invasive tumors. Prophylactic treatment may

be needed for patients with a history of multiple lesions and/or extensive diffuse AK or field cancerization. Oral retinol and synthetic retinoids (eg, acitretin[467], isotretinoin, etretinate) have been tested in prospective studies in patients at high risk for multiple AKs or SCCs, including transplant recipients,[468-473] patients with xeroderma pigmentosa,[474] or with psoriasis and PUVA (psoralen plus UV-A) exposure.[475] By comparison with placebo or with SCC incidence during treatment-free periods, data from these studies support that oral retinol and oral retinoids significantly reduce the incidence of new CSCCs in patients at very high risk for multiple lesions.[469-472,474,475] Outside of these very-high-risk groups, the effectiveness of retinol/retinoid therapy for prophylaxis is less clear.[476-478] Side effects may be significant and include mucocutaneous, such as cheilitis, excessive peeling of the skin, and hair disorders,[473] but musculoskeletal, vascular, hepatic triglyceride, and neurologic adverse events have also been reported.[472,474,477,479] In addition, these agents are teratogenic and must be used with extreme caution in women of child-bearing age.[480-482]

The NCCN guidelines do *not* recommend topical retinoids as prophylactic treatment for patients at high risk for multiple AKs or CSCCs. Results of a large randomized trial in patients with a history of ≥2 BCCs/SCCs showed that prophylactic topical tretinoin (0.1%) did not reduce the development of new cutaneous BCCs or SCCs compared with vehicle control.[483] A double-blind randomized study showed that topical tazarotene had a chemo-preventative effect in only 6% of patients with basal cell nevus syndrome, a condition associated with frequent development of primary BCCs.[484]

Results from a recent randomized controlled study suggest that prophylactic nicotinamide may be effective at preventing the development of CSCC recurrence or metastases in patients at high risk.[485] Nicotinamide was associated with a 30% reduction in the 12-month rate of new SCCs (P = 0.05), and a 20% reduction in development of new BCCs (P = 0.12) compared to placebo. During the subsequent 6 months off treatment, there was a trend toward increased rates of new SCCs for the nicotinamide arm compared with placebo (59% relative difference; P = .07). Although there are currently no clinical trial data directly comparing nicotinamide with oral retinoids for CSCC prophylaxis, nicotinamide has a much better safety profile. Further clinical research is needed to determine whether nicotinamide provides long-term clinical benefit for patients at risk of developing multiple NMSCs and AK lesions.

Patient Education for High-Risk Patients

Patient education is especially important for those at high risk for CSCC progression or recurrence. Treatment delay is associated with larger tumor size, larger defect size from surgical removal, and more Mohs layers taken to obtain clear margins.[130,486-489] Significant prognostic factors for patient delay in seeking care include serious comorbidity, low education level, non-recognition of the seriousness of symptoms, and SCC arising on pre-existing chronic lesions.[490,491] Low education level is also associated with large NMSC tumor area at presentation.[492] Educational interventions and physician advice have been shown to increase the likelihood of patients undergoing a complete skin exam, and patients with more knowledge of skin cancer are more likely to get regular complete skin exams.[282,493,494]

Patient education should begin, in the case of organ transplant recipients, at transplantation and in the case of xeroderma pigmentosum, at birth or diagnosis. Education should include discussion of individual risk assessment and the need for stringent sun avoidance and protection methods. Regular sunscreen use can significantly reduce the rate of development of new AKs and CSCCs, and increases remission rates of AKs.[495-498] Knowledge of more than one method for UV protection is associated with higher rates of using some form of protection,[499] as is awareness of susceptibility/risk and overall education level.[500,501]

Having a prior NMSC has proved to be insufficient motivation for altering patient behavior regarding UV protection and avoidance. Although those with prior NMSC are more likely to use sunscreen and to avoid sun exposure, adoption of preventative measures was low: only 54% used sunscreen, and 20% to 45% used other avoidance/protective methods.[502] Another cross-sectional study showed that tanning bed use was similar among those with and without prior NMSC.[503]

Randomized trials have shown that educational interventions can effect significant changes in use of solar protection in outdoor workers and transplant patients.[494,504-509] While both extensive and repetitive education improve patient knowledge, repetitive education is needed to effect long-term change in patient behavior.[510] This is especially important for transplant patients, as preoccupation with other medical concerns may make them unreceptive to skin cancer education.[511] For transplant patients, an intervention including text messaging reminders was shown to be more effective at improving patient knowledge and changing sun protective behaviors compared with more traditional approaches.[512]

Monthly self-examination is recommended, and should include all skin surfaces and LNs. Patients should be taught the proper method for systematic self-examination of the skin and lymph nodes. A randomized controlled trial has shown that educational intervention increased the frequency and sensitivity of self-examination of the skin among transplant patients.[513] In addition to more frequent and thorough self-examination, follow-up schedules for patients at high risk should be titrated to the frequency of tumor development, and in rare cases may be as frequently as weekly.

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