National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Squamous Cell Skin Cancer

Version 1.2021 — February 5, 2021

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Continue

NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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Continue

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NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

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.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

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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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2021 of the NCCN Guidelines for Squamous Cell Skin Cancer from Version 1.2020 include:

SCC-1
- **Clinical Presentation**
  - ▸ Workup; Sub-bullet under H&P revised: Regional lymph node exam ~~as clinically indicated.~~
  - ▸ Diagnosis; column edited: *Cutaneous* squamous cell ~~skin~~ cancer *(CSCC)* confirmed.
  - ▸ Risk Status; second category for local edited: High risk/*Very high risk.*
  - ▸ Footnote g content removed: Any high-risk factor places the patient in the high-risk category. (**Also page SCC-3**)
  - ▸ Footnotes updated to include new page headings. (**Also pages SCC-2, SCC-3, SCC-4 and SCC-6**)

SCC-2
- **Local, low-risk CSCC**
  - ▸ **Primary Treatment**
    - ◊ Bullet under Curettage and electrodesiccation (C&E): ~~If adipose reached,~~ *If tumor appears to be not confined to skin (penetrates beyond the skin),* surgical excision should generally be performed.
    - ◊ Positive margins, the pathway was revised: Mohs micrographic surgery *(MMS)* or ~~resection with~~ *other forms of* CCPDMA...
  - ▸ Footnote k revised by adding: **See Principles of CCPDMA Technique (SCC-G).**

SCC-3
- Header revised: Local high-risk ~~squamous cell skin cancer (if patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate)~~/*very-high-risk* CSCC
  - ▸ **Primary Treatment**
    - ◊ First option revised: MMS or ~~resection with~~ *other forms of* CCPDMA *(preferred for very high risk)*.
    - ◊ Standard excision, positive margins pathway was revised: MMS or ~~resection with~~ *other forms of* CCPDMA, if feasible.
  - ▸ Footnote m content added: If patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate. (**Also page SCC-4**)
  - ▸ Footnote o added: In patients with very-high-risk CSCC and normal exam of nodal basin, discuss and consider radiologic imaging of nodal basin.
  - ▸ Footnote p added: Discuss and consider sentinel lymph node biopsy (SLNB) for patients with 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 w added: For tumors in cheeks, forehead, scalp, neck, and pretibia that are <6 mm 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).**

Continued

UPDATES

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2021 of the NCCN Guidelines for Squamous Cell Skin Cancer from Version 1.2020 include:

SCC-4
- **Clinical Staging and Preoperative Assessment**
  - ▸ First column, parenthetical content moved to footnote m: If patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate.
  - ▸ Primary Treatment, surgical evaluation pathway was revised: Inoperable *or not fully resectable* disease.
  - ▸ Change to biopsy recommendation: ...open lymph node ~~biopsy~~ *excision.*
  - ▸ Footnote y revised: ~~Based on clinical findings, brain MRI with contrast.~~ *MRI of the brain may be considered to rule out subclinical cortical involvement in cases with bone invasion.*
  - ▸ Footnote cc added: 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.

SCC-5
- **Regional Lymph Nodes**
  - ▸ First pathway revised to include patients with Solitary ~~node ≤3 cm~~ *or multiple ipsilateral nodes.*
    - ◊ Treatment recommendation revised as follows*:* Excision of primary tumor and ipsilateral ~~selective~~ neck dissection as indicated.
  - ▸ Removed pathway for Solitary node >3 cm, or multiple ipsilateral nodes.
    - ◊ Treatment recommendation removed: Excision of primary tumor and ipsilateral comprehensive neck dissection as indicated.
  - ▸ Pathway for patients with Bilateral nodes was revised: Excision of primary tumor and ~~comprehensive~~ bilateral neck dissection as indicated.
- Pathologic findings; Any node with ECE pathway was revised: RT and consider concurrent systemic therapy ~~within the context of a clinical trial~~.

SCC-6
- Follow-up: recommendations is this column were significantly revised.
- Footnote hh 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 CT imaging can be employed for confirmation and to gauge extent of disease.

SCC-A
- **Principles of Pathology**
  - ▸ The Principles were significantly revised.

SCC-B
- *Stratification to Determine Treatment Options and Follow-up for Local CSCC Based on* Risk Factors for Local Recurrence, ~~or~~ Metastases, *or Death From Disease*
  - ▸ This page was significantly revised.

UPDATES

Updates in Version 1.2021 of the NCCN Guidelines for Squamous Cell Skin Cancer from Version 1.2020 include:

SCC-C
- **Header revised: Identification and Management of** ~~High Risk~~ **Patients** *at High Risk for Multiple Primary CSCCs*
  - ‣ **After Definition, the following was revised***:* ~~Xeroderma pigmentosum~~ *Genetic syndromes predisposing to CSCC formation.*
  - ‣ **Footnote a added: 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.**
  - ‣ **Follow up, bullet revised: Follow-up schedules should be titrated to the frequency of tumor development.**~~, and in rare cases may be as frequently as weekly.~~
  - ‣ **Patient education, fourth bullet revised: Monthly self examination of all skin surfaces is recommended.** *If a patient has* ~~with~~ **a history of invasive skin cancer, self examination of the lymph nodes should be taught and performed.**
  - ‣ **Prevention, second bullet revised: Use of nicotinamide may be effective in reducing the development of CSCCs.** *Therapeutic effects disappear shortly after cessation of the drug.*

SCC-E
- **General Principles**
  - ‣ **Fifth bullet revised: There are insufficient long-term efficacy and safety data to support the routine use of** *radioisotope or* **electronic surface brachytherapy.**
  - ‣ **Bullet removed: Radioisotope brachytherapy could be considered in highly selected cases.**

SCC-F
- **Principles of Systemic Therapy for Squamous Cell Skin Cancer**
  - ‣ **Significant changes made to this page.**

SCC-G
- **Principles of CCPDMA Technique was added to the Guidelines.**

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL PRESENTATION	WORKUP	DIAGNOSIS	RISK STATUS

Lesion suspicious for skin cancer[a]

→

- **H&P**
  - ‣ Complete skin exam
  - ‣ Regional lymph node exam
- **Biopsy:**[b]
  - ‣ If more than superficial lesion, inclusion of deep reticular dermis preferred[c]
- **Imaging studies of area of interest as indicated for suspicion of extensive disease**[d,e]

→

Cutaneous squamous cell cancer (CSCC) confirmed[f]

Local
- Low risk[c] → See Primary Treatment (SCC-2)
- High risk/Very high risk[c] → See Primary Treatment (SCC-3)

Clinically or radiographically concerning regional lymph nodes → See Clinical Staging and Preoperative Assessment (SCC-4)

or

Distant metastatic disease → See Regional recurrence or distant metastases (SCC-6)

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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. 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).
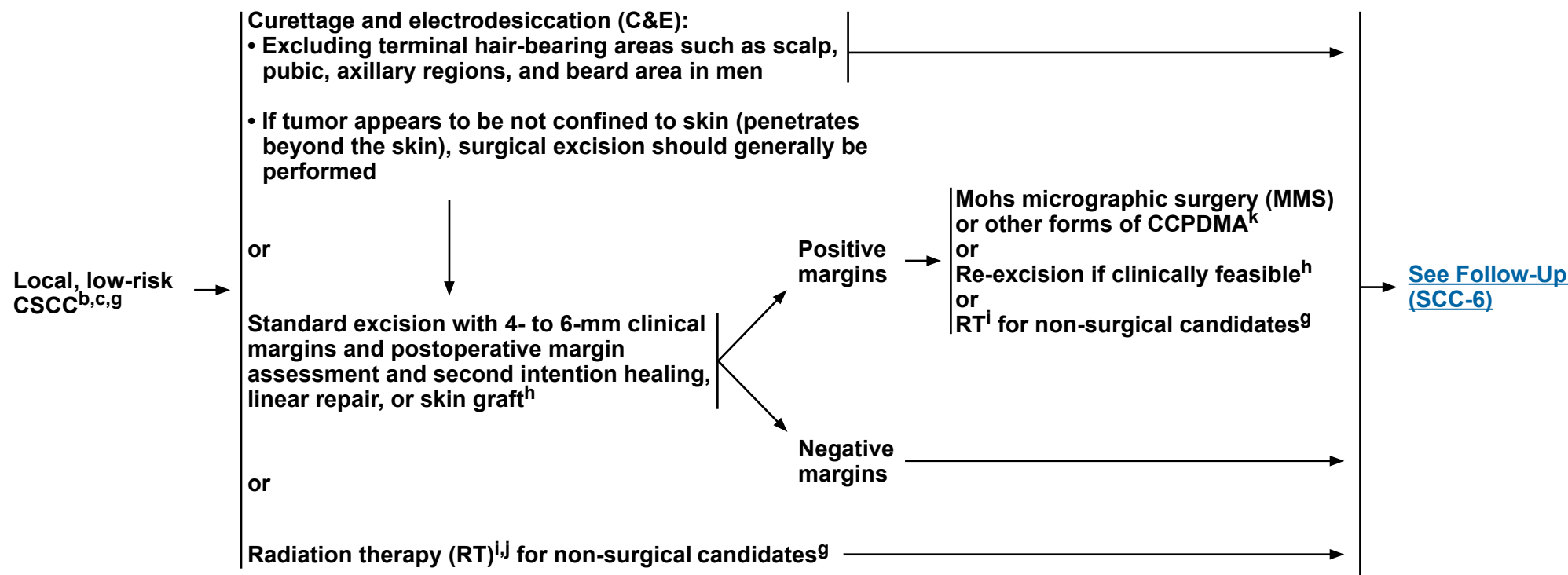
[f] Including CSCC in situ (showing full-thickness epidermal atypia, excluding actinic keratoses).

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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.

PRIMARY TREATMENT[g]

Local, low-risk CSCC[b,c,g] →

Curettage and electrodesiccation (C&E):
• **Excluding terminal hair-bearing areas such as scalp, pubic, axillary regions, and beard area in men**

• **If tumor appears to be not confined to skin (penetrates beyond the skin), surgical excision should generally be performed**

or

Standard excision with 4- to 6-mm clinical margins and postoperative margin assessment and second intention healing, linear repair, or skin graft[h]

or

Radiation therapy (RT)[i,j] for non-surgical candidates[g] —————→ **See Follow-Up (SCC-6)**

Positive margins → **Mohs micrographic surgery (MMS) or other forms of CCPDMA[k] or Re-excision if clinically feasible[h] or RT[i] for non-surgical candidates[g]** → **See Follow-Up (SCC-6)**

Negative margins ————→ **See Follow-Up (SCC-6)**

[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).
[g] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-D).
[h] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[i] See Principles of Radiation Therapy for Squamous Cell Skin Cancer (SCC-E).
[j] RT is often reserved for patients older than 60 years because of concerns about long-term sequelae.
[k] Excision with complete circumferential peripheral and deep margin assessment (CCPDMA) with permanent section analysis or intraoperative frozen section analysis is an alternative to MMS. See Principles of CCPDMA Technique (SCC-G).
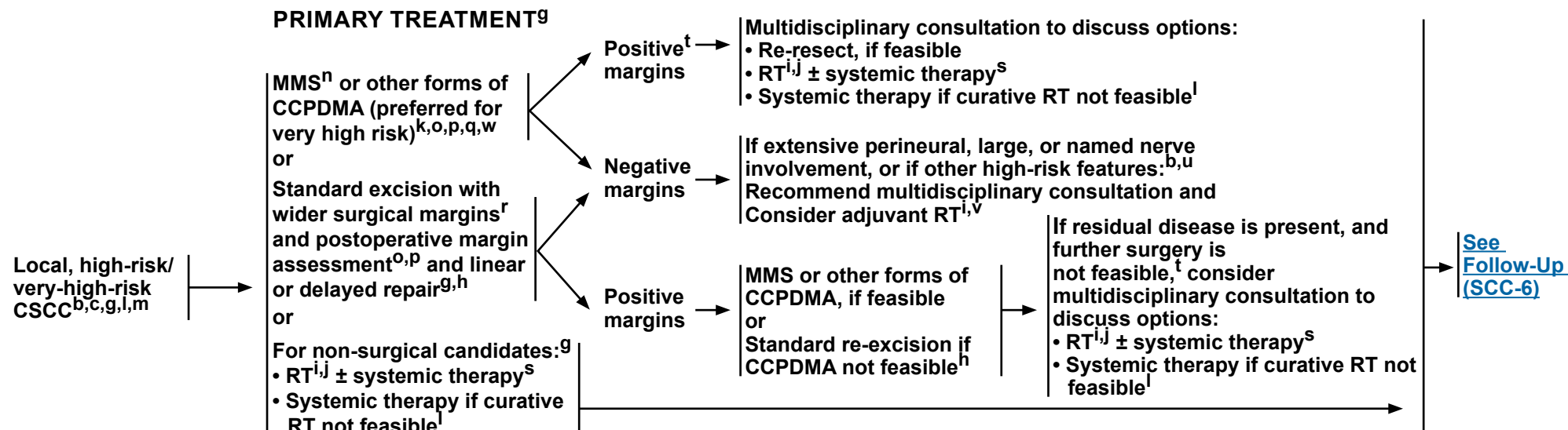
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PRIMARY TREATMENT[g]

Local, high-risk/very-high-risk CSCC[b,c,g,l,m] →

MMS[n] or other forms of CCPDMA (preferred for very high risk)[k,o,p,q,w]
or
Standard excision with wider surgical margins[r] and postoperative margin assessment[o,p] and linear or delayed repair[g,h]
or
For non-surgical candidates:[g]
• **RT[i,j] ± systemic therapy[s]**
• **Systemic therapy if curative RT not feasible[l]**

Positive[t] margins →
Multidisciplinary consultation to discuss options:
• **Re-resect, if feasible**
• **RT[i,j] ± systemic therapy[s]**
• **Systemic therapy if curative RT not feasible[l]**

Negative margins →
If extensive perineural, large, or named nerve involvement, or if other high-risk features:[b,u] Recommend multidisciplinary consultation and Consider adjuvant RT[i,v]

Positive margins →
MMS or other forms of CCPDMA, if feasible
or
Standard re-excision if CCPDMA not feasible[h]

If residual disease is present, and further surgery is not feasible,[t] consider multidisciplinary consultation to discuss options:
• **RT[i,j] ± systemic therapy[s]**
• **Systemic therapy if curative RT not feasible[l]**

→ See Follow-Up (SCC-6)

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[b] See Principles of Pathology (SCC-A).
[c] See Stratification to Determine Treatment Options and Follow-up for Local CSCC Based on Risk Factors for Local Recurrence, Metastases, or Death from Disease (SCC-B) and Identification and Management of Patients at High Risk for Multiple Primary CSCCs (SCC-C).
[g] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-D).
[h] Closures like adjacent tissue transfers, in which significant tissue rearrangement occurs, are best performed after clear margins are verified.
[i] See Principles of Radiation Therapy for Squamous Cell Skin Cancer (SCC-E).
[j] RT is often reserved for patients older than 60 years of age because of concerns about long-term sequelae.
[k] Excision with CCPDMA with permanent section analysis or intraoperative frozen section analysis is an alternative to MMS. See Principles of CCPDMA Technique (SCC-G).
[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 (cemiplimab-rwlc or clinical trial). See Principles of Systemic Therapy (SCC-F).
[m] If patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate.
[n] When MMS 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.
[o] In patients with very-high-risk CSCC and normal exam of nodal basin, discuss and consider radiologic imaging of nodal basin.

[p] Discuss and consider sentinel lymph node biopsy (SLNB) for patients with 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).
[q] If invasion to parotid fascia, superficial parotidectomy is indicated.
[r] 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.
[s] RT may be supplemented by systemic therapy in select patients. See Principles of Systemic Therapy (SCC-F).
[t] Negative margins unachievable by MMS or more extensive surgical procedures.
[u] Large nerve involvement is defined by AJCC 8th edition for CSCC of the head and neck as ≥0.1 mm; most nerves deep to the dermis are >0.1 mm.
[v] The outcome benefit of adjuvant RT following resection of any CSCC with negative surgical margins is uncertain.
[w] For tumors in cheeks, forehead, scalp, neck, and pretibia that are <6 mm 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).

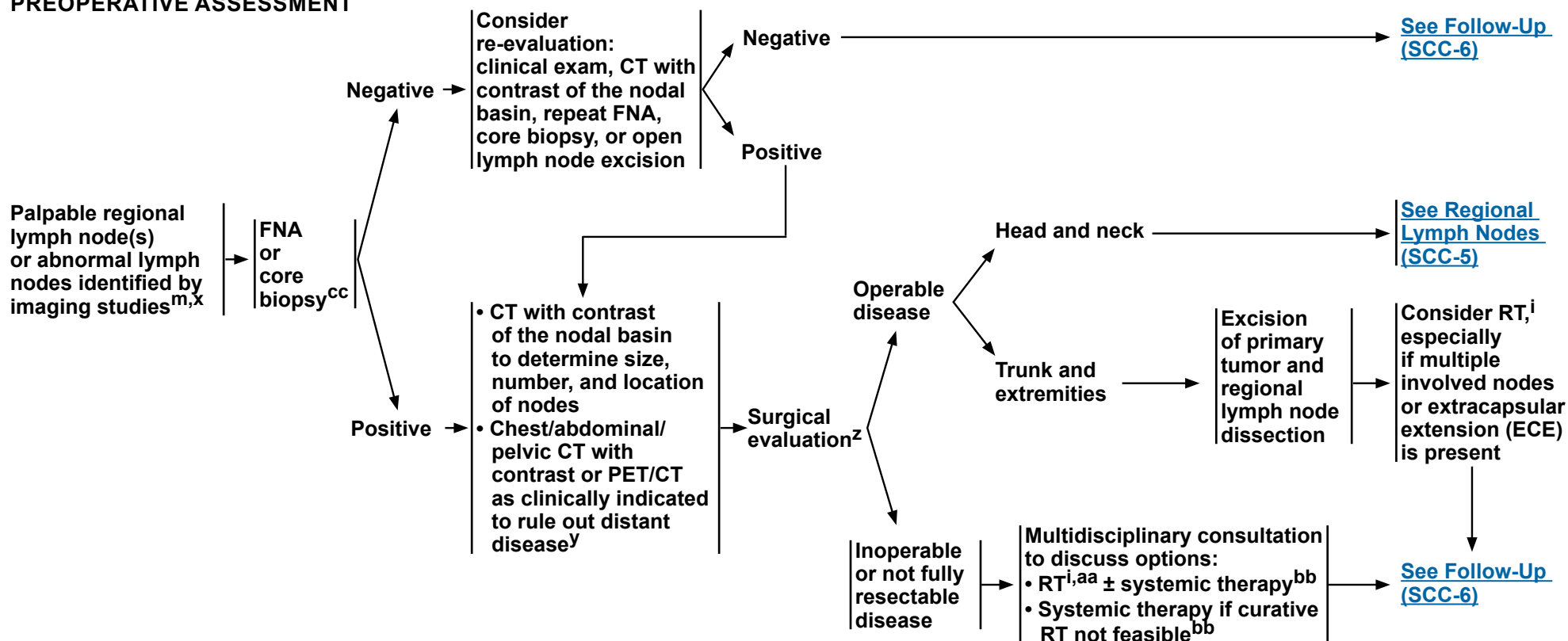**Note: All recommendations are category 2A unless otherwise indicated.**
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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

CLINICAL STAGING AND PREOPERATIVE ASSESSMENT

PRIMARY TREATMENT[g]

Palpable regional lymph node(s) or abnormal lymph nodes identified by imaging studies[m,x] →

FNA or core biopsy[cc]

Negative →
Consider re-evaluation: clinical exam, CT with contrast of the nodal basin, repeat FNA, core biopsy, or open lymph node excision

→ **Negative** → See Follow-Up (SCC-6)

→ **Positive** →

Positive →
- CT with contrast of the nodal basin to determine size, number, and location of nodes
- Chest/abdominal/pelvic CT with contrast or PET/CT as clinically indicated to rule out distant disease[y]

→ **Surgical evaluation[z]**

→ **Operable disease** →
- **Head and neck** → See Regional Lymph Nodes (SCC-5)
- **Trunk and extremities** → **Excision of primary tumor and regional lymph node dissection** → **Consider RT,[i] especially if multiple involved nodes or extracapsular extension (ECE) is present** → See Follow-Up (SCC-6)

→ **Inoperable or not fully resectable disease** → **Multidisciplinary consultation to discuss options:**
- RT[i,aa] ± systemic therapy[bb]
- Systemic therapy if curative RT not feasible[bb]
→ See Follow-Up (SCC-6)

[g] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-D).
[i] See Principles of Radiation Therapy for Squamous Cell Skin Cancer (SCC-E).
[m] If patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate.
[x] See Identification and Management of Patients at High Risk for Multiple Primary CSCCs (SCC-C).
[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. SBRT may also be considered in select patients.
[bb] See Principles of Systemic Therapy (SCC-F).
[cc] 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.
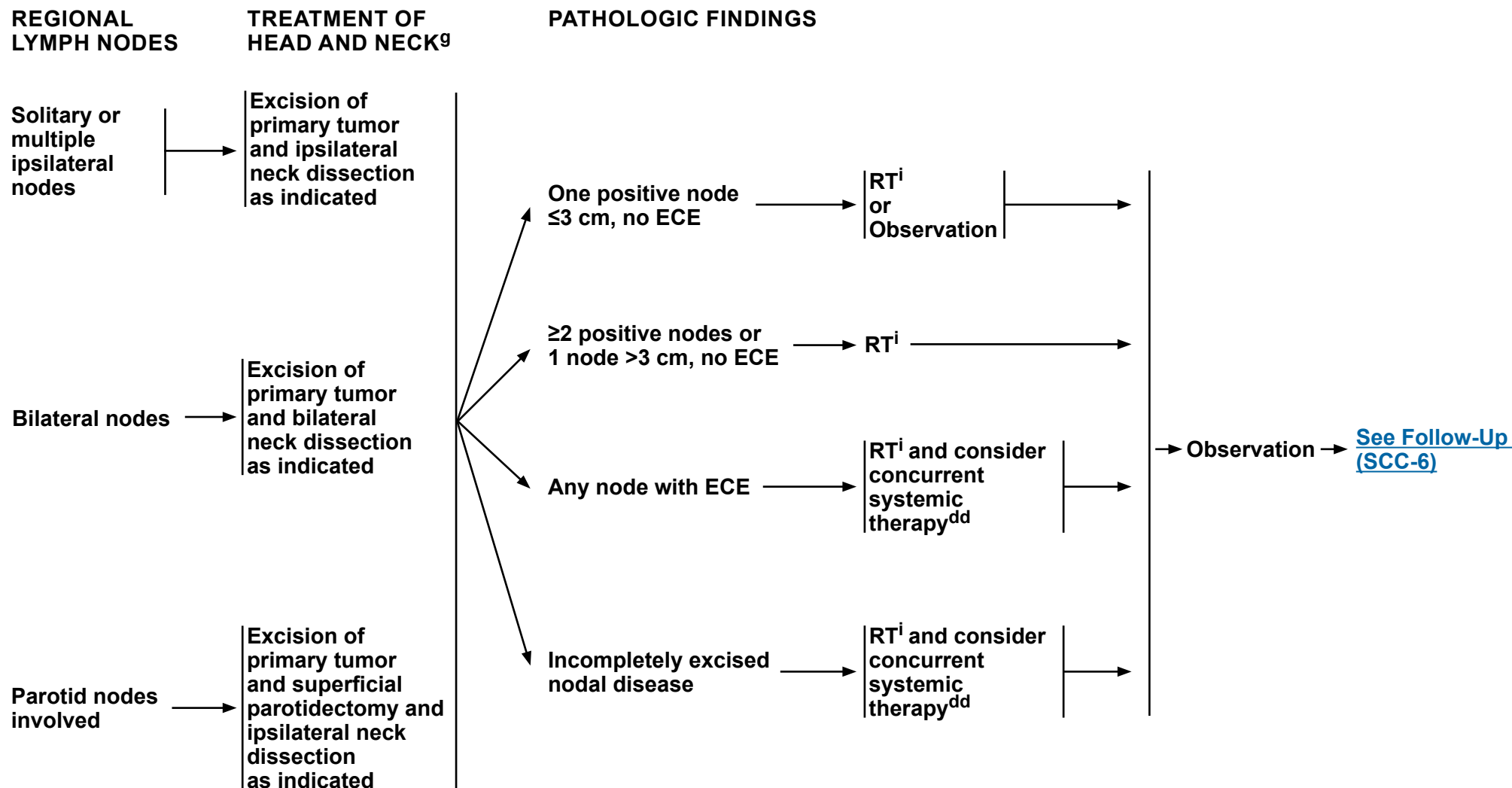
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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

REGIONAL LYMPH NODES	TREATMENT OF HEAD AND NECK[g]	PATHOLOGIC FINDINGS

Solitary or multiple ipsilateral nodes → Excision of primary tumor and ipsilateral neck dissection as indicated

Bilateral nodes → Excision of primary tumor and bilateral neck dissection as indicated

Parotid nodes involved → Excision of primary tumor and superficial parotidectomy and ipsilateral neck dissection as indicated

One positive node ≤3 cm, no ECE → RT[i] or Observation

≥2 positive nodes or 1 node >3 cm, no ECE → RT[i]

Any node with ECE → RT[i] and consider concurrent systemic therapy[dd]

Incompletely excised nodal disease → RT[i] and consider concurrent systemic therapy[dd]

→ Observation → See Follow-Up (SCC-6)

[g] See Principles of Treatment for Squamous Cell Skin Cancer (SCC-D).
[i] See Principles of Radiation Therapy for Squamous Cell Skin Cancer (SCC-E).
[dd] Multidisciplinary consultation recommended. See Principles of Systemic Therapy (SCC-F).

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FOLLOW-UP

Local disease:

- **H&P**[ee,ff]
  - ▸ **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**[hh]
- **Patient education**
  - ▸ **Sun protection**
  - ▸ **Self examination of skin**

Regional disease:

- **H&P**[ee,ff,gg]
  - ▸ **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**[gg,hh]
- **Patient education**
  - ▸ **Sun protection**
  - ▸ **Self examination of skin and lymph nodes**
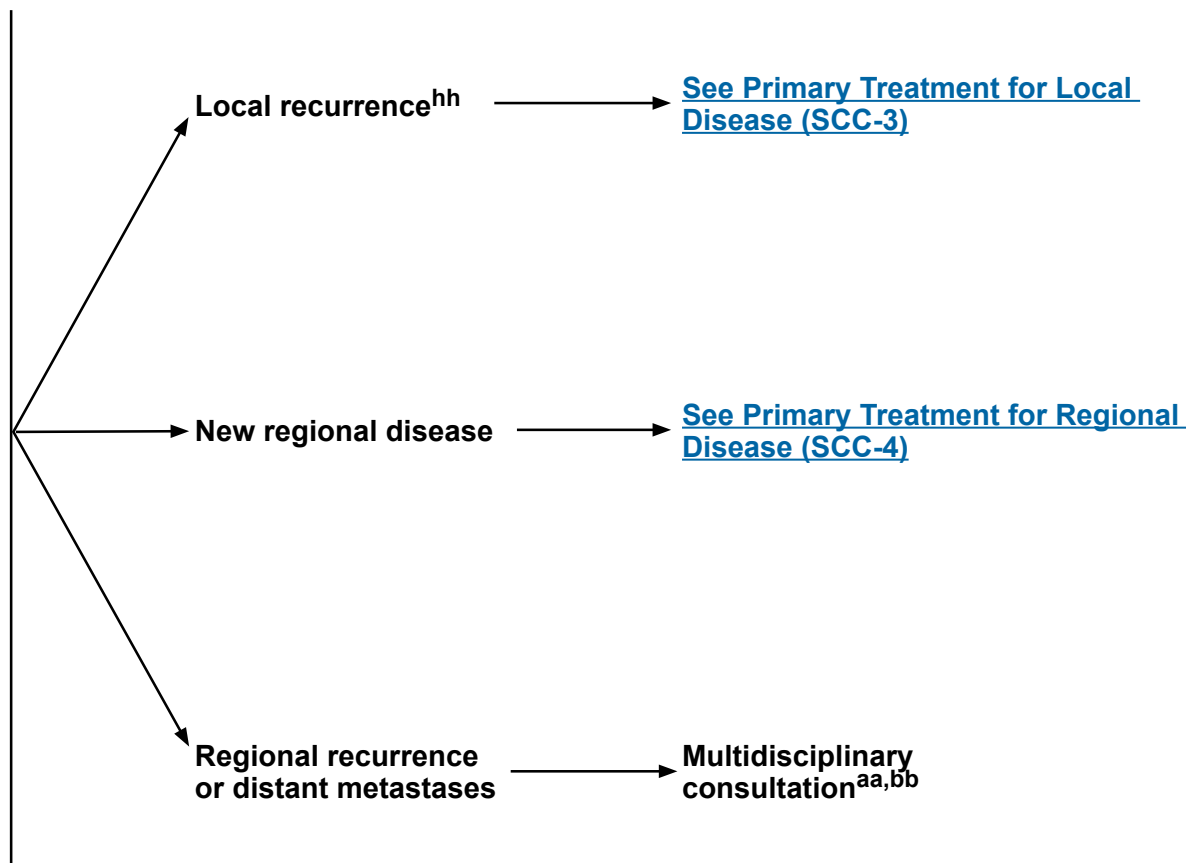
Local recurrence[hh] → **See Primary Treatment for Local Disease (SCC-3)**

New regional disease → **See Primary Treatment for Regional Disease (SCC-4)**

Regional recurrence or distant metastases → **Multidisciplinary consultation**[aa,bb]

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[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).

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

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

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

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

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

[hh] 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 imaging can be employed for confirmation and to gauge extent of disease.

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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 micrographic 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 AJCC tumor staging.[1,2]
• Immunohistochemistry may be utilized as needed to help identify lymphovascular or nerve invasion, or to identify single or few-cell tumor foci.

Recommended Elements for Pathology Reporting of Excisional Specimens (including Mohs micrographic 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.

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> 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.

NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

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

[1] Risk stratification 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 AJCC 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 MMS/CCPDMA 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, drug-induced, HIV)
  ‣ Genetic syndromes predisposing to CSCC formation[a]
- 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.

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[a] 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)
- Actinic keratoses should be treated at first development.
  ‣ Accepted treatment modalities include cryotherapy, topical 5-fluorouracil (5-FU) with or without calcipotriol (calcipotriene), topical imiquimod, topical ingenol mebutate, 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 secondary approaches.
- 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.

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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, 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.

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NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF TREATMENT FOR SQUAMOUS CELL SKIN CANCER

- **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's 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 MMS 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.**

- **Use of nicotinamide may be effective in reducing the development of CSCCs.**

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SCC-D

PRINCIPLES OF RADIATION THERAPY FOR SQUAMOUS CELL SKIN CANCER

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 in 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.
- There are insufficient long-term efficacy and safety data to support the routine use of radioisotope or electronic surface brachytherapy.

General Treatment Information

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

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SCC-E

PRINCIPLES OF SYSTEMIC THERAPY FOR SQUAMOUS CELL SKIN CANCER

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

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 inoperable or incompletely resected regional disease, multidisciplinary consultation 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[2]

Table 2: Options for Systemic Therapy Alone		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**

• Cemiplimab-rwlc[3,4] (if curative RT not feasible[1] for locally advanced or metastatic)
• Pembrolizumab[3,4] (if curative RT not feasible[1] for recurrence or metastases)
• 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]

[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] Recently published phase I–II trial data have shown high response rates (approximately 50%) to cemiplimab-rwlc in patients with locally advanced or metastatic CSCC. Emerging phase II data show approximately 34% response to pembrolizumab in patients with metastatic and/or locally recurrent unresectable cutaneous squamous cell carcinoma. Preliminary data and the clinical experience of NCCN Panel members suggest that other anti–PD-1 inhibitors may also be effective in this setting.
[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.

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PRINCIPLES OF CCPDMA TECHNIQUE

- Complete circumferential peripheral and deep margin assessment (CCPDMA), 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]

- A surgical procedure can be described as CCPDMA 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.

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[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 CCPDMA TECHNIQUE

- **Visualization of the entire marginal surface of an irregular surgical specimen may be challenging, but is critical to the success of CCPDMA 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 CCPDMA.**
- **CCPDMA 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 CCPDMA; 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 CCPDMA 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

Tubingen torte technique

OR

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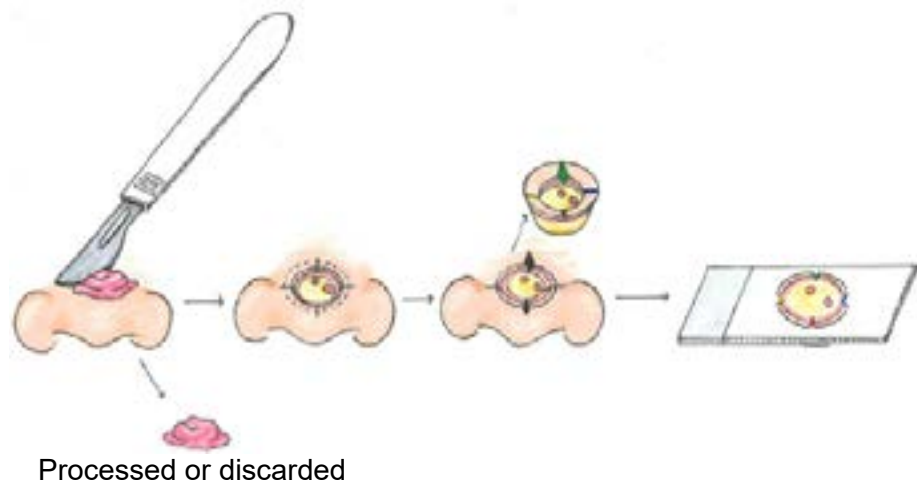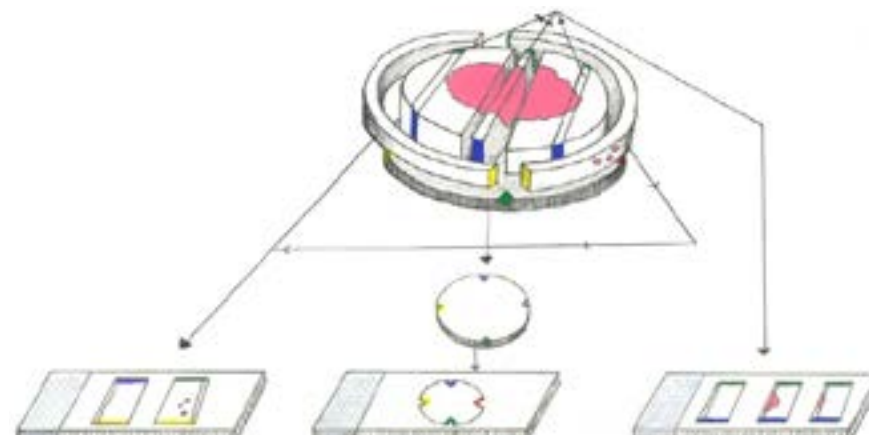
[2] Leigheb M, Zavattaro E, Bellinzona F, Furlan G, Leigheb G. Micrographic surgery (Tubingen torte technique) for the treatment of an invasive dermatofibrosarcoma protuberans with muscular involvement. G Ital Dermatol Venereol 2010;145:309-311.

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PRINCIPLES OF CCPDMA TECHNIQUE

- **Published examples of CCPDMA include:**
  ‣ **MMS[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 CCPDMA:**
  ‣ **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 CCPDMA.**

CCPDMA 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 CCPDMA. If any of the above are marked No, the procedure does not achieve CCPDMA.

[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]

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.

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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]

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.

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NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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.

Discussion

This discussion corresponds to the NCCN Guidelines for Squamous Cell Skin Cancer. Last updated October 5, 2017.

Table of Contents

Overview

Basal cell and squamous cell skin cancers, collectively known as non-melanoma skin cancers (NMSCs) or keratinocyte carcinomas, are more prevalent than all other cancers combined.[1] It is estimated that over 5 million keratinocyte carcinoma cases were treated in the United States in 2012, with roughly half of those cases being cutaneous squamous cell carcinomas (cSCCs).[2] Squamous cell carcinoma (SCC) is the second most common skin cancer.[3-9] Numerous population-based studies have demonstrated that the incidence of cSCC is rising rapidly.[2,3,10-16] Some studies show that cSCC incidence rates are rising more rapidly than basal cell carcinoma (BCC), reducing the difference in incidence between these two skin cancers.[4,5,8,9,13] Although rarely metastatic, cSCC can produce substantial local destruction along with disfigurement and may involve extensive areas of soft tissue, cartilage, and bone. cSCCs generally have a good prognosis, with 5-year survival ≥90%.[3,17,18]

A number of risk factors are associated with development of cSCC. 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 cSCC.[6,15,19-26] Due to the link with chronic sun exposure, cSCC rates are higher in occupations involving outdoor work.[20,27-30] As a result of cumulative sun exposure, the risk of cSCC increases with age, particularly in sun-exposed sites.[4,12-15,25]

Indoor tanning is also significantly associated with cSCC. According to a large meta-analysis, including 80,661 participants, any exposure to indoor tanning increases the risk of cSCC by 67%.[31] A meta-analysis based on a total of 406,696 individuals showed that the prevalence of indoor tanning is much higher than previously thought, with 35% of adults in the United States having some exposure to indoor tanning (95% CI, 27%–44%), and 13% using indoor tanning in the past year (95% CI, 11%–16%).

Prevalence of indoor tanning was even higher among university students, with 59% having some exposure (95% CI, 42%–77%), and 43% (95% CI, 22%–65%) having used indoor tanning in the past year.[32]

Individuals with fair skin, hair, and eye color who have received too much sun exposure are at the greatest risk for cSCC due to susceptibility to oncogenic UV damage in genes associated with pigmentation.[19-21,23,26,33,34] Most of these tumors develop on sun-exposed skin sites, especially the head and neck area.[9,12,14,15,35]

cSCCs are also known to develop in association with scars or chronic wounds (Marjolin's ulcer).[36-39] SCC is the most common type of malignancy developing in chronic scars or chronic ulcers.[36,40-47] SCC lesions arising in scars or chronic wounds tend to have poor prognosis and are difficult to treat (ie, have higher risk of recurrence after treatment).[48-54]

Actinic keratoses are sun-induced precancerous lesions, while Bowen's disease refers to cSCC in situ. Both lesions, if left untreated, can progress to invasive cSCC with the potential for metastasis.[29,55-64]

Certain genetic syndromes greatly predispose affected individuals to cSCC formation, such as albinism (in which skin pigment is absent)[44,65-72] and xeroderma pigmentosum (in which defects exist in UV light-induced unscheduled DNA repair).[73-79]

Certain settings of immunosuppression (most notably organ transplantation, lymphoma, chronic lymphocytic leukemia, drug-induced immunosuppression, and HIV) also predispose affected individuals to cSCC.[80-96] Analyses of transplant registries have reported a 5-fold to 113-fold increase in incidence of cSCC in transplant recipients compared to the general population.[82,83,93,97]

Clinical Presentation and Workup

On clinical presentation of the patient with a suspicious lesion, workup for cSCC begins with a history and physical examination, with an emphasis on a complete skin and regional lymph node 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.[12,16,29,98-107] 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.[108,109] 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. The workup for cSCC is also recommended for cSCC in situ showing full-thickness epidermal atypia, excluding actinic keratoses. Although basosquamous carcinoma may behave as aggressively as cSCC, it is a subtype of BCC and should be treated as such.[110-113]

Imaging studies of the area of interest should be done when extensive disease is suspected, such as bone or deep soft tissue involvement, and perineural, lymphatic, or vascular invasion, as it may alter treatment selection.[114,115] Because of its higher sensitivity, MRI with contrast is preferred over CT with contrast if perineural disease or deep soft tissue involvement is suspected.[116-118] Although rare, skin cancers may present with the appearance of deep extension, for example, into bone or the orbit. In such cases, preoperative imaging studies may be useful to help assess the extent of soft tissue or bony involvement. If bone disease is expected, CT with contrast is preferred unless contraindicated.

The presence of a palpable regional lymph node or abnormal lymph nodes identified by imaging studies should prompt a fine-needle aspiration (FNA) or core biopsy of suspicious node(s) and further workup for clinical staging and preoperative assessment (see *Regional Lymph Node Involvement in SCC*).

Risk Stratification

After workup, a risk assessment of the primary tumor should be performed to determine the treatment plan and follow-up for patients. For localized disease, the NCCN panel examined risk factors for cSCC associated with recurrence and metastasis. These are listed in table format in the algorithm (See *Risk Factors for Local Recurrence or Metastases* in the algorithm). If any high-risk feature is present, the patient should be managed according to the high-risk treatment pathway for local cSCC.

The AJCC 7th edition staging system for cSCC reflects many but not all of the features that the NCCN panel has incorporated to designate local high-risk primary tumors (T2 vs. T1).[119,120] Alternative staging systems have been proposed to more accurately define high-risk groups among patients with clinically localized disease,[17,121,122] and have been independently tested.[107,123-125] These studies and other emerging data[126-128] have led to significant revisions to criteria for determining T-stage in the recently published AJCC 8th edition staging system of cSCC.[129]

Risk Factors for SCC Local Recurrence or Metastasis

Location and Size
Anatomic location has been known to be a risk factor for cSCC recurrence and metastasis for many years.[48,126,130,131] In general, cSCCs that develop in the head and neck area are more likely to recur than those developing on the trunk and extremities. SCCs that develop on the genitalia, mucosal surfaces, and ears are also at greater risk of metastasizing.[17,48,125,131,132]

The concept of a so-called high-risk "mask area of the face" dates back at least to 1983.[133,134]

For cSCC tumors with diameter less than 2 cm, risk stratification by location and size is largely based on extrapolation from older data in BCC.[135,136] This 27-year retrospective review of 5755 BCCs showed that high-risk sites correspond roughly to the mask areas of the face, and that recurrences after standard excision or curettage and electrodesiccation (C&E) were significantly more common when tumors in high-risk locations were 6 mm or more in diameter and when tumors in moderate-risk locations were 10 mm or more in diameter. Therefore, for the purpose of determining which tumors should be removed with Mohs micrographic surgery (MMS) or excision with complete circumferential peripheral and deep margin assessment (CCPDMA) rather than standard excision or C&E, the NCCN panel has defined the following as high risk: 1) tumors in area L (low-risk region) that are ≥20 mm; 2) tumors in area M (moderate-risk region) that are ≥10 mm; and 3) tumors in area H (high-risk region) of any size. Areas L, M, and H are defined in detail in the algorithm under *Risk Factors for Local Recurrence or Metastases*. Similar cutoffs are recommended in the appropriate use criteria (AUC) for MMS from the American Academy of Dermatology (AAD) in collaboration with the American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and American Society for Mohs Surgery.[137]

Size also has been shown to be a risk factor for cSCC metastasis.[48,49,126,138-140] Although various different divisions have been used, the most recent and robust data support that tumors >2 cm are at higher risk of metastasis and poorer disease-specific survival.[17,48-50,121,122,125,126,141,142]

Primary Versus Recurrent Disease
The higher risk of recurrence and metastasis for recurrent versus primary disease has been extensively documented in the literature.[48,51,141,143,144]

Immunosuppression
In addition to increasing the risk of cSCC development, immunosuppression has been shown to be associated with poorer outcomes in large meta-analyses,[48,125] and prospective[126] and retrospective studies.[121,145-155] Each of these studies showed that immunosuppression was associated with at least one measure of poor outcome (recurrence, metastasis, or death), but results are inconsistent regarding which of these outcomes are effected. These studies cover a broad range of extent of disease and treatment approaches, suggesting that immunosuppression is associated with poor prognosis regardless of treatment approach used or the stage of disease at time of treatment.

A few studies from the organ transplant literature have evaluated other risk factors that might be linked to the higher rates of SCC recurrence and metastasis among transplant patients.[124,154,156,157] A retrospective review of 307 patients with cSCC confirmed that those who received organ transplants had more aggressive disease than those who did not, and that SCCs in transplant patients were more likely to have deep tissue spread and perineural and lymphatic invasion at presentation.[154] Other retrospective 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 versus non-transplant patients.[156,158] Two other 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.[124,157] The presence of multiple primaries has been shown to be associated with development of high-grade disease;[107] however, uncertainty remains whether the increased rate of SCC metastasis in transplant patients is simply because of a greater number of tumors per patient or reflects more aggressive tumor behavior at the biological level. Because organ transplant recipients have collectively worse outcomes, these patients and their neoplasms are designated as high risk.

MS-4

Site of Prior Radiotherapy or Chronic Inflammatory Process

Tumors developing in sites of prior radiotherapy refer to primary cSCCs arising in areas previously irradiated for unrelated conditions. (All recurrent tumors, irrespective of prior therapy, are defined as high risk, for reasons described above.) Data from older studies and one more recent study support that prior radiotherapy for unrelated (frequently benign) conditions is a risk factor for NMSC recurrence or metastasis.[52,141,159]

Retrospective studies and meta-analyses have documented increased rates of metastasis for cSCC arising in the setting of chronic scarring or inflammation.[48,49,51,144,160-162]

Neurologic Symptoms

In tumors with perineural involvement, clinical symptoms suggesting possible involvement of sensory or motor nerves may occur in up to 40% of cases. Symptoms may include pain, burning, stinging, anesthesia, paresthesia, facial paralysis, diplopia, and blurred vision.[163,164] Any suggestion of neurologic involvement in the region of a cSCC should place that tumor in a high-risk category, as perineural invasion (PNI) is associated with recurrence, metastasis, and poor outcomes.[17,48,121,125,131,138,141,162,165-167] As discussed below, the presence of neurologic symptoms is associated with poorer survival, and recurrence-free survival correlates with the extent of neuronal involvement.[121,168-172]

Pathologic Risk Factors for SCC

Degree of Differentiation

In their extensive meta-analysis of risk factors for local recurrence and metastasis of cSCC, Rowe and colleagues found that patients with well-differentiated tumors fared significantly better than those patients with poorly differentiated lesions.[48] Another cohort study of 315 patients also associated differentiation grade with overall survival.[162] Eroglu and colleagues reported differentiation to be a significant risk factor of recurrence in an analysis of 1039 patients.[49] Many other studies, including

some very large retrospective studies (n > 1000) provide supporting evidence that poor differentiation is correlated with cSCC recurrence, metastasis, disease-specific survival, and overall survival.[17,121,122,125,131,140,141,143,144,173-175] Although Broders originally divided cSCC histologically into four groups or grades in 1920, the modern trend has been to reduce the divisions to two groups: 1) well or moderately differentiated; and 2) poorly differentiated.[120,122] The NCCN panel has adopted this modern approach in this guideline.[120,122]

Histology

The histologic subtypes of acantholytic (adenoid), adenosquamous (or mucin-producing), and metaplastic (carcinosarcomatous) SCC are rare histologic subtypes.[176] Only case reports and case series document the outcomes of patients with these subtypes, and thus their prognostic significance is debated.[177-184] However, because 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 high-risk histologic feature reported in the literature is the presence of desmoplasia. In studies from Germany, desmoplastic cSCC was shown to pose a greatly increased risk of both recurrence and metastasis.[126,185] 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).[139] The significance of desmoplasia as a risk factor was confirmed by multivariable analysis. A more recent review of 72 patients with desmoplastic SCC reported a high rate of recurrence of 80%.[186]

Although the risk of metastasis from SCC in situ (full-thickness atypia) is negligible, the risk of recurrence, as with the superficial form of BCC, depends on the presence or absence of any of the risk factors listed in the algorithm.

MS-5

Depth

Data from many large studies support that risk of recurrence and metastasis increases with increasing lesion depth.[17,48,121,122,125,139-143,187] cSCC lesion depth can be quantified as thickness in mm or by anatomic layer(s) invaded. A standard Breslow measurement per the College of American Pathologists (CAP) 2013 protocol would be the distance from the deepest point of tumor invasion to the granular layer or base of ulcer if present,[188] excluding parakeratosis or scale crust.

Brantsch and colleagues[126] prospectively examined potential risk factors for metastasis and local recurrence of cSCC in 615 patients over a 20-year period. With a median follow-up of 43 months, metastasis occurred in 0% of tumors 2.0 mm in thickness, 4% of tumors 2.1 mm to 6.0 mm in thickness, and 16% of tumors thicker than 6.0 mm. Thicker lesions also had a higher risk of local recurrence. A large retrospective analysis and a very large meta-analysis (n = 17,248) provide data supporting that risk of recurrence and metastasis is significantly higher for lesions with thickness >2 mm.[125,140,142] Meta-analyses have shown that 4-mm and 6-mm thickness cutoffs are also prognostic for recurrence and metastasis,[48,125] and one retrospective study showed by multivariate analysis that risk for recurrence and metastasis increases significantly for every 1-mm increase in tumor depth.[127]

Retrospective studies and meta-analyses support that anatomic level of invasion is significantly correlated with cSCC recurrence and metastasis. 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.[48,139] Other studies have shown that lesions with invasion into the subcutaneous fat significantly increases rates of recurrence and metastasis.[17,121,122,125,141,142]

Both tumor thickness and anatomic level of invasion have been included in the T classification of the AJCC 7th and 8th Edition staging for cSCC.[120,129]

NCCN has chosen to include both thickness and Clark level in the guidelines, and recommends that tumors ≥2 mm thick or Clark level IV-V 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

Perineural involvement is uncommon in any NMSC (2%–6%), but develops more frequently and is more aggressive in cSCC versus BCC.[170,171,189-192] cSCC with perineural involvement poses a greatly increased risk 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 (mucin producing), desmoplastic, and metaplastic (carcinosarcomatous) subtypes.[17,48,121,125,131,138,141,162,165-167,186,193-196] In a prospective cohort study of 315 patients with cSCC of the head and neck, Kyrgidis and colleagues identified perineural involvement as a factor associated with lower overall survival and recurrence-free survival.[162] Even among patients with other risk factors, PNI is an independent risk factor for lymph node metastasis, as demonstrated by multivariate analysis of a prospective study of high-risk patients.[167] 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.[116,117,164,171,172,197] SCC involving unnamed small nerves (<0.1 mm in caliber) may have a low risk of poor outcomes in the absence of other risk factors.[122,128]

Lymphatic or Vascular Involvement

Two prospective studies of patients with local or regional cSCC have shown significant association between lymphovascular invasion (LVI) and lymph node metastasis.[144,167] Retrospective studies corroborate this finding and also show that LVI is prognostic for parotid involvement.[166,194]

One retrospective study of 114 patients with cSCC and PNI or neurotropism showed by multivariate analysis that in this high-risk population LVI was significantly associated with disease-specific death and all-cause death.[128] The presence of LVI from the primary tumor is important to note, especially in patients with other risk factors, and should increase the suspicion of subclinical nodal disease.

Patients at High Risk of Developing Multiple SCCs

Certain patient groups are at high risk of developing multiple squamous cell skin cancers and tumors that can behave aggressively. These include individuals with an immunocompromised status, such as solid organ transplant recipients, or patients with lymphoma, chronic lymphocytic leukemia, drug-induced immunosuppression, or HIV.[48,107,121,125,126,145-155,198,199] Patients with rare genetic disorders such as albinism or xeroderma pigmentosum are at high risk of developing multiple cSCCs.[73-79,200] Within these high-risk groups, individual high-risk patients should be identified for closer follow-up. See *Management of Patients at High Risk of Developing Multiple SCCs* for a discussion of NCCN recommendations on treatment of precancers, treatment of cSCC, prevention of cSCC, and education for patients with high risk of multiple cSCCs.

Local Treatment for SCC

The primary goals of treatment of squamous cell skin cancer 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. Localized cSCC, (ie, without clinically or radiographically concerning regional lymph nodes) is most commonly treated with surgery. Traditional techniques such as C&E are mostly supported by older studies, and data from prospective trials with long-term follow-up are limited. Although surgical approaches often offer the most effective and efficient means for accomplishing cure, consideration of function, cosmetic

outcome, and patient preference may lead to the choice of radiation therapy (RT) as primary treatment in order to achieve optimal overall results.

Curettage and Electrodesiccation

C&E is the process of alternately scraping away tumor tissue with a curette down to a firm layer of normal dermis and denaturing the area by electrodessication. Up to 3 cycles may be performed in a session. Although a fast and cost-effective technique for superficial lesions, it does not allow histologic margin assessment. Retrospective and observational data with long-term follow-up (>5 y) indicate that cure rates are between 95% and 96% for patients with primary cSCC lesions treated with C&E.[48,201,202] 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.[203,204]

The NCCN panel considers this technique effective for properly selected, low-risk tumors 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. Because subcutaneous adipose is even softer than tumor tissue, the ability of the curette to

distinguish, and therefore to selectively and completely remove tumor cells, disappears.

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.

Excision with Postoperative Margin Assessment

A common therapeutic option for cSCC is standard surgical excision followed by postoperative pathologic evaluation of margins. This technique has been reported to achieve 5-year disease-free rates of 91% or higher for cSCC.[48,187] Retrospective analyses and prospective observational studies of patients who received surgical excision of non-metastatic primary cSCC have reported rates of recurrence or metastasis ranging from 0% and 14%, with most studies reporting rates of 6% or lower.[48,142,173,175,187,202,205-211] Distant metastasis was rarely observed, and rates of regional metastasis (lymph node involvement), when reported separately from local recurrence, were highly variable across studies, ranging from 0% to 13%.[173,175,187,205,208,211] Variability in reported recurrence and metastasis rates could be due to differences in margin size, percent of patients with clear margins, length of follow-up, and the prevalence of risk factors (patient and lesion characteristics) in the populations sampled. One large meta-analysis found that post-excision recurrence rates were lower for primary tumors versus local recurrences, both for analyses with follow-up less than 5 years (5.7% vs. 17.3%) and those with longer follow-up (8.1% vs. 23.3%).[48]

The clinical margins chosen by the panel for low-risk tumors are based on the work of Brodland and colleagues using MMS to determine the width of clinical margin needed to achieve histologically clear margins in primary cSCCs (n = 141).[212] 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. 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. Other retrospective analyses of cSCCs removed with MMS have reported the subclinical extension or the margin size or number of stages needed for complete histologic clearance.[213-216] Results from these studies further support that larger excision margins are needed as tumor diameter increases and when other risk factors are present (eg, poor differentiation, high-risk location, PNI).[213-215] Compared with primary tumors, recurrent tumors have larger subclinical extension and require more Mohs stages for complete removal.[215,216] Extensive subclinical spread was found in 14% to 15% of primary cSCCs and 23% to 50% of recurrent cSCCs.[215,216]

Results from retrospective and observational analyses of cSCCs removed by standard excision indicate that factors significantly associated with incomplete excision include lesion location, thickness, PNI, and invasion into the deep fascia.[205,208,217-224] Although results vary between studies, some of these analyses have suggested additional factors associated with incomplete excision: recurrent tumors (vs. primary), re-excision of residual primary (vs. initial excision of primary lesions), and tumor differentiation.[175,218,221,224] Mohs studies have shown that subclinical extension is more likely and more extensive in recurrent compared with primary cSCCs.[216] A few studies have indicated that incomplete excision rates vary between surgeons.[219,224]

As noted below, excision with comprehensive intraoperative margin control is the preferred surgical technique for high-risk cSCC. However, if

standard excision with postoperative margin assessment is used for treatment of a high-risk tumor due to patient-related clinical circumstances or other variables, wider surgical margins than those recommended for low-risk lesions must be taken and increased recurrence rates should be expected. 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.

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.[175,187,206,225-227] Re-excision with postoperative margin assessment is therefore among the recommended treatment options for positive margins after excision of low-risk primary cSCC.

If lesions can be excised with the recommended margins, then linear closure, skin grafting, or secondary intention healing (ie, closures that do not rotate tissue around and/or alter anatomy where residual "seeds" of tumor may remain) are all appropriate reconstructive approaches. However, if tissue rearrangement or skin graft placement is necessary to close the defect, the NCCN panel believes intraoperative surgical margin assessment is necessary before closure.

Mohs Micrographic Surgery or Excision with Complete Circumferential Peripheral and Deep Margin Assessment (CCPDMA)

MMS is the preferred surgical technique for high-risk cSCC because it allows intraoperative analysis of 100% of the excision margin. Retrospective analyses report cure rates of 96% for patients with primary cSCCs and 77% for recurrent cSCCs treated with MMS.[228] 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 MMS.[48] Results from this meta-analysis found that cure rates for MMS depended on tumor diameter (<2 vs. ≥2 cm: 98.1% vs. 74.8%) and differentiation (well vs poorly differentiated: 97.0% vs. 67.4%), but for each of these subgroups cure rates for MMS were higher than for treatment with non-Mohs modalities.[48] Local recurrence rates based on long-term follow-up (≥5 years) were better for MMS compared with surgical excision, both for primary lesions (3.1% vs. 8.1%) and for recurrent lesions (10% vs. 23%).[48] Retrospective and prospective observational studies of localized primary cSCCs treated with MMS have reported local recurrence rates of 1.4% to 4.1% and rates of metastases between 0% and 6.3%.[209,214,216,228-232] Compared with primary tumors, rates of local recurrence or metastasis after MMS are higher for recurrent tumors (previously treated with a non-Mohs modality).[141,216] For recurrent cSCCs treated with MMS, subsequent local recurrences occurred in 5.9% to 7.7%; metastasis in 0% to 10%.[209,214,216,228-231] Other risk factors associated with recurrence after MMS include larger subclinical extension and more levels required for clearance.[216] Risk factors associated with metastasis after MMS include: size (>2 cm), Clark's level, differentiation, location in areas of prior radiation, small tumor nests and infiltrative tumor strands, single-cell infiltration, PNI, and acantholysis.[141]

It is not uncommon to find discrepancies between pathology results from preoperative biopsy or initial debulking compared with frozen sections taken during MMS.[233-235] When MMS 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.

Excision with CCPDMA using permanent section analysis or intraoperative frozen section (IOFS) analysis is acceptable as an alternative to MMS provided that it includes a complete assessment of all deep and peripheral margins. Retrospective studies and one prospective study have reported low recurrence rates (0%–1%) for cSCC cases where histologically clear margins are achieved using this method.[236] It is important to note, however, that truly histologically negative margins are not necessarily achieved by IOFS alone, without CCPDMA. Both prospective and retrospective studies have reported that for cSCC tumors with negative margins upon frozen section analysis, permanent paraffin section analysis indicates positive margins in 10% to 20%.[234,235,237-239] One study showed that discrepancies between results from frozen versus permanent section analysis were due to unrepresentative sampling of the margins, and reported a much higher recurrence rate for IOFS cases in which permanent section showed positive margins.[239] The descriptive term CCPDMA underscores the panel's belief that complete assessment of all tissue margins is the key to optimal tumor removal for high-risk tumors.

Sentinel Lymph Node Biopsy

Sentinel lymph node biopsy (SLNB) has been used to try to identify patients with cSCC who may be candidates for completion lymph node dissection or adjuvant RT. Prospective observational, retrospective and meta-analyses have reported that among patients with high-risk non-anogenital cSCC who underwent successful SLNB, sub-clinical nodal metastases were identified in 7% to 21%, with most studies reporting rates between 12% to 17%.[123,166,167,240-247] Variability in rates of sentinel lymph node (SLN) positivity is likely due to small sample size of these studies (N < 200), and differences in the type and number of high-risk factors represented in patient populations selected for SLNB. 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, angiolymphatic invasion,

PNI, and the presence of multiple high-risk factors.[166,167,245] Most of these studies excluded patients with anogenital SCC, but one study reported subclinical nodal metastases in 24% of 585 patients with anogenital SCC who received successful SLNB.[240]

Several studies reported that among patients with localized SCC and negative SLNB results, nodal metastases were later detected in 2% to 7% of patients.[123,166,167,240,242-244,246-248] In addition to false negatives, in some studies there were patients with a negative SLNB who developed local recurrences or metastases outside of the previously biopsied LN basin, such that the overall rate of recurrence/metastases ranged from 7% to 12%.[167,240,242]

For most cSCC studies comparing outcomes for patients with a negative versus positive SLN, results show that despite receiving completion lymph node dissection, patients with a positive SLN had higher rates of postoperative recurrence/metastases, ranging from 33% to 45%.[166,167,242,245] Patients with a positive SLN were also more likely to die from SCC, and two studies (1 prospective, 1 retrospective) showed significantly lower 3-year disease-specific survival rate compared with SLN-negative patients.[167,240,245] Although these findings support that SLNB may have prognostic value, they also underscore that despite interventions for SLN-positive patients, it is unclear whether SLNB followed by completion lymph node dissection or adjuvant RT will improve patient outcomes. The criteria for selecting patients for SLNB are also unclear.

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 disease without lymph node involvement. A large meta-

analysis reported 5-year recurrence rates of 6.7% and 10% after RT of primary and recurrent SCC, respectively.[48] Subsequent retrospective analyses on smaller samples of patients with primary cSCCs treated with first-line RT (37–233 patients) have reported a large range of recurrence rates, from 2.8% to 30%, the latter for patients with locally advanced disease (size >2 cm or deeply invasive).[249-254] The larger studies (n > 50) that include a cross-section of patients with primary lesions (range of sizes and T-stage) report 5-year cure rates after RT between 90% and 93% and 5-year recurrence rates between 4% and 7%.[251,253-255] The risk of recurrence appears to increase with increasing lesion size and T-stage.[252,254,256] 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.[251,254]

Radiation is an effective treatment option for selected patients with SCC in situ who have large or multiple lesions and those who refuse surgery.[257] 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%.[253,254,258-262]

Adjuvant Radiation

The value of adjuvant RT is widely debated due to lack of prospective randomized clinical trial data. For local SCC (ie, without lymph node involvement), the NCCN panel recommends adjuvant radiotherapy for any SCC that shows evidence of extensive perineural or large nerve involvement. Adjuvant RT is also a recommended option if tissue margins are positive after definitive surgery. Data supporting these recommendations are limited to retrospective studies with heterogenous populations. In retrospective studies that included patients with SCC and PNI treated with MMS/surgery plus adjuvant RT, the results reported are for pooled populations that included patients treated with other modalities (eg, surgery/MMS alone, RT alone, chemotherapy), patients with other

types of skin cancer (BCC and metatypical BCC), patients with lymph node metastases, and a mix of patients with primary and recurrent skin lesions, with and without positive margins.[168,169,195,263,264] These studies suggest that postoperative RT for patients with PNI may improve local control and disease-free survival, but there is likely no survival benefit.

Radiotherapy Safety

RT is often reserved for patients older than 60 years because of concerns about long-term sequelae, including secondary malignancies.[159,256,259,265-276] Large cohort and population-based studies (n > 1000) have shown by multivariate analysis 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.[271-273,275] 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.

Radiotherapy can result in poor cosmetic outcomes, including telangiectasia, changes in skin pigmentation, and fibrosis. More serious long-term complications include non-healing ulcers; soft tissue, cartilage, bone, or brain necrosis; decreased sensation; and cataracts (for lesions in the periorbital region).[254,256,259,261,268-270] For SCC in situ, a few studies have reported that RT treatment can result in non-healing ulcers in up to 25% of lesions.[258-260]

Administration of Radiation

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[277-283]), and relatively contraindicated in patients with connective tissue diseases (eg, lupus, scleroderma).[284-287] Given

higher rates of poor cosmesis and complications with increasing cumulative radiation dose,[256,270,288] reirradiation should not be routinely utilized for recurrent disease within a prior radiation field. As described in the previous section, RT is often reserved for patients >60 years of age due to concerns about risk of RT-related subsequent malignancies. Protracted fractionation is associated with improved cosmetic results,[268,270,289-291] and should be utilized for poorly vascularized or cartilaginous areas. Retrospective studies have found that for patients with cSCC and PNI, failures tend to occur along involved nerves, suggesting that extending the radiation field along involved nerves may help reduce risk of recurrence.[169,292,293] The NCCN panel recommends that for extensive PNI, 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.

Selection of target area margins and RT modality is left to clinical judgement and based on the experience and expertise available at the treating institution. A variety of external beam options have been shown to be effective for treating cSCC and have similar cosmetic/safety results,[256,270,289,294-296] and are generally accepted as standard of care. Brachytherapy, however, is not considered a standard-of-care approach for treatment of skin cancer. There are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy, and radioisotope brachytherapy should only be considered in highly selected cases.

Superficial Therapies

Given the limited penetration beyond epidermis and lower cure rates than with surgical techniques, superficial therapies should be reserved for those patients with SCC in situ.[297-299] Recommended superficial therapies include topical fluorouracil (5-FU), topical imiquimod, photodynamic therapy (PDT), and cryotherapy.

Topical Therapies

Retrospective studies, meta-analyses, and an open-label phase II trial have shown that imiquimod was effective for treating patients with SCC in situ, with reasonably high rates of initial clearance (70%–100%) and low rates of recurrence.[300-305] One small (n = 31) double-blind randomized trial showed that imiquimod led to the resolution of 73% of lesions compared to 0% of lesions resolving with vehicle control ($P < .001$).[306] Side effects include inflammatory skin reactions, such as erythema, pruritus, and pain, and often lead to discontinuation of imiquimod before the treatment course is complete. [302,304] Discontinuation after lesion clearance has not been shown to lead to recurrence.

5-FU is another agent used topically to treat SCC in situ. Clearance rates with 5-FU tend to be lower than those for topical imiquimod, and vary widely, ranging from 27% to 93%.[302,305,307-309] Toxicities are similar to imiquimod, being primarily inflammatory skin reactions such as severe eczematous reactions, ulceration, and erosions.[302,308,309]

Cryosurgery/Cryotherapy

Cryosurgery, which destroys tumors cells by freeze-thaw cycles, 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.[48,310-313] For SCC in situ, recurrence rates after cryotherapy range from 1% to 13% in retrospective studies[258,298,299,313] and 0% to 50% in prospective studies.[297,309,312,314,315] Variability in reported recurrence rates may be due in part to patient selection, variable follow-up durations, and differences in technique and operator skill. Common adverse events associated with cryosurgery include edema/blistering, scabbing, ulceration, loss of pigment, and postoperative pain. [297,314,316] Less common adverse events include scarring and infection.[297,312,314-316] One prospective comparative study reported that patients were much

more likely to experience pain with cryotherapy compared with curettage and cautery, and time to complete healing was also significantly longer with cryotherapy.[297] A randomized controlled trial showed that cryotherapy was associated with poorer cosmetic outcomes compared with topical 5-FU for treatment of SCC in situ.[309]

Photodynamic Therapy

PDT involves the application of a photosensitizing agent on the skin followed by irradiation with a light source. Photosensitizing agents often used include methyl aminolevulinate (MAL) and 5-aminolevulinic acid (ALA). For SCC in situ, rates of initial complete clearance following PDT with ALA or MAL range between 52% and 98% according to prospective studies (n = 23–96 lesions).[308,317-328] Most of these studies report recurrences, such that durable complete response rates range from 48% to 89%.[308,309,317-320,322-326,328,329] Small randomized trials have shown that differences in PDT techniques can cause significant differences in clearance rate for SCC in situ,[318,326] which likely contributes to the broad range of rates reported in the literature. One small randomized trial showed that fewer treatments were required for complete clearance with PDT versus cryotherapy, and two randomized trials showed that durable complete response rates were higher with PDT.[309,314] Another small randomized trial in patients with SCC in situ showed that PDT was associated with higher rates of initial complete clearance compared with 5-FU, and two randomized trials showed that and durable complete response rates were higher with PDT.[308,309]

PDT is associated with itching, tingling, stinging, burning during the application of the topical agent, and mild to moderate pain during the phototreatment.[318-323,325,330,331] Other less common toxicities include severe pain, ulceration, crusting, edema, erythema, scarring, and pigmentary alterations.[320-323,325,331-333] Most of these resolve within days or weeks of treatment, but there have been reports of long-term scarring and pigmentary alterations.

Results from randomized trials in patients with SCC in situ suggest that 5-FU may be associated with lower risk of adverse events compared with PDT or cryotherapy, but due to inconsistent results across trials it is unclear whether risk of toxicity differs between cryotherapy and PDT.[308,309,314] All three treatment modalities are associated with risk of pain and various manifestations of inflammation at the treated site, including erythema, burning, crusting, stinging, itching, edema/blistering, and ulceration/erosions. All three also occasionally lead to pigmentary changes, or scarring.

Currently, PDT is being utilized at some NCCN Member Institutions for SCC in situ lesions. Although MAL is an approved photosensitizer for PDT, it is no longer produced in the United States.

Systemic Therapy for Local High-Risk SCC

Case reports and a few small studies have reported results for patients with high-risk, localized, nonmetastatic cSCC treated with chemotherapy or radiochemotherapy.[334-345] Most of these studies included patients with large, deeply invasive primary tumors that were unlikely to be cured by surgery or RT.[334,338-340,342-344] A few studies reported results from patients with operable disease who refused surgery or with residual disease after surgery.[337,341,342] Results show that some patients with locally advanced non-metastatic cSCC respond to cytotoxic therapy.[337-339,341-344] Epidermal growth factor receptor (EGFR) inhibitors such as cetuximab have also been tested in a small number of patients with nonmetastatic locally advanced disease, and responses have been reported.[346-352] In the absence of data from prospective comparative studies, however, it is unclear which systemic therapies are appropriate for localized disease in cases where surgery is not possible, especially in the context of

concomitant RT. In contrast, large randomized trials have tested systemic therapy options for head and neck mucosal SCCs. 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 recommended for mucosal SCC in the NCCN Guidelines for Head and Neck Cancers.

NCCN Recommendations for Treating Local SCC

For patients with SCC presenting with palpable or abnormal lymph nodes, please see *Regional Lymph Node Involvement in SCC*.

Low-Risk Local SCC

Primary treatment options for low-risk local SCC include: 1) C&E in areas without hair growth (ie, excluding terminal hair-bearing regions, such as the scalp, pubic and axillary regions, and beard area in men), provided that the treatment be changed to excision if the adipose tissue is reached; 2) standard excision if the lesion can be excised with 4- to 6-mm clinical margins and repaired with linear closure, secondary intention healing, or skin graft; and 3) RT for non-surgical candidates, generally limited to those older than 60 years of age because of risk of long-term toxicity.

If margins are positive after excision, patients should receive additional therapy. MMS, resection with CCPDMA with frozen or permanent section, or standard re-excision for area L regions (trunk and extremities, excluding pretibia, hands, feet, nail units, and ankle) are recommended, while radiation may be administered to non-surgical candidates.

The NCCN panel discussed the use of alternative therapies for first-line treatment in patients with SCC in situ (Bowen's disease). Although cure rates may be lower than with surgical treatment modalities, alternative therapies the panel recommends considering include 5-FU, imiquimod, PDT with porfimer sodium or ALA, or vigorous cryotherapy. Data suggest that the cure rates of these approaches may be lower compared with

surgery.[297-299] On the other hand, panelist experience indicates that they may be effective for anatomically challenging locations, and recurrences are often small and manageable.

High-Risk Local SCC

Recommended options for high-risk lesions include: 1) standard excision, using wider margins with linear or delayed repair; 2) MMS or resection with CCPDMA with frozen or permanent section; and 3) RT for non-surgical candidates.

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 SCC. Keen awareness of the subclinical extension of SCC 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. If negative margins are not achieved after standard excision, patients should undergo MMS or resection with CCPDMA, or receive RT. If residual disease is still present after second-line treatment and further surgery is contraindicated, the NCCN panel recommends a multidisciplinary consultation to consider chemoradiation or clinical trial.

Similarly, patients treated with MMS or resection with CCPDMA as first-line therapy should receive subsequent therapy if clear margins cannot be achieved. Recommended options include radiation (of primary site) and/or multidisciplinary consultation to consider chemoradiation or clinical trial. Appropriate chemotherapy agents can be found in the NCCN Guidelines for Head and Neck Cancers. If invasion into parotid fascia is discovered during MMS or resection with CCPDMA, then superficial parotidectomy is indicated.

Adjuvant RT to the primary site is recommended for patients with negative margins after surgery if there is large nerve or extensive perineural

involvement. Due to the potential for skull involvement and intracranial extension, an MRI with contrast of the area of interest should be considered if large-nerve invasion is suspected for tumors on the head and neck.

For certain high-risk SCCs, SLNB mapping may be considered. A systematic review of 692 patients with SCC reported positive sentinel nodes in 24% and 21% of anogenital and non-anogenital patients, respectively.[240] The survival benefit of and indication for SLNB remains unclear.

Management of Patients at High Risk of Developing Multiple SCCs

As described in the section entitled *Patients at High Risk of Developing Multiple cSCCs*, certain patient groups are at high risk of developing multiple squamous cell skin cancers and tumors that can behave aggressively. This section describes considerations and recommendations for management of these patients.

Treatment of Precancers in High-risk Patients

Actinic keratoses are a premalignant skin condition that should be treated at first development, particularly in patients with diffuse actinic keratoses and/or field cancerization, as these patients are at high risk of developing multiple primary cSCCs. C&E and cryotherapy have been used to treat actinic keratosis for many decades, despite lack of prospective randomized trials comparing them with placebo. In more recent years large prospective randomized trials in patients with actinic keratoses (n > 100) have shown that each of the following therapies provides better complete clearance rates compared with placebo: topical 5-FU,[353-357] topical imiquimod,[358-361] topical ingenol mebutate,[362-364] and PDT (either with ALA or MAL).[365-372] [373,374] The utility of topical diclofenac is less clear, as efficacy results vary across large randomized trials testing topical

diclofenac in hyaluronan, with some studies reporting no significant difference from hyaluronan alone.[357,375-377] Large randomized trials have also shown that diclofenac/hyaluronan is inferior to MAL-PDT and to 5-FU for the treatment of actinic keratoses.[378,379] The panel therefore assigns category 2B for diclofenac in this setting.

For the commonly used treatments known to be effective at clearing actinic keratoses (cryosurgery, PDT, 5-FU, and imiquimod), prospective randomized trials, including some intraindividual studies, have reported pair-wise comparisons, but results are not entirely consistent. For example, large randomized trials comparing PDT with cryotherapy have shown better cosmetic outcomes for PDT, but efficacy results vary across studies.[365,367,370,380-382] Other treatments directly compared in prospective randomized trials include PDT compared with imiquimod,[383,384] 5-FU,[385-387] or ingenol mebutate;[388-390] cryotherapy compared with 5-FU or imiquimod;[391-393] and 5-FU compared with imiquimod[394] or ingenol mebutate.[395,396] Meta-analyses of RCTs have attempted to determine an order of preference among the commonly used treatments for actinic keratosis. A meta-analysis of 32 prospective randomized trials reporting short-term (<1 y) rates of complete clearance (by patient) derived the following efficacy ranking: 5-FU 5% > 5-FU 0.5% > ALA-PDT ≈ imiquimod ≈ ingenol mebutate ≈ MAL-PDT > cryotherapy > diclofenac /hyaluronan > placebo.[373] Given the complexity of comparing so many treatment options, the NCCN panel considers cryotherapy, topical 5-FU, topical imiquimod, topical ingenol mebutate, PDT, and C&E to all be reasonable options for treating actinic keratosis.

Fewer high-quality data are available regarding the efficacy and safety of several other treatments that are sometimes used and may be considered for treating actinic keratoses: chemical peels (trichloroacetic acid) and ablative skin resurfacing (eg, dermabrasion, laser).[397-404] These studies have all confirmed that laser resurfacing or chemical peel significantly

reduced the quantity of actinic keratoses, 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.

Actinic keratoses that have an atypical clinical appearance or do not respond to appropriate therapy should be biopsied for histologic evaluation.

Actinic keratosis on the lip, known as actinic cheilitis, may require a different approach. Prospective studies on the treatment of actinic cheilitis are limited, and most of these studies are small and noncomparative. Therapies tested in this setting 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.[405-416] 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 that can be used to treat multiple lesions in a single visit may be preferable. Examples of appropriate destructive techniques include C&E and cryotherapy. 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. 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. In patients who develop multiple adjacent tumors in close proximity, if surgical excision of invasive disease does not include surrounding in situ disease then tissue rearrangement should be minimized so that the remaining in situ disease can be treated with secondary approaches.

Compared to the low-risk population, RT is used more frequently as an adjuvant therapy in high-risk patients and for perineural disease.[417] Satellite lesions and in-transit cutaneous metastases may occur more frequently and are more likely to progress in this population.[418,419] cSCC can progress quickly in high-risk patients with satellite or in-transit metastasis, so these patients must be treated aggressively with multidisciplinary tumor board consultation.

One feasible 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 inhibition. Multivariate 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.[420-422] Prospective randomized trials in transplant patients 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.[423-431] 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.[432]

Prevention in High-Risk Patients

Treatment of precancers at first development can help prevent the development of subsequent invasive tumors, but prophylactic treatment may be needed for patients who have a history of multiple lesions and/or extensive diffuse actinic keratosis or field cancerization. Oral retinol and

synthetic retinoids (eg, acitretin, isotretinoin, etretinate) have been tested in prospective studies in patients at high risk for multiple actinic keratoses or SCCs, including transplant recipients,[433-438] patients with xeroderma pigmentosa,[439] or with psoriasis and PUVA (psoralen plus UV-A) exposure.[440] By comparison with placebo or with SCC incident rates during treatment-free periods, data from these studies support that oral retinol and oral retinoids significantly reduce the incidence of new cSCCs in these patients at very high risk for multiple lesions.[434-437,439,440]

Outside of these very-high-risk groups the effectiveness of retinol/retinoid therapy for prophylaxis is less clear. Several large prospective randomized trials have evaluated the impact of oral retinol or retinoids on development of new actinic keratoses or NMSCs in patients with multiple prior lesions but no major predisposing factors such as transplant or genetic disease. The SKICAP-AK double-blind randomized trial showed that for 2297 patients with 10 or more prior actinic keratoses (at least 1 in the past year) but no more than 2 prior SCC/BCC lesions, the hazard ratio (HR) for developing a new SCC was 0.74 (95% CI, 0.56–0.99; $P = .04$) for oral retinol compared with placebo, but the probability of developing a new BCC was not different across treatment arms.[441] The SKICAP-BCC/SCC double-blind randomized trial compared oral retinol (n = 173) and isotretinoin (n = 178) with placebo (n = 174) in patients with at least 4 prior BCCs and/or SCCs and the most recent tumor diagnosed in the past year.[442] Results showed a similar number of new BCCs and new SCCs across all three treatment arms, and no significant difference in time to first new lesion. In another randomized trial, 70 nontransplant patients with at least 2 prior BCCs/SCCs were randomized to receive either oral acitretin or placebo for 2 years.[443] Although there was a trend toward fewer patients with new NMSCs on acitretin (19 [54%] vs. 26 [74%] for placebo), the effect was not statistically significant, and the level of actinic damage was not affected.

Side effects associated with oral retinoids may be significant. Most adverse events are mucocutaneous, such as cheilitis, excessive peeling of the skin, and hair disorders,[438] but musculoskeletal, vascular, hepatic triglyceride, and neurologic (eg, emotional, headaches) adverse events have also been reported.[437,439,442,444] In addition, these agents are teratogenic and must be used with extreme caution in women of child-bearing age.[445-447] To determine whether these side effects could be avoided, the topical tretinoin cream (0.1%) was compared with vehicle control in a large randomized trial (N = 1131) in patients with at least 2 prior BCC or SCC lesions in the previous 5 years (but free of disease at baseline).[448] Patients at very high risk for recurrence were excluded (eg, xeroderma pigmentosum, prior RT, organ transplant, arsenic exposure, prior PUVA-PDT). Unfortunately, after a follow-up of 1.5 to 5 years, there was no significant difference between treatment arms for any of the metrics related to development of new invasive or in situ SCCs, BCCs, or total number of actinic keratoses.

The NCCN guidelines do *not* recommend topical retinoids as prophylactic treatment for patients at high risk for multiple actinic keratoses 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.[448] A double-blind randomized cross-over study showed that topical tazarotene had a chemopreventative effect in only 6% (1/27) of patients with basal cell nevus syndrome, a condition associated with frequent development of primary BCCs.[449]

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.[450] Patients with a NMSC in the past 5 years were randomized to either placebo or oral nicotinamide 500 mg BID (n = 193 patients per arm) for 12 months,

followed by 6 months off the study drug. After 12 months of treatment the rate of new NMSCs was 23% lower (P = .02), as was the number of actinic keratoses (13% lower, P = .001). Nicotinamide was associated with a 30% reduction in the 12-month rate of new SCCs (P = .05), and a 20% reduction in development of new BCCs (P = .12). Safety signals did not differ significantly between study arms. 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 NMSC and AK lesions.

Celecoxib, an inhibitor of cyclooxygenase 2 (COX-2), has been tested in randomized trials as a chemopreventative measure for reducing the development of precancers and NMSCs in patients at high risk.[451] A phase II-III randomized double-blind trial found that compared with placebo, oral celecoxib did not reduce the rate of new actinic keratoses, but did significantly reduce the rate of new BCCs and new cSCCs in patients with numerous actinic keratoses (n = 10–40 lesions per patient).[451] However, a meta-analysis of data from this trial and two large case-control studies[452,453] found that skin cancer incidence was not lowered by celecoxib.[454] The phase II-III trial did not find increased risk of cardiovascular adverse events with celecoxib versus placebo, but studies comparing celecoxib with placebo in other clinical settings showed significantly increased risk of serious and sometimes fatal cardiovascular and gastrointestinal (GI) toxicities.[455,456] The prescribing information for celecoxib includes a blackbox warning that celecoxib is associated with increased risk of serious cardiovascular thrombotic events, including stroke and myocardial infarction, and increases risk of serious GI adverse events including GI bleeding, ulceration, and perforation.[457] Due to safety

concerns the NCCN panel does not recommend celecoxib for prevention of actinic keratoses, cSCC or BCC.

Patient Education for High-Risk Patients

Patient education is especially important for those at high risk for cSCC progression or recurrence. A primary goal of patient education is to facilitate early detection and rapid entrance into the health care delivery system at the onset of tumor development, as early treatment is critical for preventing development of metastatic disease. Treatment delay is associated with larger tumor size, larger defect size from surgical removal, and more Mohs layers taken to obtain clear margins.[174,458-461] 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.[462,463] Low education level is also associated with large NMSC tumor area at presentation.[464] Educational interventions and advice given by physicians 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.[465-467]

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 to prevent development of further disease. Prospective randomized trials have shown that regular sunscreen use (compared with use at patient's discretion) significantly reduces the rate of development of new actinic keratoses and cSCCs, and increases remission rates of actinic keratoses.[468-471]

Both extensive and repetitive patient education regarding sun avoidance and protection is required. Having a prior NMSC has proved to be

insufficient motivation for altering patient behavior regarding UV protection and avoidance. A recent survey of over 30,000 non-Hispanic white adults in the United States showed that although those with prior NMSC are more likely to use sunscreen and to and avoid sun exposure (compared to those without prior NMSC), adoption of preventative measures was low: only 54% used sunscreen, and 20% to 45% used other avoidance/protective methods.[472] Among those with prior NMSC, 30% had experienced a recent sunburn. Another cross-sectional study in the United States based on a survey of >14,400 non-Hispanic white adults showed that tanning bed use was similar among those with and without prior NMSC.[473]

Education has been shown to effect change in preventative behaviors. Randomized trials have shown that educational interventions can effect significant changes in use of solar protection in outdoor workers and transplant patients.[467,474-477] A prospective randomized trial comparing educational interventions showed that while both extensive and repetitive education improves patient knowledge of skin cancer risks and appropriate methods for UV protection, repetitive education is needed to effect long-term change in patient behavior.[478] Repeated educational interventions are especially important for transplant patients, as preoccupation with other medical concerns may make them unreceptive to skin cancer education, especially during the first year after receiving their transplant.[479] One randomized trial in transplant patients showed that an intervention including text messaging reminders was more effective at improving patient knowledge and changing sun protective behaviors compared with more traditional education approaches.[480] Knowledge of more than one method for UV protection is associated with higher rates of using some form of protection,[481] as is awareness of susceptibility/risk and overall education level.[482,483] Among transplant patients, use of photoprotective measures was higher among those seen at a specialist organ transplant dermatology clinic.[484] Those least likely to know or follow

preventative methods are young people, men, members of lower socioeconomic class, or those with lower education level.[485]

Monthly self-examination is recommended, and should include all skin surfaces and lymph nodes. 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.[486] 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.

Regional Lymph Node Involvement in SCC

For patients with SCC, regional nodal involvement significantly increases the risk of recurrence and mortality.[50,140,143] Nodal metastasis also commonly coincides with other adverse histopathologic findings such as LVI, poor differentiation, and PNI.[17,121,122,131,140,141,143,144] About 60% to 82% of patients presenting with nodal disease show involvement in the parotid gland, while cervical neck node disease without parotid invasion is observed in 18% to 41% of cases.[487]

NCCN Recommendations for Workup for Suspicion of Regional Lymph Node Involvement

The presence of palpable regional lymph nodes or suspicious lymph nodes identified by imaging studies should prompt an 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

Data on SCC with nodal metastasis are limited to retrospective or observational studies. Some of these studies have shown that treating regional disease with RT alone results in poorer survival and/or regional/local control than those who received surgery plus adjuvant RT.[145,488-491] This was true for patients with parotid involvement, neck lymph node metastases, or a combination of the two, which is why the NCCN panel recommends resection of regional disease over radiation or chemotherapy. Radiation with or without concurrent therapy is reserved for patients who are not surgical candidates.

Most studies of patients with regional involvement of cSCC focus on treatment of parotid and/or cervical nodes either with surgery alone (parotidectomy and/or neck dissection) or surgery plus adjuvant radiotherapy.[51,145-149,151,152,488-507] In these studies the extent of resection and whether adjuvant RT was given depended on the treating clinician's assessment of the extent of the disease and risk of recurrence. Although some institutions have standard practices guiding treatment, published data from studies at these institutions may include cases in which the clinician deviated from that standard practice. Many of these studies used highly heterogeneous patient populations, including a wide range of levels of lymphatic and/or parotid involvement, a mix of primary and recurrent disease, and a mix of immunosuppressed and immunocompetent patients. In addition, some studies included a few patients treated with adjuvant chemotherapy, [147-149,494,500-502,507] and a few included patients who received RT or chemotherapy alone (no surgery).[51,145,489-492]

For studies where the majority of patients receive at least surgery plus adjuvant RT for parotid and/or neck LN metastases, recurrence rates are usually between 20% to 35%,[145-147,149,488,491,493,494,496,497,506,507] and estimates of 5-year disease-free survival and disease-specific survival are between 59% to 83%[147,149,151,500] and 63% to 83%,[145,148,149,151,152,488,489,491-497,499], respectively.

Due to the heterogeneity of study populations and treatment selection bias in these retrospective/observational studies, direct comparison of treatment outcomes is not appropriate. However, multivariate analyses provide some insight into factors and treatment options associated with better outcomes.

Studies of patients with cSCC metastases to the parotid and/or lymph nodes in the neck from several Australian centers (ie, Royal Prince Alfred Hospital, Westmead Hospital, Peter MacCallum Cancer Centre) have found by multivariate analysis that adjuvant RT improved local regional control or disease-free survival.[493,497,501] This finding was corroborated by a study from University of Texas Southwestern Medical Center.[503] Another study from Westmead Hospital that included patients with LN metastases of the neck but excluded those with parotid involvement found by multivariate analysis that adjuvant RT improved disease-free survival.[147] In contrast, studies from 2 different centers (ie, Toowoomba Hospital, Greenlane Hospital) found no significant association between adjuvant RT and improved disease-free survival or recurrence rate in patients with involvement of the parotid and/or cervical nodes.[149,150] Survival results are also mixed. Whereas several studies showed by multivariate analysis that adjuvant RT improved overall survival in patients with parotid and/or neck lymph node involvement,[146,151,501,505] and one study showed that this was also true for the subset of patients with neck lymph node involvement alone (no parotid involvement),[147] data from the Royal Prince Alfred

Hospital showed no significant association between adjuvant RT and overall survival.[494]

Such variability in results across studies suggests that there may be subsets of patients who derive more clinical benefit from adjuvant RT than other patients. Based on these retrospective and observational analyses, it is difficult to determine distinguishing features for identifying patients most likely to derive clinical benefit from adjuvant RT. Adjuvant RT is therefore a recommended option for all patients following resection of regional cSCC.

Many retrospective and observational studies have attempted to identify prognostic factors and determine how to best risk stratify patients with regional cSCC. Even among studies with multivariate analyses, results vary for all of the prognostic factors frequently considered, including patient characteristics (age, current/prior immunosuppression), features of the primary tumor (size, LVI, PNI, differentiation, positive margins after excision), and features of the regional disease (LN size, extracapsular extension (ECE), number of involved nodes, involvement of parotid, neck nodes, or both).[145-149,151,152,488,489,492-494,499,501,505,508] For each of these there are some analyses showing that they are significantly associated with regional control or survival, and other analyses showing no significant association.

Several staging systems have been proposed for regional cSCC, as shown in Table 1. O'Brien proposed a staging system that separated parotid involvement from neck LN involvement based on multivariate analysis showing improved local control for P1 compared with P2/P3.[493]

Multivariate analysis of 126 patients corroborated the finding that P2/P3 were associated with reduced locoregional control,[145] but two other multivariate analyses found that P-stage was not significantly associated with disease-free survival.[489,500] Results from multivariate analyses of survival also yielded mixed results regarding the prognostic value of O'Brien P-stage.[145,146,151,152,493,500] O'Brien also showed by multivariate analysis that survival was significantly better for patients with N0/N1 compared with N2.[493] One other multivariate analysis (n = 170) supported this result,[151] but several other multivariate analyses did not find a significant association with survival or locoregional control.[145,146,152,489,500]

The AJCC 7th edition staging for regional cSCC reflects the results from multiple studies, and therefore does not separate parotid from cervical lymph node involvement. The AJCC 7th edition staging includes both 3-cm and 6-cm cutoffs for largest lymph node dimension. A subsequent analysis by Forest and colleagues in 2010 found that lymph node size was related to ECE, and that the 3-cm cutoff was significantly associated with survival as long as ECE was excluded from the model.[494] Their multivariate analysis did not confirm the 6-cm cutoff, so they proposed a new staging system that only includes the 3-cm cutoff. Risk stratification per the NCCN Guidelines takes into account data from multivariate analyses showing that ECE and margin status after resection are prognostic for recurrence and/or survival.[146,489,493,499,500,508] The recent update of the AJCC staging system also now includes extranodal extension as a criterion for determining N-stage.[129] It should be noted that there are other multivariate analyses that showed no significant association between outcomes and ECE or margin status.[151,489,500,501]

NCCN Guidelines Version 1.2021
Squamous Cell Skin Cancer

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

O'Brien 2002 Staging System[493]

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[119]

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[129]

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[494]

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

MS-22

Systemic Therapy for Regional Disease

Regional cSCC has been shown to respond to systemic cytoxic therapies and to EGFR inhibitors in a number of prospective (noncomparative) and retrospective studies.[341,343,352,509-512] However, in the absence of prospective comparative trial data it is unclear whether these systemic therapies provide additional clinical benefit when used postoperatively in combination with RT. Several retrospective studies were unable to show that the addition of chemotherapy to postoperative RT significantly improved any disease-related outcome in patients with regional disease,[148,508] but at least one retrospective study showed improved relapse-free survival by multivariate analysis.[345]

A wide variety of cytotoxic therapies have been tested in patients with regional or distant metastatic cSCC. Those most commonly used are cisplatin, carboplatin, and 5-FU, either as monotherapy or combination regimens.[148,341,343-345,508-511,513,514] Among EGFR inhibitors, cetuximab is most commonly used in this setting,[347-349,352,508,512,515-517] but there have also been prospective studies on gefitinib,[351] erlotinib,[350] panitumumab,[518] and lapatinib.[346] Results from retrospective studies and meta-analyses attempting to compare platinum-based cytotoxic therapy with cetuximab have yielded inconsistent results,[348,511,519] so it is not clear which of these agents is more effective at treating regional or distant metastatic cSCC. Several studies have reported on patients treated with combinations of EGFR inhibitors and cytotoxic agents,[347,510,516] but it is not yet clear whether the combination improves outcomes in patients with regional or distant metastatic cSCC.

NCCN Recommendations for Treatment of Regional Disease

The preferred treatment for cSCC with lymph node involvement is excision of the primary tumor and regional lymph node dissection unless the patient is not a surgical candidate. Because surgery is the preferred treatment approach, surgical candidacy should be assessed by a clinician with experience in performing regional lymph node dissections.

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. Dosage information can be found in the *Principles of Radiation Therapy for Squamous Cell Skin Cancer* section of the algorithm.

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. Patients with a solitary positive lymph node should receive ipsilateral selective neck dissection. Comprehensive ipsilateral neck dissection is recommended for patients with a solitary positive node larger than 3 cm and those with multiple positive ipsilateral nodes. For patients with bilateral positive nodes, comprehensive bilateral neck dissection is appropriate. If parotid nodes are involved, the panel recommends superficial parotidectomy and ipsilateral neck dissection as indicated.

Truly radical neck dissection is no longer used and is not recommended. Because the definition of modified radical neck dissection varies across institutions, the NCCN Guidelines use the term "comprehensive neck dissection" to refer to all types of modified radical neck dissections, provided that they are more extensive procedures compared with selective neck dissections.

For patients with nodal metastasis to the head and neck, postoperative adjuvant treatment should depend on the pathologic findings after surgery—namely the extent resection, number of positive nodes, and presence or absence of ECE. Postoperative radiation is recommended in all cases, although observation is a reasonable alternative for patients with only one small (≤3 cm) node and no ECE. Patients with ECE or incompletely excised nodes are at high risk of recurrence. They should

receive adjuvant RT and also consider concurrent systemic therapy depending on individual toxicity tolerance. 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.

Patients with inoperable nodal disease should be treated with radiation of the nodal bed and multidisciplinary consultation to consider concurrent systemic therapy. Systemic therapies recommended for use with radiation to treat head and neck squamous cell carcinomas should be considered.

Patients should be re-evaluated for surgical candidacy for lymph node dissection after radiation. CT with contrast may be indicated to evaluate the extent of residual disease.

Recurrence and Metastasis

Systemic Therapy for Distant Metastatic Disease

Cutaneous SCC with distant metastasis, while rare, is more common than metastatic BCC. A 10-year cohort study involving 985 patients with SCC found that patients with 1 primary cSCC have a 3.7% risk of lymph node metastasis and 2.1% risk of disease-specific death.[17] Risk of nodal disease is even lower in patients with only one primary cSCC.[107] Risk of distant metastatic disease is only 0.4%.[17] Unfortunately, evidence regarding systemic therapy for the condition is limited. There are no prospective phase III studies available. Whereas a number of small studies have reported responses to cytotoxic therapy in patients with local or regional cSCC (See *Systemic Therapy for Local High-Risk SCC* and *Systemic Therapy for Regional Disease*),[334,342,343,509,511,513,520] few of these studies included patients with distant metastatic cSCC.[340,341,344,510] Cisplatin either as a single agent or combined with 5-FU or vindesine has occasionally produced useful responses in patients with distant metastases from cSCC, but data supporting efficacy are limited.[340,341,510] In

the only phase II study of biochemotherapy with interferon alfa, cis-retinoic acid, and cisplatin, 35 patients were assessed for response, 11 of whom had distant metastases.[344] One of the 11 patients experienced a complete response. This lends some credence to a cisplatin-based regimen for distant metastatic disease.

The status of evidence supporting EGFR inhibitors for treatment of distant metastatic cSCC is similar to that for cytotoxic therapy. Multiple small studies, including some phase II trials, have shown responses to EGFR inhibitors in patients with locally advanced or regional disease,[338,347,351,516] but only a few have reported responses in patients with distant metastases, including 2 responses reported in phase II trials.[346,352,512,515,518] The low toxicity profile of cetuximab holds an advantage over the toxic cisplatin regimen.

Neoadjuvant systemic therapy in preparation for subsequent surgery and/or radiation has been used for locoregional cSCC that is very large and/or deeply invasive. 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 after RT.[334,341,343,347,351,352,511,512,516] The efficacy of this approach has not been demonstrated for patients with distant metastatic cSCC.

In addition to several trials testing new approaches to treating locally advanced unresectable or metastatic cSCC with cytotoxic or targeted agents,[521-524] checkpoint immunotherapies are also being tested in this setting.[525-530] Preliminary data from these studies and case reports have shown responses to anti-PD-1 (nivolumab, pembrolizumab, REGN2810) and anti-CTLA-4 (ipilimumab) agents.[526,531-537] FDA recently approved nivolumab and pembrolizumab monotherapy for the treatment of patients with recurrent or metastatic head and neck squamous cell cancer with

disease progression on or after platinum-containing chemotherapy.[538,539] However, neither the phase 3 trial supporting the nivolumab approval (Checkmate 041; NCT02105636) nor the phase 1b trial supporting the pembrolizumab approval (KEYNOTE-012; NCT01848834) included any patients with *cutaneous* SCC.[540-542]

NCCN Recommendations

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. Possible agents include cisplatin monotherapy, cisplatin plus 5-FU, EGFR inhibitors such as cetuximab, or immune checkpoint inhibitors. Currently there are insufficient published data to support recommending any specific immunotherapies for treatment of cSCC. If the patient is a solid organ transplant recipient taking immunosuppressive therapy, one should consider reducing the doses of immunosuppressive agents where appropriate or minimizing the doses of calcineurin inhibitors and/or antimetabolites in favor of mTOR inhibitors.[543] For symptomatic sites, a palliative RT or surgery should be considered. Stereotactic body RT (SBRT) may be appropriate in select patients.

Follow-Up

Two well-established points about patients with SCC underlie the follow-up schedules. One point is that 30% to 50% of these patients will develop another SCC within 5 years.[102,105] This represents at least a 10-fold increase in risk compared to the general population.[104,105] 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.[99,105] Therefore, continued long-term surveillance of these patients is essential, as is patient education about the values of sun protection and regular self-examination of the skin. A second point is that 70% to 80% of all cutaneous SCC recurrences develop within 2 years of the initial therapy.[17,48,107,122,127,544] Therefore, close follow-up of these patients during this time period is critical.

NCCN Recommendations

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 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. For local SCC, monitoring during the first 2 years is the most critical, and exams should occur at least every 3 to 12 months during this timeframe. If no further skin cancer develops in the first 2 years, then exams every 6 to 12 months for another 3 years, then annually for life is recommended. For regional SCC, a history and physical should be performed every 1 to 3 months for 1 year, then every 2 to 4 months for 1 year, every 4 to 6 months for another 3 years, and then every 6 to 12 months for life. For patients with regional disease, surveillance using CT with contrast may be warranted to screen for recurrence in the regional lymph node basin or distant metastatic disease. The target areas and frequency of these scans depends on the patient-specific clinical factors, and should ideally be determined by a multidisciplinary tumor board consultation.

In certain patients at high risk for multiple primary tumors, increased
surveillance and consideration of prophylactic measures may be indicated.

Discussion
update in
progress

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Discussion update in progress