National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Squamous Cell Skin Cancer

NCCN Evidence Blocks™

Version 2.2025 — March 10, 2025

NCCN.org

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

NCCN Evidence Blocks™

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

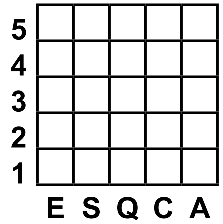
See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

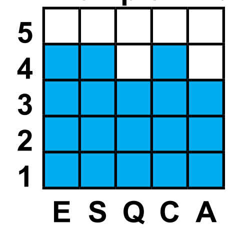
NCCN Guidelines for Patients® available at www.nccn.org/patients

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

CLINICAL PRESENTATION
- Lesion suspicious for skin cancer →

PRELIMINARY WORKUP
- H&P
- Biopsy[a]:
  - If more than superficial lesion, inclusion of deep reticular dermis preferred[b]
- Imaging studies of area of interest as indicated for suspicion of locally, extensive or metastatic disease[c,d,e,f]

→ **DIAGNOSIS**
- Cutaneous squamous cell cancer (CSCC) confirmed[g]

→ **ADDITIONAL WORKUP**
- Complete skin exam
- Regional lymph node exam as indicated for suspicion of nodal disease

RISK STATUS → **PRIMARY TREATMENT**
- Local
  - Field cancerization[h]/Confluent epidermal dysplasia → SCC-2
  - Low-risk[b] → SCC-3
  - High-risk/Very-high risk[b] → SCC-4 and SCC-5
  - Locally advanced (laCSCC) disease[i] → SCC-6
- Clinically or radiographically concerning regional lymph nodes → SCC-7
- or Satellitosis/In-transit metastasis (S-ITM) → SCC-8
- or Distant metastatic disease → SCC-10

[a] Principles of Pathology (SCC-A).
[b] 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).
[c] Extensive disease includes deep involvement such as bone, named nerves, and deep soft tissue. If disease of named nerve(s) is suspected, MRI with and without contrast is preferred. If bone disease is suspected, CT with contrast is preferred unless contraindicated.
[d] For rare cases that present with distant metastatic disease at diagnosis, treat per distant metastases pathway on SCC-10.
[e] 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 sufficient to diagnose local recurrence, but MRI with and without contrast can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or other imaging modalities can be used for confirmation and to gauge extent of disease.
[f] MRI with and without contrast of the brain may be considered to rule out subclinical cortical involvement in cases with bone invasion.
[g] Including CSCC in situ (showing full-thickness epidermal atypia).
[h] Field cancerization defined as ultraviolet (UV) induced confluent dysplasia clinically manifested as diffuse actinic keratoses and superficial (in situ) SCC. Willenbrink TJ, et al. J Am Acad Dermatol 2020;83:709-717.
[i] A cure is unlikely to result from surgery and/or RT or there are concerns of significant functional impairment. Multidisciplinary discussion and multimodality treatment (including neoadjuvant and adjuvant therapy) merits consideration.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

FIELD CANCERIZATION/CONFLUENT EPIDERMAL DYSPLASIA

PRIMARY TREATMENT[j,k,l,m]

Field cancerization[h]/ Confluent epidermal dysplasia →

- **Prevention:**
  - **Daily sunscreen[n]**
  - **Nicotinamide[o]**
- **Accepted treatment modalities**
  - **Topical:**
    - **5-fluorouracil (5-FU)-based regimens are preferred**
      - **Topical 5-FU ± calcipotriol (calcipotriene)[p]**
  - **Destructive:**
    - **Ablative laser vermilionectomy (may be of value in the treatment of extensive actinic cheilitis)**
    - **Ablative skin resurfacing (eg, laser, dermabrasion)**
    - **Chemical peels (trichloroacetic acid)**
    - **Cryotherapy**
    - **Curettage and electrodesiccation (C&E)**
  - **Other modalities that may be considered:**
    - **Photodynamic therapy (PDT) (eg, topical aminolevulinic acid [ALA], porfimer sodium)**
    - **Systemic retinoids[q] (eg, acitretin, isotretinoin)**
    - **Capecitabine[m,r] (for severe refractory disease that has progressed on oral retinoids)**

See Evidence Blocks on SCC-F (EB-2)

[h] Field cancerization defined as UV induced confluent dysplasia clinically manifested as diffuse actinic keratoses and superficial (in situ) SCC. Willenbrink TJ, et al. J Am Acad Dermatol 2020;83:709-717.
[j] Principles of Systemic Therapy (SCC-F 1 of 4).
[k] Actinic keratoses that have an atypical clinical appearance or do not respond to appropriate therapy should be biopsied for histologic evaluation.
[l] Actinic keratoses should be treated at first development.
[m] Cornejo CM, et al. J Am Acad Dermatol 2020;83:719-730.
[n] Green AC, et al. J Clin Oncol 2011;29:257-263.
[o] Oral nicotinamide may be effective in reducing the development of CSCCs. Chen AC, et al. N Engl J Med 2015;373:1618-1626; Allen NC, et al. N Engl J Med 2023;388:804-812; Mainville L, et al. J Cutan Med Surg 2022;26:297-308; Chen AC, et al. Br J Dermatol 2016;175:1073-1075.
[p] The longest duration of prophylaxis against SCC has been demonstrated with topical 5-FU plus calcipotriol. Cunningham TJ, et al. J Clin Invest 2017;127:106-116; Jansen MHE, et al. N Engl J Med 2019;380:935-946.
[q] Use of oral retinoids (eg, acitretin, isotretinoin) is a therapeutic option used to reduce the development of actinic keratoses. Side effects of oral retinoids may be significant, especially in patients of childbearing potential, and therapeutic benefits are limited to the duration of the regimen. Topical retinoids were shown not to reduce development of actinic keratosis. Badri O, et al. Dermatol Surg 2021;47:125-126.
[r] Endrizzi B, et al. Dermatol Surg 2013;39:634-645.

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LOW-RISK CSCC | **PRIMARY TREATMENTS[s]** | **ADDITIONAL TREATMENT**

Low-risk CSCC[a,b,s] →

- **C&E[t]**
  or
  Shave removal[u,v] → Follow-up (SCC-10)
- or
  Standard excision with 4- to 6-mm clinical margins and postoperative margin assessment. Tissue rearrangement (eg, flap reconstruction, extensive undermining) should not be undertaken until clear margins are identified (second intention healing, linear repair, or skin graft are acceptable)
  - **Positive margins** → **Mohs[w,x,y] or other forms of PDEMA[z]** or **Re-excision if clinically feasible** or **RT[aa,bb] for non-surgical candidates[s]** → Follow-up (SCC-10)
  - **Negative margins** → Follow-up (SCC-10)
- or
  Mohs[w,x,y] or other forms of peripheral and deep en face margin assessment (PDEMA)[z] → Follow-up (SCC-10)
- or
  Radiation therapy (RT)[aa,bb] for patients declining surgery → Follow-up (SCC-10)

Follow-up (SCC-10)

[a] Principles of Pathology (SCC-A).
[b] 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).
[s] Principles of Treatment (SCC-D).
[t] C&E may have a lower cure rate than excision.
[u] Shave removal (shaving of epidermal or dermal lesion) is a sharp removal by transverse bowl-shaped slicing to remove epidermal and dermal lesions (without including fat) and does not require suture closure. Emmett AJ, et al. Plast Reconstr Surg 1987;80:47-54.
[v] If tumor appears to extend beyond the dermis, surgical excision should generally be performed rather than C&E or shave removal.
[w] When Mohs is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.
[x] As per other appropriate use Guidelines. Task Force/Committee Members, Vidal CI, Armbrect EA, et al. J Am Acad Dermatol 2019;80:189-207.e11.
[y] Mohs surgery should be performed by dermatologic surgeons who have specialized training and experience in this procedure.
[z] PDEMA with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G).
[aa] Principles of Radiation Therapy (SCC-E).
[bb] Determination of the appropriateness of RT should be performed together with a radiation oncologist.

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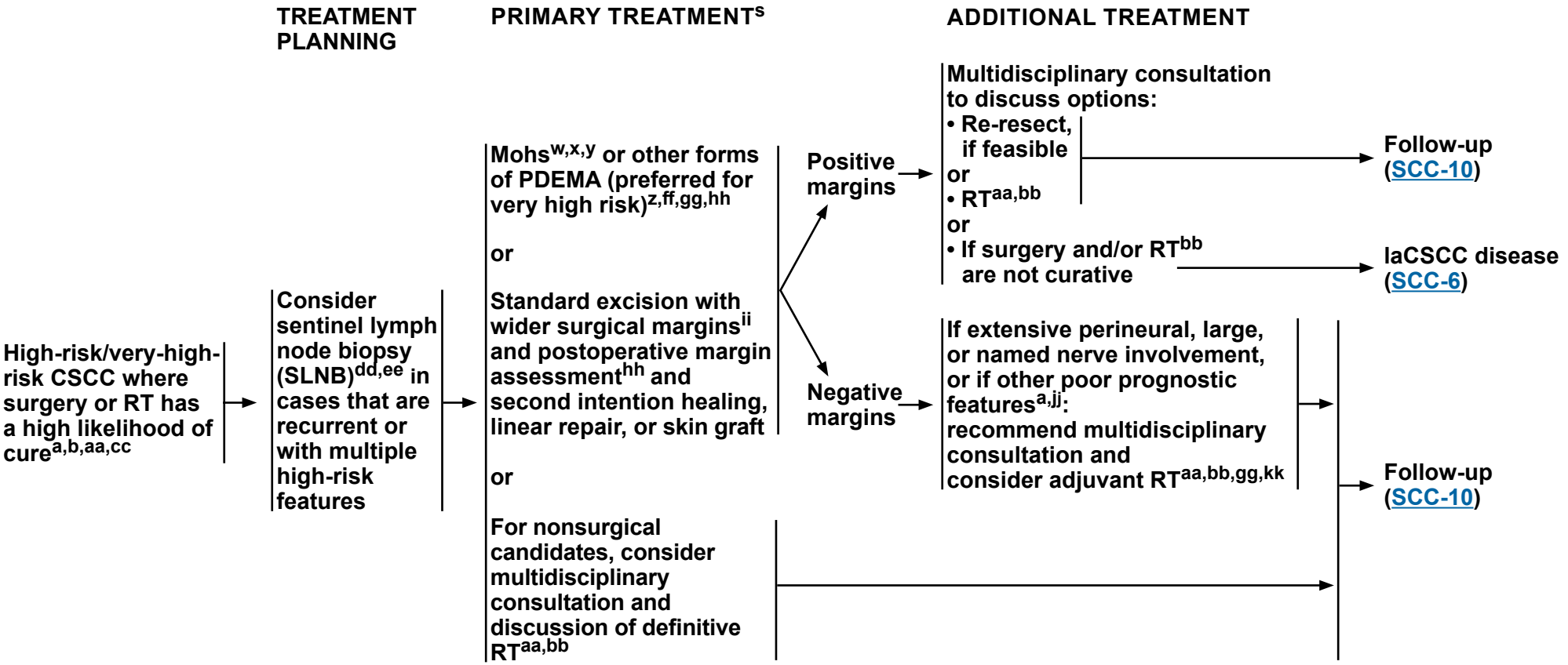
HIGH-RISK/VERY-HIGH-RISK CSCC



Footnotes on SCC-4A

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
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FOOTNOTES

[a] Principles of Pathology (SCC-A).
[b] 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).
[s] Principles of Treatment (SCC-D).
[w] When Mohs is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.
[x] As per other appropriate use Guidelines. Task Force/Committee Members, Vidal CI, Armbrect EA, et al. J Am Acad Dermatol 2019;80:189-207.e11.
[y] Mohs surgery should be performed by dermatologic surgeons who have specialized training and experience in this procedure.
[z] PDEMA with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G).
[aa] Principles of Radiation Therapy (SCC-E).
[bb] Determination of the appropriateness of RT should be performed together with a radiation oncologist.
[cc] For complicated cases, consider multidisciplinary consultation.
[dd] Discuss and consider SLNB prior to or at time of PDEMA for patients with very-high-risk CSCCs that are recurrent or have multiple risk factors placing them in the very-high-risk group and have normal exam of draining nodal basin (category 2B).
[ee] For positive SLNB: Recommend multidisciplinary discussion after obtaining radiologic staging of the neck, chest, abdomen, and pelvis if not yet completed. In the absence of metastatic disease consider completion lymphadenectomy of the affected nodal basin. If surgery is not an option due to patient preference or poor performance status, then consider radiation therapy. Following neck dissection, refer to SCC-5 for additional recommendations.
[ff] In patients with very-high-risk CSCC and normal exam of nodal basin, discuss and consider radiologic imaging of nodal basin.
[gg] If invasion to parotid fascia, superficial parotidectomy may be indicated.
[hh] For tumors being considered for SLNB, delay reconstruction if not able to close primarily with minimal undermining.
[ii] Appropriate margins should be determined case by case based on tumor and patient-specific factors.
[jj] Large nerve involvement is defined by the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition for CSCC of the head and neck as ≥0.1 mm or nerve involvement deeper than the dermis. Most nerves deep to the dermis are >0.1 mm.
[kk] Adjuvant RT can be considered for CSCCs with gross clinical radiologic perineural invasion (PNI), multifocal histologic nerve invasion, ≥6 cm tumor diameter, recurrent tumors, high risk for regional or distant metastasis, close surgical margins where further surgery cannot be performed, and desmoplastic or infiltrative tumors in patients who are chronically immunosuppressed. Ruiz ES, et al. J Am Acad Dermatol 2022;87:87-94.

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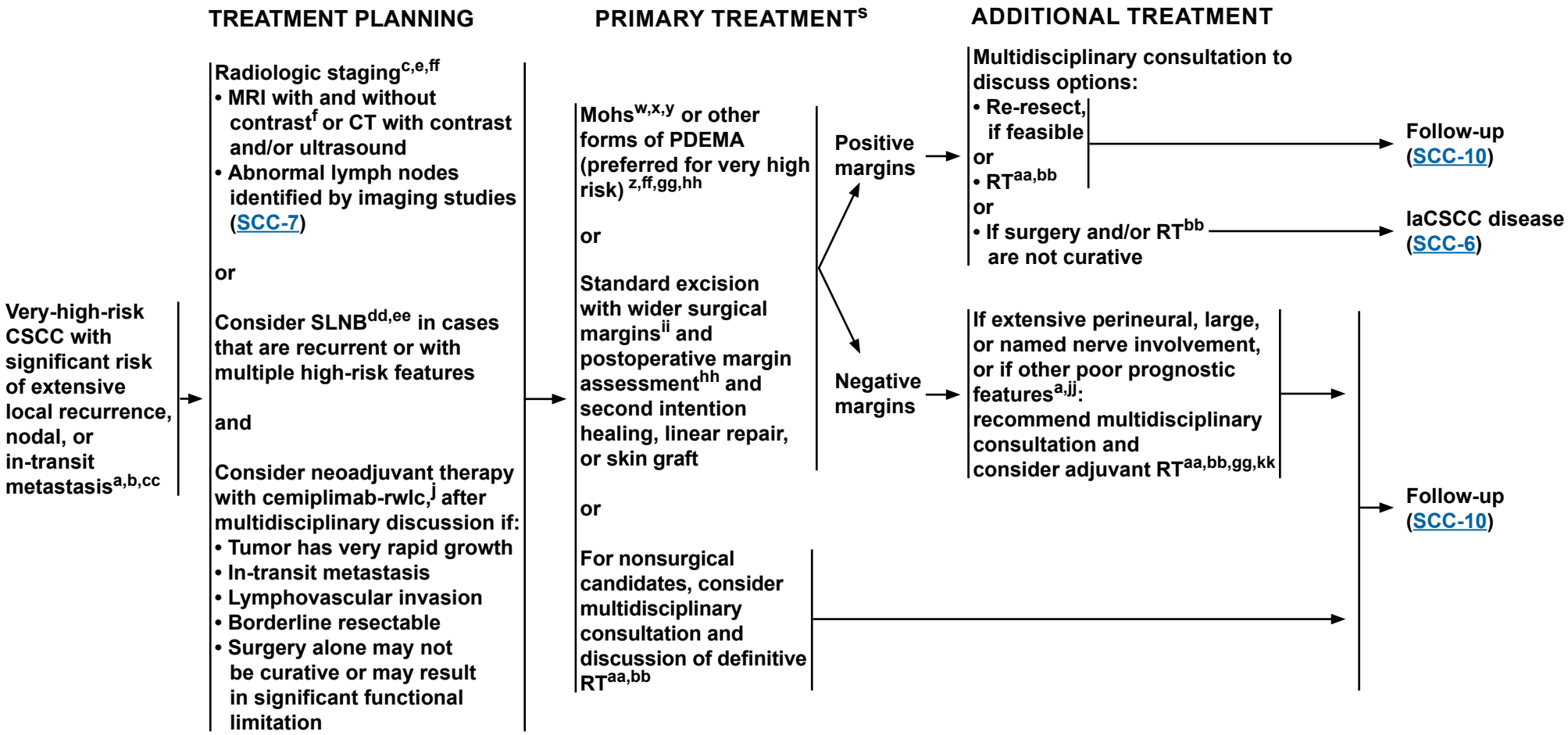
VERY-HIGH-RISK CSCC



Footnotes on SCC-5A

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FOOTNOTES

[a] Principles of Pathology (SCC-A).
[b] 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).
[c] Extensive disease includes deep involvement such as bone, named nerves, and deep soft tissue. If disease of named nerve(s) is suspected, MRI with and without contrast is preferred. If bone disease is suspected, CT with contrast is preferred unless contraindicated.
[e] 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 sufficient to diagnose local recurrence, but MRI with and without contrast can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or other imaging modalities can be used for confirmation and to gauge extent of disease.
[f] MRI with and without contrast of the brain may be considered to rule out subclinical cortical involvement in cases with bone invasion.
[j] Principles of Systemic Therapy (SCC-F 2 of 4).
[s] Principles of Treatment (SCC-D).
[w] When Mohs is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.
[x] As per other appropriate use Guidelines. Task Force/Committee Members, Vidal CI, Armbrect EA, et al. J Am Acad Dermatol 2019;80:189-207.e11.
[y] Mohs surgery should be performed by dermatologic surgeons who have specialized training and experience in this procedure.
[z] PDEMA with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G).
[aa] Principles of Radiation Therapy (SCC-E).
[bb] Determination of the appropriateness of RT should be performed together with a radiation oncologist.
[cc] For complicated cases, consider multidisciplinary consultation.
[dd] Discuss and consider SLNB prior to or at time of PDEMA for patients with very-high-risk CSCCs that are recurrent or have multiple risk factors placing them in the very-high-risk group and have normal exam of draining nodal basin (category 2B).
[ee] For positive SLNB: Recommend multidisciplinary discussion after obtaining radiologic staging of the neck, chest, abdomen, and pelvis if not yet completed. In the absence of metastatic disease, consider completion lymphadenectomy of the affected nodal basin. If surgery is not an option due to patient preference or poor performance status, then consider radiation therapy. Following neck dissection, refer to SCC-5 for additional recommendations.
[ff] In patients with very-high-risk CSCC and normal exam of nodal basin, discuss and consider radiologic imaging of nodal basin.
[gg] If invasion to parotid fascia, superficial parotidectomy may be indicated.
[hh] For tumors being considered for SLNB, delay reconstruction if not able to close primarily with minimal undermining.
[ii] Appropriate margins should be determined case by case based on tumor and patient-specific factors.
[jj] Large nerve involvement is defined by the AJCC Cancer Staging Manual, 8th Edition for CSCC of the head and neck as ≥0.1 mm or nerve involvement deeper than the dermis. Most nerves deep to the dermis are >0.1 mm.
[kk] Adjuvant RT can be considered for CSCCs with gross clinical radiologic PNI, multifocal histologic nerve invasion, ≥6 cm tumor diameter, recurrent tumors, high risk for regional or distant metastasis, close surgical margins where further surgery cannot be performed, and desmoplastic or infiltrative tumors in patients who are chronically immunosuppressed. Ruiz ES, et al. J Am Acad Dermatol 2022;87:87-94.

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LOCALLY ADVANCED CSCC

laCSCC (Primary or recurrent extensive disease where surgery and/or RT may not result in a cure or would possibly produce a significant functional impairment.[ll] Multidisciplinary discussion and multimodality treatment [including neoadjuvant and adjuvant therapy] merits consideration)[a,b,cc,mm]

PRIMARY TREATMENT[s]

- **Consider neoadjuvant therapy with cemiplimab-rwlc[j,nn] and/or clinical trial after multidisciplinary discussion**
  - **Mohs[w,x,y] or other forms of PDEMA[z,gg,hh]**
  - **Standard excision with wider surgical margins[ii] and postoperative margin assessment[hh] and second intention healing, linear repair, or skin graft**
    - **Positive margins** → ADDITIONAL TREATMENT: **Multidisciplinary consultation to discuss options:**
      - **Re-resect, if feasible**
      - **or**
      - **RT[aa,bb] ± systemic therapy[j]**
      - **or**
      - **Systemic therapy[j] if curative RT[bb] is not feasible**
      - → **Follow-up (SCC-10)**
    - **Negative margins** → ADDITIONAL TREATMENT: **If extensive perineural, large, or named nerve involvement, or if other poor prognostic features[a,jj]: Recommend multidisciplinary consultation and Consider adjuvant RT[aa,bb,gg,kk]**
      - → **Follow-up (SCC-10)**
- **For nonsurgical candidates, due to comorbidities, extent of disease, risk of functional or cosmetic defects, inability to clear disease with surgery:**
  - **RT[aa,bb] ± systemic therapy[j]**
  - **Systemic therapy[j] if curative RT[bb] is not feasible**
  - → **Follow-up (SCC-10)**

Footnotes on SCC-6A

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FOOTNOTES

[a] Principles of Pathology (SCC-A).
[b] 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).
[j] Principles of Systemic Therapy (SCC-F 2 of 4).
[s] Principles of Treatment (SCC-D).
[w] When Mohs is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.
[x] As per other appropriate use Guidelines. Task Force/Committee Members, Vidal CI, Armbrect EA, et al. J Am Acad Dermatol 2019;80:189-207.e11.
[y] Mohs surgery should be performed by dermatologic surgeons who have specialized training and experience in this procedure.
[z] PDEMA with permanent section analysis or intraoperative frozen section analysis is an alternative to Mohs. See Principles of PDEMA Technique (SCC-G).
[aa] Principles of Radiation Therapy (SCC-E).
[bb] Determination of the appropriateness of RT should be performed together with a radiation oncologist.
[cc] For complicated cases, consider multidisciplinary consultation.
[gg] If invasion to parotid fascia, superficial parotidectomy may be indicated.
[hh] For tumors being considered for SLNB, delay reconstruction if not able to close primarily with minimal undermining.
[ii] Appropriate margins should be determined case by case based on tumor and patient-specific factors.
[jj] Large nerve involvement is defined by the AJCC Cancer Staging Manual, 8th Edition for CSCC of the head and neck as ≥0.1 mm or nerve involvement deeper than the dermis. Most nerves deep to the dermis are >0.1 mm.
[kk] Adjuvant RT can be considered for CSCCs with gross clinical radiologic PNI, multifocal histologic nerve invasion, ≥6 cm tumor diameter, recurrent tumors, high risk for regional or distant metastasis, close surgical margins where further surgery cannot be performed, and desmoplastic or infiltrative tumors in patients who are chronically immunosuppressed. Ruiz ES, et al. J Am Acad Dermatol 2022;87:87-94.
[ll] Bertrand N, et al. eClinicalMedicine 2021;5:100844.
[mm] If patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate.
[nn] Consider neoadjuvant therapy with cemiplimab-rwlc, after multidisciplinary discussion, if the tumor has very rapid growth, in-transit metastasis, lymphovascular invasion, is borderline resectable, or surgery alone may not be curative or may result in significant functional limitation.

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CLINICAL STAGING AND PREOPERATIVE ASSESSMENT

PRIMARY TREATMENT[s]

- **Palpable regional lymph node(s) or abnormal lymph nodes identified by imaging studies[mm,oo]** → **FNA or core biopsy[pp]**
  - **Negative** → **Consider re-evaluation: clinical exam, CT with contrast of the nodal basin, repeat fine needle aspiration (FNA), core biopsy, or excisional biopsy[qq]**
    - **Negative** → **Follow-up (SCC-10)**
    - **Positive** → (see workup below)
  - **Positive** → **• CT with contrast of the nodal basin to determine size, number, and location of nodes • Chest/abdomen/pelvis CT with contrast or FDG-PET/CT as clinically indicated to rule out distant disease[f]** → **Surgical and clinical trial evaluation[rr]**
    - **Operable disease[ss]**
      - **Head and neck** → **Regional Lymph Nodes (SCC-9)**
      - **Trunk and extremities** → **Excision of primary tumor and regional lymph node dissection** → **Consider RT,[aa,bb] especially if multiple involved nodes or extranodal extension (ENE) is present** → **Follow-up (SCC-10)**
    - **Unresectable, inoperable, or incompletely resected disease[ss]** → **Multidisciplinary consultation to discuss options:**
      - **RT[aa,bb,tt] ± systemic therapy[j]**
      - **Systemic therapy[j] if curative RT[bb] not feasible**

      → **Follow-up (SCC-10)**

[f] MRI with and without contrast of the brain may be considered to rule out subclinical cortical involvement in cases with bone invasion.
[j] Principles of Systemic Therapy (SCC-F 2 of 4).
[s] Principles of Treatment (SCC-D).
[aa] Principles of Radiation Therapy (SCC-E).
[bb] Determination of the appropriateness of RT should be performed together with a radiation oncologist.
[mm] If the patient is immunosuppressed, consider modification or reduction of immunosuppression as appropriate.
[oo] Identification and Management of Patients at High Risk for Multiple Primary CSCCs (SCC-C).
[pp] 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.
[qq] An excisional biopsy may be considered to confirm a negative initial FNA or core lymph node biopsy if clinical suspicion remains high.
[rr] Regional lymph node dissection is preferred unless the patient is not a surgical candidate.
[ss] Cemiplimab-rwlc, in one study of 79 patients with CSCC, showed a 51% complete histologic response in the neoadjuvant setting. Therefore it may be considered in patients who are considered borderline resectable, unresectable, or for whom surgery may carry a high morbidity.
[tt] Consider palliative RT/surgery for symptomatic sites. Stereotactic body RT (SBRT) may also be considered in select patients.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

SATELLITOSIS/IN-TRANSIT METASTASIS (S-ITM)

TREATMENT PLANNING

Tissue sampling confirmed S-ITM →
- Imaging of the anatomic region (ie, CT with contrast) capturing S-ITM to determine geographic footprint
- Chest/abdomen/pelvis CT with contrast or FDG-PET/CT as clinically indicated to rule out distant disease

→ **Multidisciplinary discussion**

PRIMARY TREATMENT[s]

- **Operable disease**[ss] → **Consider neoadjuvant systemic therapy**[j] **(followed by resection) or upfront resection with consideration of adjuvant therapy**[uu,vv]
- **Unresectable or incompletely resected disease**[ss] → **Multidisciplinary consultation to discuss options:**
  - **Systemic therapy**[j] **± RT**[aa,bb]

  → **Follow-up ([SCC-10](#))**

[j] Principles of Systemic Therapy (SCC-F 2 of 4).
[s] Principles of Treatment (SCC-D).
[aa] Principles of Radiation Therapy (SCC-E).
[bb] Determination of the appropriateness of RT should be performed together with a radiation oncologist.
[ss] Cemiplimab-rwlc, in one study of 79 patients with CSCC, showed a 51% complete histologic response in the neoadjuvant setting. Therefore it may be considered in patients who are considered borderline resectable, unresectable, or for whom surgery may carry a high morbidity.
[uu] Porceddu SV, et al. Int J Clin Oncol 2018;36:1275-1283.
[vv] Marti-Marti I, et al. J Am Acad Dermatol 2023;89:119-127.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page [EB-1](#).
All recommendations are category 2A unless otherwise indicated.

REGIONAL LYMPH NODES	TREATMENT OF HEAD AND NECK[s]	PATHOLOGIC FINDINGS			
Solitary or multiple ipsilateral nodes →	Excision of primary tumor and ipsilateral neck dissection as indicated	One positive node ≤3 cm, no ENE →	RT[aa,bb] or Observation →	Observation →	Follow-up (SCC-10)
Bilateral nodes →	Excision of primary tumor and bilateral neck dissection as indicated	≥2 positive nodes or one node >3 cm, no ENE →	RT[aa,bb] →	Observation →	Follow-up (SCC-10)
Parotid nodes involved →	Excision of primary tumor and parotidectomy (generally superficial) and ipsilateral neck dissection as indicated	Any node with ENE →	RT[aa,bb] and consider concurrent systemic therapy[j,ww] →	Observation →	Follow-up (SCC-10)
		Incompletely excised nodal disease →	RT[aa,bb] and consider concurrent systemic therapy[j,ww] →	Observation →	Follow-up (SCC-10)

(All three treatments of head and neck lead to each of the pathologic findings.)

[j] Principles of Systemic Therapy (SCC-F 2 of 4).
[s] Principles of Treatment (SCC-D).
[aa] Principles of Radiation Therapy (SCC-E).
[bb] Determination of the appropriateness of RT should be performed together with a radiation oncologist.
[ww] Multidisciplinary consultation recommended.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

FOLLOW-UP

Local disease:

- **H&P[xx,yy,zz]**
  - **For patients who are low risk:** Every 3–12 mo for 2 y, then every 6–12 mo for 3 y, then annually for life[b]
  - **For patients who are high risk:** Every 3–6 mo for 2 y, then every 6–12 mo for 3 y, then annually for life[b]
  - **For patients who are very high risk:** Every 3–6 mo for 2 y, then every 6 mo for 3 y, then every 6–12 mo for life[b]
- **Consider imaging:**
  - **If clinical exam is insufficient for following disease**
  - **If there is appreciable risk of subclinical local or nodal recurrence[e]**
- **Patient education**
  - **Sun protection**
  - **Self examination of skin**

Regional/S-ITM disease:

- **H&P[xx,yy,zz]**
  - **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 is insufficient for following disease**
  - **If there is appreciable risk of subclinical local or nodal recurrence[e,aaa]**
- **Patient education**
  - **Sun protection**
  - **Self examination of skin and lymph nodes**

→ **Local recurrence[e]** → SCC-4 and SCC-5

→ **Locally advanced (laCSCC) recurrence[e]** → SCC-6

→ **New or recurrent S-ITM** → SCC-8

→ **New regional disease** → SCC-7 and SCC-9

→ **Regional recurrence or distant metastases** → **Multidisciplinary consultation[j,tt,bbb]**

[b] 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).

[e] 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 sufficient to diagnose local recurrence, but MRI with and without contrast can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or other imaging modalities can be used for confirmation and to gauge extent of disease.

[j] Principles of Systemic Therapy (SCC-F 2 of 4).

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

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

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

[zz] Follow-up with a dermatologist is strongly recommended if any of the following criteria are met: past or imminent solid organ, marrow, or stem cell transplant, one or more cutaneous melanomas in the past 5 years, or four or more non-melanoma skin cancers in the past 5 years.

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

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

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGY

Principles of Biopsy Reporting

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

Principles of Excision Reporting (including Mohs excisions)

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

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

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

[1] Kim JYS, Kozlow JH, Mittal B, et al; Invited Reviewers; Work Group. Guidelines of care for the management of cutaneous squamous cell carcinoma. J Am Acad Dermatol 2018;78:560-578.
[2] Califano JA, Lydiatt WM, Nehal KS, et al. Cutaneous squamous cell carcinoma of the head and neck. In: Amin MB, Edge S, Greene F, et al, eds. AJCC Cancer Staging Manual (Eighth Edition). New York: Springer International Publishing; 2017:171-181.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

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[a]	Low Risk	High Risk	Very High Risk
Treatment options	SCC-3	SCC-4	SCC-4 and SCC-5
H&P			
Location/diameter (cm)	Trunk, extremities ≤2 cm	Trunk, extremities >2 cm – ≤4 cm	>4 cm (any location)
		Head, neck, hands, feet, pretibia, and anogenital area (any size)[e]	
Clinical borders	Well-defined	Poorly-defined	
Primary vs. recurrent	Primary	Recurrent	
Immunosuppression	(-)	(+)	
Site of prior RT or chronic inflammation	(-)	(+)	
Rapidly growing tumor	(-)	(+)	
Neurologic symptoms	(-)	(+)	
Pathology (SCC-A)			
Degree of differentiation	Well or moderately differentiated		Poor differentiated
Histologic subtype[b]	(-)	(+)	(+)
Depth[c,d]: Thickness or level of invasion	<2 mm thick and no invasion beyond subcutaneous fat	2–6 mm depth 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	(-)	(-)	(+)

[a] Risk category assignment should be based on the highest risk factor present. The high-risk group has elevated risk of local recurrence; the very-high-risk group has elevated risk of local recurrence and elevated risk of metastasis.
[b] Acantholytic (adenoid), adenosquamous, metaplastic (carcinosarcomatous), or desmoplastic subtypes in any portion of the tumor.
[c] If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.
[d] Deep invasion is defined as invasion beyond the subcutaneous fat OR >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor, consistent with the AJCC Cancer Staging Manual, 8th Edition).
[e] Narrow excision margins due to anatomic and functional constraints are associated with increased recurrence rates with standard histologic processing. Complete margin assessment with Mohs/PDEMA is recommended. 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.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

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

Definition

- **Certain patient groups are at high risk for developing multiple CSCCs and tumors that can behave aggressively. These include:**
  - **Organ transplant recipients**
  - **Other settings of immunosuppression (eg, lymphoma, chronic lymphocytic leukemia [CLL], drug-induced, HIV)**
  - **Genetic syndromes predisposing to CSCC formation[a]**
- **Within these high-risk groups, individual patients who are high risk 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.**

[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, KID syndrome (keratitis, ichthyosis, deafness), and Ferguson-Smith disease.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

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

Treatment of Skin Cancers

- Because patients in high-risk groups may develop multiple lesions in short periods of time, destructive therapy (eg, C&E, cryotherapy) may be a preferred treatment for clinically low-risk tumors because of the ability to treat multiple lesions at a single patient visit. If C&E has been performed based solely on the clinical appearance of a low-risk tumor, the pathology from the biopsy taken at the time of C&E should be reviewed to make sure there are no high-risk pathologic features that would suggest the need for further therapy beyond C&E.
- In patients who develop multiple adjacent tumors in close proximity, surgical excision of invasive disease sometimes does not include surrounding in situ disease, and tissue rearrangement should be minimized. In situ disease may then be treated with topical approaches similar to actinic keratoses/field cancerization.
- Compared to the low-risk population, RT is used more frequently as an adjuvant therapy in patients who are high risk 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.

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 recipients of organ transplant, at transplantation, and in the case of xeroderma pigmentosum, at birth or diagnosis.

Prevention

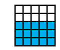
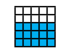
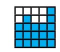
- Regular sunscreen use prevents CSCC long term.[1]
- Use of oral retinoids (eg, acitretin, isotretinoin) is effective in reducing the development of CSCC in some patients who are high risk. Side effects of oral retinoids may be significant. Therapeutic effects disappear shortly after cessation of the drug. Oral retinoids are teratogenic and must be used with extreme caution in patients of childbearing potential. Topical retinoids have been shown not to reduce development of CSCC. (See SCC-2)
- 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.

See Evidence Blocks on SCC-C (EB-1)

[1] Green AC, Williams GM, Logan V, Strutton GM. Reduced melanoma after regular sunscreen use: randomized trial follow-up. J Clin Oncol 2011;29:257-263.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PREVENTION: THERAPY TO PREVENT DEVELOPMENT OF ACTINIC KERATOSES AND SCC (See SCC-C 2 of 2)

Acitretin	
Isotretinoin	
Nicotinamide	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

PRINCIPLES OF TREATMENT

- **The primary goals of treatment of CSCCs are the complete removal of the tumor and the maximal preservation of function and cosmesis. All treatment decisions should be customized to account for the particular factors present in the individual case and for the patient's preference.**

- **Surgical approaches often offer the most effective and efficient means for accomplishing cure, but considerations of function, cosmesis, and patient preference may lead to choosing RT/topical therapy/systemic therapy 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]).**

- **Epidermally limited CSCC may be treated with nonsurgical options. (See SCC-2 and Principles of Systemic Therapy SCC-F).**

- **When Mohs with margin assessment is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for vertical paraffin-embedded permanent sections or documentation of staging parameters in Mohs report is recommended.**

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

General Principles

- Refer to the ASTRO Guideline on Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin[1] for general indications and dose recommendations.
- Protracted fractionation is associated with improved cosmetic results and should be utilized for poorly vascularized or cartilaginous areas.
- For extensive perineural invasion (PNI) or involvement of named nerves (particularly in the head and neck region), consider including the course of the cranial nerve proximally.
- Perineural tumor spread (PNTS), defined as clinically or radiographically apparent macroscopic spread along nerves, is considered higher risk and warrants comprehensive coverage of the involved, and potentially interconnected, cranial nerve pathways.[2,3]
- For patients with very-high-risk CSCC such as those with PNTS, consider referral to a high-volume center given potential for severe toxicity when irradiating cranial nerves adjacent to critical optic and neurologic structures.
- RT is contraindicated for genetic conditions predisposing to skin cancer (eg, basal cell nevus syndrome [Gorlin syndrome]) and relatively contraindicated for patients with connective tissue diseases (eg, scleroderma).
- Given higher complication rates, reirradiation should not be routinely utilized for recurrent disease within a prior radiation field.
- Isotope-based brachytherapy can be an effective treatment for certain sites of disease, particularly on the head and neck.[a]
- There are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy.[a]
- Image-guided radiation therapy (IGRT) is considered best practice when treating with intensity-modulated radiation therapy (IMRT), proton beam radiotherapy, or 3-D conformal radiation. The use of IGRT for other types of radiotherapy to treat skin cancer is considered unnecessary.[a]
- Radiation treatments should be given by a practicing radiation oncologist with radiation physics support to meet established quality assurance and dosimetric constraints.

RT Dosing Table on SCC-E (2 of 2)

Footnote

[a] See Discussion.

References

[1] Likhacheva A, Awan M, Barker CA, et al. Definitive and postoperative radiation therapy for basal and squamous cell cancers of the skin: Executive summary of an American Society for Radiation Oncology Clinical Practice Guideline. Pract Radiat Oncol 2020;10:8-20.
[2] Porceddu SV, Daniels C, Yom SS, et al. Head and Neck Cancer International Group (HNCIG) Consensus Guidelines for the Delivery of Postoperative Radiation Therapy in Complex Cutaneous Squamous Cell Carcinoma of the Head and Neck (cSCCHN). Int J Radiat Oncol Biol Phys 2020;107:641-651.
[3] Bakst RL, Glastonbury CM, Parvathaneni U, et al. Perineural invasion and perineural tumor spread in head and neck cancer. Int J Radiat Oncol Biol Phys 2019;103:1109-1124.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

Continued

PRINCIPLES OF RADIATION THERAPY

Primary Tumor	RT Dosing
Definitive RT	BED10 of 70–93 Gy for conventional fractionation BED10 of 56–88 Gy for hypofractionation
Postoperative Adjuvant RT[2]	BED10 of 60–79 Gy for conventional fractionation BED10 of 56–70 Gy for hypofractionation
Regional Disease	
• Lymph node regions, after lymph node dissection ‣ Negative margins, no ENE ‣ Positive margins or ENE	 50–60 Gy over 5 to 6 weeks 60–66 Gy over 6 to 7 weeks
• Lymph node regions, without lymph node dissection ‣ Clinically positive	 60–70 Gy over 6 to 7 weeks
• Clinically at-risk nerves	50–60 Gy over 5 to 6 weeks
S-ITM	
• Resected • Unresected	50–60 Gy over 5 to 6 weeks 60–70 Gy over 6 to 7 weeks

- BED = Biologically Effective Dose.
- Conventionally fractionated radiotherapy consists of five daily treatments per week.
- Hypofractionated radiotherapy consists of daily treatments or two to four treatments per week. Fraction sizes larger than 6 Gy are not routinely recommended outside of the palliative setting.

[2] Porceddu SV, Daniels C, Yom SS, et al. Head and Neck Cancer International Group (HNCIG) Consensus Guidelines for the Delivery of Postoperative Radiation Therapy in Complex Cutaneous Squamous Cell Carcinoma of the Head and Neck (cSCCHN). Int J Radiat Oncol Biol Phys 2020;107:641-651.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

Field Cancerization/Confluent Epidermal Dysplasia (SCC-2)[1]

- Actinic keratoses should be treated at first development.
  - Accepted treatment modalities (in addition to SCC-2) include topical imiquimod and topical tirbanibulin. For hyperkeratotic actinic keratoses, pretreatment with topical tazarotene, curettage, or topical keratolytics (topical urea, lactic acid, and salicylic acid) prior to above therapies and select therapies listed in table 1 may be considered. Another modality that may be considered is topical diclofenac (category 2B).
- Actinic keratoses that have an atypical clinical appearance or do not respond to appropriate therapy should be biopsied for histologic evaluation.
- Use of oral retinoids (eg, acitretin, isotretinoin) is a therapeutic option used to reduce the development of actinic keratoses. Side effects of oral retinoids may be significant, especially in patients of childbearing potential, and therapeutic benefits are limited to the duration of the regimen. Topical retinoids were shown not to reduce development of actinic keratosis.
- In patients with CSCC in situ (Bowen disease), therapies such as topical 5-FU, topical imiquimod, and photodynamic therapy (eg, ALA, porfimer sodium) may be considered.[a]
- Vigorous cryotherapy[2] may be considered for discrete lesions (not field cancerization).
- Focal squamous cell carcinoma in situ arising within actinic keratosis is not appropriate for surgery and should be treated topically.

Table 1: Therapy Options for Field Cancerization/Confluent Epidermal Dysplasia

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Topical 5-FU based regimens ‣ Topical 5-FU ± calcipotriol (calcipotriene)[b,3,4]	• Topical aminolevulinic acid (in conjunction with PDT)	• Acitretin[5] • Capecitabine[1,6] (for severe refractory disease that has progressed on oral retinoids) • Isotretinoin • Porfimer sodium (in conjunction with PDT)

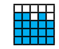
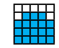
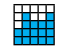
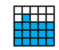
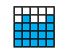
See Evidence Blocks on SCC-F (EB-1) and SCC-F (EB-2)

[a] Cure rates are approximately 10% lower than for surgical treatment modalities. Jansen MHE, et al. J Invest Dermatol 2018;138:527-533; Drew BA, et al. Dermatol Surg 2017;43:1423-1430.
[b] The longest duration of prophylaxis against SCC has been demonstrated with topical 5-FU plus calcipotriol.

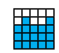
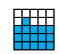
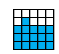
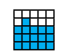
References on SCC-F (4 of 4)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

TREATMENT FOR ACTINIC KERATOSES (See SCC-2 and SCC-F 1 of 4)

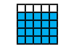
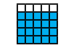
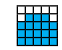
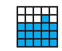
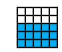
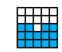
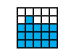
Topical imiquimod	
Topical tirbanibulin	
Topical diclofenac	
Pretreatment for hyperkeratotic actinic keratoses	
Topical tazarotene	
Topical keratolytics (topical urea, lactic acid, and salicylic acid)	

ALTERNATIVE THERAPY FOR SCC IN SITU (BOWEN'S DISEASE) (See SCC-F 1 of 4)

Topical 5-fluorouracil	
Topical imiquimod	
Photodynamic therapy with ALA	
Photodynamic therapy with porfimer sodium	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

FIELD CANCERIZATION/CONFLUENT EPIDERMAL DYSPLASIA (See SCC-F 1 of 4)

Preferred Regimens	
Topical 5-FU	
Topical 5-FU + calcipotriol (calcipotriene)	
Other Recommended Regimen	
Topical aminolevulinic acid (in conjunction with PDT)	
Useful in Certain Circumstances	
Acitretin	
Capecitabine (for severe refractory disease that has progressed on oral retinoids)	
Isotretinoin	
Porfimer sodium (in conjunction with PDT)	

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

PRINCIPLES OF SYSTEMIC THERAPY

Very-High-Risk Disease (SCC-5)
- Consider neoadjuvant cemiplimab-rwlc if the tumor has very rapid growth, in-transit metastasis, lymphovascular invasion, is borderline resectable, or surgery alone may not be curative or may result in significant functional limitation.

Primary and Recurrent laCSCC Disease[c] (SCC-6)
- If surgery is not feasible, recommend RT, and multidisciplinary teams can consider concurrent systemic therapy in select cases (Table 2).
- If curative surgery and curative RT[d] are not feasible, recommend multidisciplinary consultation to consider systemic therapy alone (Table 3).

S-ITM (SCC-8)
- For S-ITM, multidisciplinary team can consider systemic therapy alone (Table 3) or in combination with local therapies such as RT or surgery (Table 2).

New Regional Disease (SCC-7 and SCC-9)
- For most cases of fully resected regional disease, adjuvant systemic therapy is not recommended, unless within a clinical trial.
- For resected high-risk regional disease of head and neck, consider RT ± systemic therapy (Table 2).
- For unresectable, inoperable, or incompletely resected disease, multidisciplinary consultation is needed to consider:
  - RT ± systemic therapy (Table 2)
  - Systemic therapy alone if curative RT[d] is not feasible (Table 3).

Regional Recurrence or Distant Metastatic Disease (SCC-10)
- For regional recurrence or distant metastases, multidisciplinary team can consider systemic therapy alone (Table 3) or in combination with RT (Table 2).

Table 2: Systemic Therapy Options for Use with RT (or Surgery for Regional Recurrence Following Systemic Treatment)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cisplatin[e,7] • Clinical trial	• Carboplatin ± paclitaxel[e,11,12] • EGFR inhibitors (eg, cetuximab)[e,13]	• Cisplatin + 5-FU[e,20]

Table 3: Options for Systemic Therapy Alone

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Cemiplimab-rwlc[f,g] (if curative RT[d] or surgery is not feasible for locally advanced, recurrent, or metastatic disease)[8,9] • Pembrolizumab[f,g] (if curative RT[d] or surgery is not feasible for locally advanced, recurrent, or metastatic disease)[10] • Clinical trial	• Cosibelimab-ipdl (if curative RT[d] or surgery is not feasible for locally advanced [category 2B] or metastatic disease)[14] • Nivolumab[h] • If ineligible for or progressed on immune checkpoint inhibitors and clinical trials, consider: ‣ Carboplatin + paclitaxel ± cetuximab[15-19] ‣ EGFR inhibitors (eg, cetuximab)[e,13]	• Neoadjuvant cemiplimab-rwlc[g,8] • If ineligible for or progressed on immune checkpoint inhibitors and clinical trials, consider: ‣ Capecitabine[21,22] ‣ Cisplatin[e,7] ‣ Cisplatin + 5-FU[e,20]

See Evidence Blocks on SCC-F (EB-3) and SCC-F (EB-4)

Footnotes on SCC-F (3 of 4)

References on SCC-F (4 of 4)

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

SYSTEMIC THERAPY FOR SQUAMOUS CELL SKIN CANCER (See SCC-F 2 of 4)

Systemic Therapy Options for Use with RT

	Locally Advanced Disease in Non-Surgical Candidates	New Regional Disease – resected high-risk	New Regional Disease – inoperable or incompletely resected	Regional Recurrence or Distant Metastatic Disease	Satellitosis/In-transit Metastasis (S-ITM)
Preferred Regimen					
Cisplatin					
Other Recommended Regimens					
Carboplatin					
Carboplatin/paclitaxel					
Cetuximab					
Useful in Certain Circumstances					
Cisplatin + 5-FU					

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

SYSTEMIC THERAPY FOR SQUAMOUS CELL SKIN CANCER (See SCC-F 2 of 4)

Options for Systemic Therapy Alone

	Locally Advanced Disease in Non-Surgical Candidates	New Regional Disease – inoperable or incompletely resected	Regional Recurrence or Distant Metastatic Disease	Satellitosis/In-transit Metastasis (S-ITM)
Preferred Regimens				
Cemiplimab-rwlc				
Pembrolizumab				
Other Recommended Regimens				
Carboplatin/paclitaxel				
Carboplatin/paclitaxel/ cetuximab				
Cetuximab				
Cosibelimab-ipdl	*	*	*	*
Nivolumab				
Useful in Certain Circumstances				
Capecitabine				
Cisplatin				
Cisplatin + 5-FU				
Neoadjuvant cemiplimab-rwlc				

*Evidence Block development in progress

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.

FOOTNOTES

[c] A cure is unlikely to result from surgery and/or RT or there are concerns of significant functional impairment. Multidisciplinary discussion and multimodality treatment (including neoadjuvant and adjuvant therapy) merits consideration.

[d] Assessment of feasibility of RT should be made by a radiation oncologist.

[e] These options have occasionally produced useful responses, but data supporting efficacy are limited.

[f] Recent published phase II trial data support the efficacy and safety of cemiplimab-rwlc and pembrolizumab in patients with laCSCC, recurrent, and metastatic CSCC. Migden MR, Khushalani NI, Chang ALS, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. Lancet Oncol 2020;21:294-305. Rischin D, Migden MR, Lim AM, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. J Immunother Cancer 2020;8:e000775. Hughes BGM, Munoz-Couselo E, Mortier L, et al. Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): an open-label, nonrandomized, multicenter, phase II trial. Ann Oncol 2021;32:1276-1285.

[g] 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.

[h] Nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

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[4] Jansen MHE, Kessels JPHM, Nelemans PJ, et al. Randomized trial of four treatment approaches for actinic keratosis. N Engl J Med 2019;380:935-946.
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[8] Gross ND, Miller DM, Khushalani NI, et al. Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma. N Engl J Med 2022;387:1557-1568.
[9] Rischin D, Migden MR, Lim AM, et al. Phase 2 study of cemiplimab in patients with metastatic cutaneous squamous cell carcinoma: primary analysis of fixed-dosing, long-term outcome of weight-based dosing. J Immunother Cancer 2020;8:e000775.
[10] Hughes BGM, Munoz-Couselo E, Mortier L, et al. Pembrolizumab for locally advanced and recurrent/metastatic cutaneous squamous cell carcinoma (KEYNOTE-629 study): an open-label, nonrandomized, multicenter, phase II trial [published correction appears in Ann Oncol 2022;33:853]. Ann Oncol 2021;32:1276-1285.
[11] Maring S, Elsayad K, Stenner M, et al. Efficacy of carboplatin/paclitaxel-based radiochemotherapy in locally advanced squamous cell carcinoma of head and neck. Oncol Res Treat 2018;41:736-743.
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Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PDEMA TECHNIQUE

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

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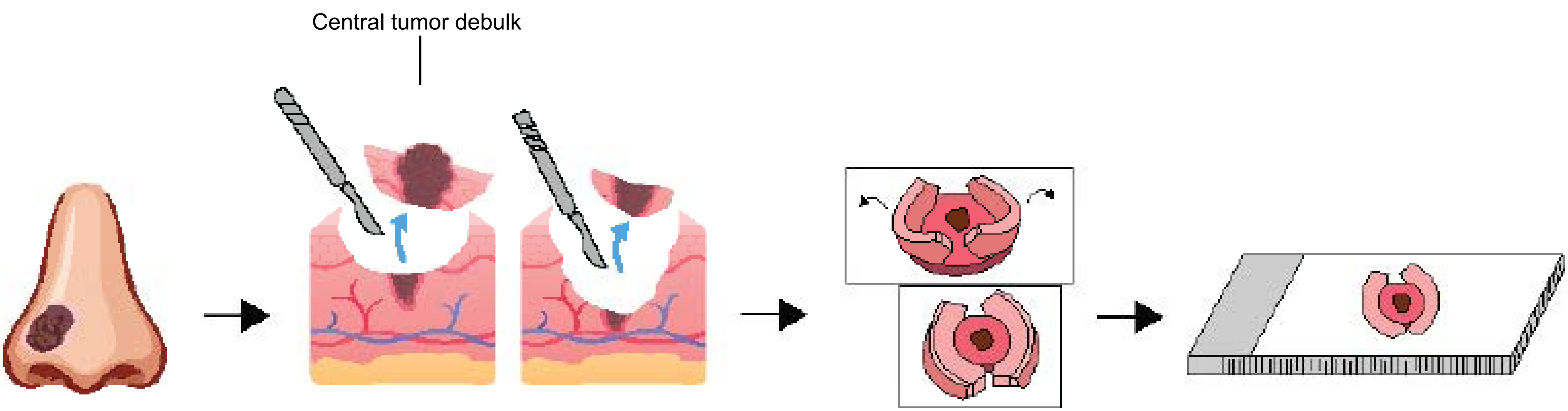
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PDEMA TECHNIQUE

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

Figure 1

Tubingen muffin technique



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

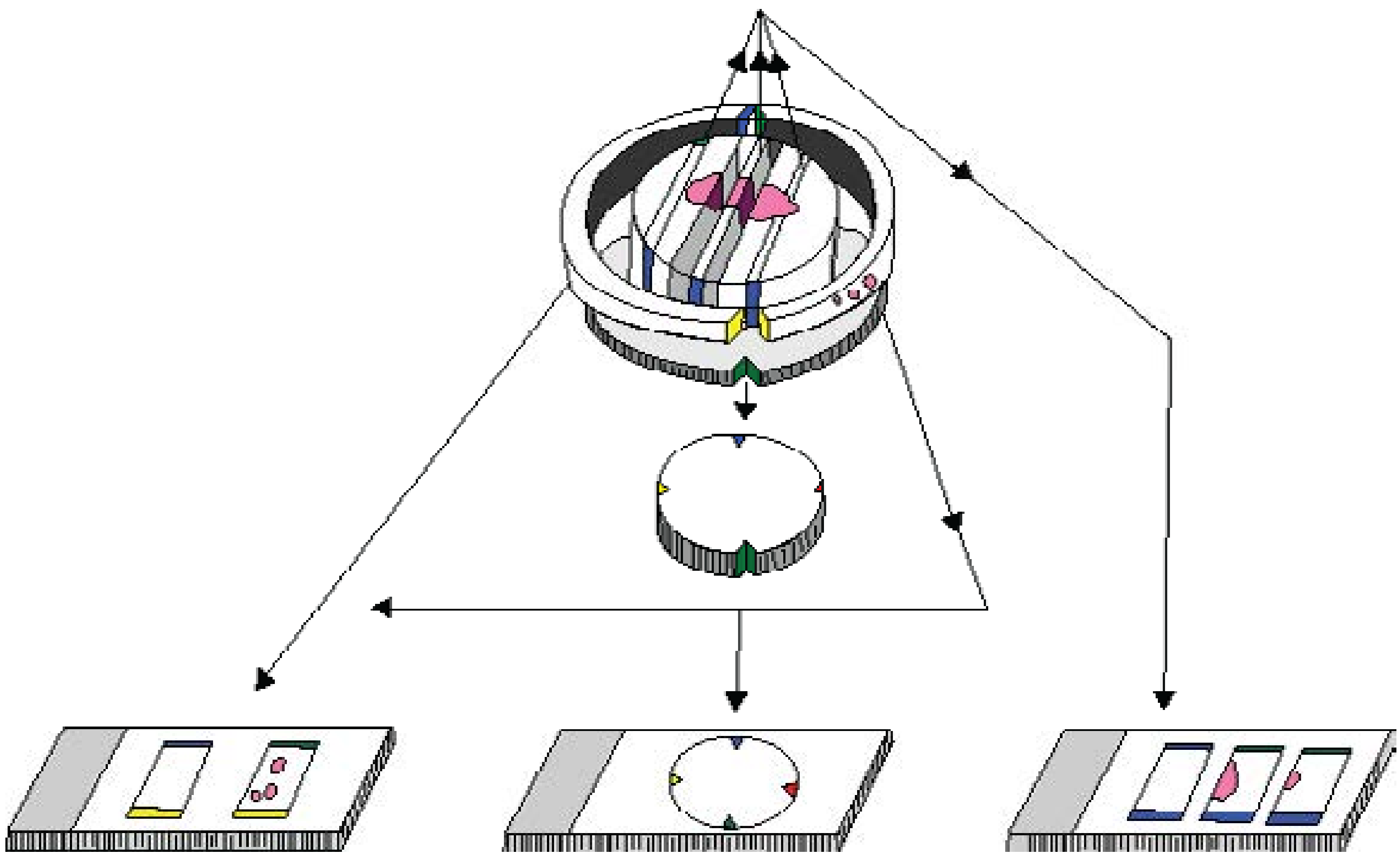
Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PDEMA TECHNIQUE

Figure 2

Tubingen torte technique

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



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PRINCIPLES OF PDEMA TECHNIQUE

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

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

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

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Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF CANCER RISK ASSESSMENT AND COUNSELING

- **The decision to offer genetic testing involves three related stages:**
  1) Pre-test counseling prior to ordering testing;
  2) Consideration of the most appropriate testing strategy; and
  3) Testing result disclosure and post-test counseling.
- **There are rare genetic syndromes that can markedly predispose patients to aggressive CSCC formations. These include xeroderma pigmentosum (XP) and recessive dystrophic epidermolysis bullosa (RDEB). Patients with these conditions should be referred to a cancer center with particular expertise in CSCC prevention and prophylaxis.**
- **It is recommended that a genetic counselor, medical geneticist, endocrinologist, oncologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics be involved at each stage whenever possible. Clinicians without direct referral access to the appropriate expertise should be aware of the telehealth genetic counseling options available. These resources can be found through the National Society of Genetic Counselors (NSGC) "Find a Genetic Counselor" tool (www.nsgc.org).**

See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate for the following:
- **Principles of Cancer Risk Assessment and Counseling (EVAL-A)**
- **Pedigree: First-, Second-, and Third-Degree Relatives of Proband (EVAL-B)**

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.

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

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

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

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

Clinical N (cN)

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

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

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

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

Continued

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

Pathological N (pN)

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

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

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis

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

***Table 2.* AJCC Prognostic Stage Groups**

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

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

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

ABBREVIATIONS

ALA	aminolevulinic acid
BED	biologically effective dose
C&E	curettage and electrodesiccation
CLL	chronic lymphocytic leukemia
CSCC	cutaneous squamous cell carcinoma
ENE	extranodal extension
FDG	fluorodeoxyglucose
FNA	fine-needle aspiration
H&P	history and physical
IGRT	image-guided radiation therapy
IMRT	intensity-modulated radiation therapy
KID	keratitis, ichthyosis, deafness
laCSCC	locally advanced cutaneous squamous cell carcinoma
NSGC	National Society of Genetic Counselors
PDEMA	peripheral and deep en face margin assessment
PDT	photodynamic therapy
PNI	perineural invasion
PNTS	perineural tumor spread
RDEB	recessive dystrophic epidermolysis bullosa
SBRT	stereotactic body radiation therapy
S-ITM	satellitosis/in-transit metastasis
SLNB	sentinel lymph node biopsy
UV	ultraviolet
XP	xeroderma pigmentosum

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2025
Squamous Cell Skin Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Squamous Cell Skin Cancer. Last updated February 07, 2025.

Table of Contents

Overview

Cutaneous squamous cell carcinoma (SCC or CSCC) is the second most common skin cancer.[1-3] Numerous population-based studies have demonstrated that the incidence of SCC is rising.[1,4-8] Some studies show that SCC incidence rates are rising more rapidly than basal cell carcinoma (BCC), reducing the difference in incidence between these two skin cancers.[2,3,9] Current estimates by the American Cancer Society indicate that 3.3 million individuals in the United States have ≥1 basal or squamous cell skin cancers where approximately 20% are SCCs.[10] Although rarely metastatic, SCC can produce substantial local destruction along with disfigurement and may involve extensive areas of soft tissue, cartilage, and bone. SCCs generally have a good prognosis, with 5-year survival of about 98%.[1,11-13] However, the treatment landscape continues to evolve to improve a patient's quality of life and minimize disease recurrence.

Guidelines Update Methodology

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

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Squamous Cell Skin Cancer, an electronic search of the PubMed database was performed to obtain key literature published since the previous Guidelines update, using the search term: cutaneous squamous cell carcinoma. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[14]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Practice Guideline; Randomized Controlled Trial; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[15] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Risk Factors for SCC

A number of risk factors are associated with the development of SCC. The most recognized environmental carcinogen is sunlight. Evidence reveals that chronic sun exposure, total site-specific exposure, and number of site-

specific sunburns are strongly correlated with development of SCC.[16-19] Due to the link with chronic and cumulative sun exposure, SCC rates are higher in occupations involving outdoor work[20-22] and increase with age, particularly in sun-exposed sites.[2,9,18] Indoor tanning is also significantly associated with SCC. According to two large meta-analyses, any exposure to indoor tanning increases the risk of SCC by 67%,[23] with the prevalence of indoor tanning much higher than previously thought among U.S. adults and college students.[24]

Individuals with light skin, hair, and eye color who have received too much sun exposure are at the greatest risk for SCC.[25-27] The incidence of ultraviolet (UV)-induced SCCs is very low in non-white populations and has been poorly quantified in people of mixed ethnicities. Most of SCCs develop on sun-exposed skin sites, especially the head and neck area.[5,17,28] Actinic keratoses (AKs) and Bowen's disease, if left untreated, can also progress to invasive SCC with the potential for metastasis.[21,29-31] Furthermore, SCCs are also known to develop in association with scars or chronic wounds (Marjolin's ulcer).[32,33] These types of SCCs occur at similar rates in people of all racial and ethnic groups. Such SCC lesions tend to be difficult to treat and have higher risk of recurrence.[34-36]

Lastly, certain genetic syndromes greatly predispose affected individuals to SCC formation, such as albinism[37-39] and xeroderma pigmentosum.[40-42] Certain settings of immunosuppression (eg, organ transplantation, lymphoma, chronic lymphocytic leukemia, drug-induced immunosuppression, and HIV) also predispose affected individuals to UV-induced SCC.[43-50] Most notably, analyses of transplant registries have reported a 5-fold to 113-fold increase in incidence of SCC in patients with transplants compared to the general population.[45,51-53] These patient groups are also at high risk of developing multiple CSCCs and tumors that can behave aggressively.[42,54-61] Within these high-risk groups, individual patients should be identified for closer follow-up (See *Identification and Management of Patients at High Risk for Multiple Primary CSCCs* in the algorithm).

Clinical Presentation and Workup

On clinical presentation of a suspicious lesion, workup for SCC begins with a history and physical examination. 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.[62,63] Skin lesions in high-risk populations may be difficult to assess clinically; therefore, a low threshold for performing skin biopsies in these patients is necessary. Basosquamous carcinoma may behave as aggressively as CSCC.[64-66]

Imaging studies of the area of interest should be done when locally, extensive or metastatic disease is suspected, which includes deep structural involvement such as bone, perineural disease, and deep soft tissue.[67,68] Due to its higher sensitivity, MRI with and without contrast is preferred for perineural disease or deep soft tissue involvement.[69-71] If bone disease is suspected, CT with contrast is preferred unless contraindicated. Imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is sufficient to diagnose local recurrence, but MRI with and without contrast can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or other imaging modalities can be used for confirmation and to gauge extent of disease. For rare instances that present with distant metastatic disease at diagnosis, the distant metastases pathway should be followed. (See *Follow-up* in the algorithm). After a CSCC diagnosis is confirmed, additional workup includes a complete skin and regional lymph node (LN) examination. A full skin

examination is recommended because individuals with a skin cancer often have additional, concurrent precancers or cancers located at other, usually sun-exposed skin sites. These individuals are also at increased risk of developing cutaneous melanoma.[60,72,73]

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

After the additional workup, a risk assessment of the primary tumor should be performed (See *Stratification to Determine Treatment Options and Follow-up for Local CSCC Based on Risk Factors for Local Recurrence, Metastases, or Death from Disease* in the algorithm). Risk category assignment should be based on the highest risk factor present. The high-risk group has elevated risk of local recurrence while the very-high-risk group has elevated risks of local recurrence and metastasis. Other staging systems, including the AJCC 8th edition staging system of CSCC, have been formulated and independently tested to define high-risk groups among patients with localized disease, and can act as additional sources of reference.[11,54,55,60,74-81]

History & Physical

Location and Diameter

Anatomic location has been known to be a risk factor for SCC recurrence and metastasis for many years.[34,55,82] In general, SCCs that develop in the head and neck area, particularly the ears and vermillion lips, are more likely to recur and metastasize than those developing on the trunk and extremities.[11,34,54,55,75,82-85] Besides the head and neck, SCCs that develop on the hands, feet, pretibial, and anogenital areas are also at greater risk of local recurrence and nodal metastasis, independent of diameter.[11,86,87]

Tumor diameter has also been shown to be a risk factor for SCC recurrence and metastasis.[34,55,85,88,89] Although different divisions have been used, robust data support that tumors >2 cm are at higher risk of recurrence, metastasis, and poor disease-specific survival (DSS).[11,34-36,54,55,74,90,91] Taken together, the NCCN Panel recommends that low-risk location (trunk, extremities) and ≤2 cm constitute low-risk CSCC. Low-risk location (trunk, extremities) and size >2 cm (but ≤4 cm), or high-risk locations (head, neck, hands, feet, pretibia, and anogenital area), constitute high-risk CSCC.

Regardless of location, the NCCN Panel recommends that a tumor diameter of >4 cm warrants the very-high risk designation. This is based on data from a large, prospective study, which demonstrate that lesion <4 cm and ≥4 cm are associated with 3-year DSS of 93% and 67% (*P* =.0003), respectively.[88] Studies have also reported that mean lesion diameter of 4.2 cm (±3.4)[92] and >5 cm[85] as significantly associated with LN metastases.

Clinical Borders

The risk factor of well-defined versus poorly-defined clinical tumor borders has been reported in the context of BCC and extrapolated to the SCC population based on clinical experience of the NCCN Panel.[93-95] The NCCN Panel considers well-defined clinical borders as a low-risk SCC feature.

Primary Versus Recurrent Disease

The higher risk of recurrence and metastasis for recurrent versus primary disease has been extensively documented in the literature.[34,88,90,92,96,97] The NCCN Panel notes that primary disease is a low-risk of recurrence feature.

Immunosuppression

In addition to increasing the risk of SCC development, immunosuppression has been shown to be associated with recurrence, metastasis, and death in multiple reports.[34,54,55,58-60,74,98,99] Studies from the organ transplant literature have further elucidated features linked with

SCCs in this unique population of patients who are immunocompromised.[58,77,100,101] A retrospective review confirmed that patients with transplants with CSCC had more primary tumors and were more likely to have deep tissue spread and perineural and lymphatic invasion.[58] Other studies found diffuse/focal spindle cell morphology, evidence of human papillomavirus (HPV) infection, and aggressive subclinical extension to be more likely in SCCs from patients with transplants.[100,102] Two large retrospective studies reported high rates of SCC recurrence and metastasis among patients with transplants despite the fact that most SCCs were stage I/II at presentation.[77,101]

Site of Prior Radiotherapy or Chronic Inflammation

Tumors developing in sites of prior radiotherapy (RT) refer to primary CSCCs arising in areas previously irradiated for unrelated conditions. All recurrent tumors are defined as high risk irrespective of prior therapy. Data support that prior RT for unrelated (frequently benign) conditions is a risk factor for SCC recurrence or metastasis.[90,103] Retrospective studies and meta-analyses have also documented increased rates of metastasis for SCC arising from sites of chronic scarring or inflammation.[34,35,92,96,104-106]

Rapidly Growing Tumor

The evidence for growth rate and prognosis is lacking in CSCC. Based on clinical experience, the NCCN Panel included rapid growth rate as a high-risk factor. A Japanese study reported tumor size and rapid growth as prognostic factor for SCC.[107] In a small retrospective series, tumor growth rate of >4 mm/month exhibits a higher risk of nodal progression and a shorter progression time to LN metastasis.[108] There is also evidence that CSCC in immunosuppressed individuals are often characterized by aggressive behavior and rapid growth.[109,110]

Neurologic Symptoms

In tumors with perineural involvement (PNI), clinical symptoms suggesting possible involvement of sensory or motor nerves are commonly absent but may occur. Symptoms include pain, burning, stinging, anesthesia, paresthesia, facial paralysis, diplopia, and blurred vision.[111,112] Any suggestion of neurologic involvement in the region of a CSCC should place that tumor in a high-risk category, as PNI is associated with recurrence, metastasis, and poor outcomes.[11,34,54,74,82,88,90,106,113-115] Poorer outcomes are associated with the presence of clinical symptoms and extent of neuronal involvement.[74,116-119]

Pathology

Degree of Differentiation

Although Broders originally divided CSCC histologically into four grades in 1920, the NCCN Panel has adopted the current trend to reduce the divisions to two groups: 1) well or moderately differentiated; and 2) poorly differentiated.[75,120] Many studies, including some very large retrospective studies (N > 1000) provide evidence that poor differentiation is correlated with CSCC recurrence, metastasis, DSS, and overall survival (OS).[11,34,35,54,74,82,85,90,92,97,106,107,121]

Histology

The histologic subtypes of acantholytic (adenoid), adenosquamous, metaplastic (carcinosarcomatous), and desmoplastic SCC are rare.[122] Only case reports and case series document the outcomes of patients with these subtypes, and thus their prognostic significance is debated.[123-128] Desmoplasia is associated with greatly increased risks of recurrence and metastasis.[55,129] 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).[89] A 2011 review of 72 patients with desmoplastic SCC reported a rate of recurrence of 80%.[130] Since these tumors may have a high risk of recurrence and likely would not be included in the high-risk category based on their degree of differentiation, the Panel decided to list them as separate risk factors.

Depth

Data from many large studies support that risk of recurrence and metastasis increases with increasing lesion depth.[11,34,54,74,75,85,89-91,97,131] CSCC lesion depth can be quantified as thickness in millimeters (mm)[132] or by anatomic layer(s) invaded, both of which have been included in the T classification of the AJCC 7th and 8th Edition staging for CSCC.[120,133]

Prospective data from Brantsch and colleagues reported metastasis rates of 0% of tumors ≤2.0 mm in thickness, 4% of tumors 2.1 to 6.0 mm in thickness, and 16% of tumors thicker than 6.0 mm, with depth measured as the greatest vertical distance from the top to the bottom of the tumor.[55] Other studies show that the risk of recurrence and metastasis is significantly higher for lesions with thickness >2 mm.[54,85,91] Meta-analyses have shown that 4-mm and 6-mm thickness cutoffs are prognostic for recurrence and metastasis,[34,54] and one retrospective study showed that risk for recurrence and metastasis increases significantly for every 1-mm increase in tumor depth.[78] Regarding anatomic level of invasion, some studies showed significantly higher risk of recurrence or metastasis for CSCC lesions with Clark levels IV–V, corresponding to invasion of the deep reticular dermis or subcutaneous fat, respectively.[34,89] Other studies have shown that lesions with invasion into the subcutaneous fat significantly increases rates of recurrence and metastasis.[11,54,74,75,88,90,91]

The NCCN Panel has chosen thickness <2 mm and no invasion beyond subcutaneous fat as low risk while >6 mm or invasion beyond subcutaneous fat is considered very high risk. If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, the Panel recommends considering narrow margin excisional biopsy to obtain accurate measurement of thickness and anatomic level of invasion.

Perineural Involvement

PNI is uncommon in any non-melanoma skin cancer (NMSC), but develops more frequently and is more aggressive in CSCC versus BCC.[117,118,134,135] PNI poses increased risks of recurrence, metastasis (nodal and distant), and death, is more common in recurrent versus primary tumors, and is associated with other risk factors, including larger lesion size, poor differentiation, and adenosquamous, desmoplastic, and metaplastic subtypes.[11,34,54,74,75,82,88,90,106,113-115,130,136-139] Specifically, PNI with tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring ≥0.1 mm has been associated with metastasis and DSS.[75,79,133] 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.[69,70,112,119,140]

Lymphatic or Vascular Involvement

Significant association between lymphovascular invasion (LVI) and LN metastasis has been reported in prospective[92,115] and retrospective studies.[114] One retrospective study showed that in high-risk CSCC populations with PNI or neurotropism, LVI was significantly associated with DSS and all-cause death.[79] Based on these data, the Panel considers lymphatic or vascular involvement an indication of very-high-risk SCC.

Field Cancerization/Confluent Epidermal Dysplasia

Field cancerization is defined as UV light induced confluent dysplasia clinically manifested as diffuse AKs and superficial (in situ) SCC.[141] AKs should be treated at first development and biopsied for histologic evaluation if they have an atypical clinical appearance or do not respond to treatment. Treatment is particularly important in patients with diffuse AKs and/or field cancerization, as these patients are at high risk of developing multiple primary CSCCs.[142] Given the limited penetration beyond the epidermis and lower cure rates than with surgical techniques, superficial therapies should be reserved for those patients with SCC in situ.[143-146] The NCCN Panel's experience indicates that they may be effective for anatomically challenging locations, and recurrences are often small and manageable.

Prevention of Actinic Keratoses

The regular use of sunscreen can significantly reduce the rate of development of new AKs and CSCCs, as well as increases remission rates of AKs.[147-150] Application of sunscreen is particularly important to areas such as the head, neck, hands, and forearms. Oral nicotinamide may also be an effective way to reduce the development of CSCC. Nicotinamide is a form of vitamin B3 that enhances UV-induced DNA damage repair and reduces the UV-induced immunity suppression.[151] A phase III randomized control trial (N = 386) concluded that the incidence of new AKs and CSCCs was 13% and 30% lower, respectively, compared to the control placebo group at 12 months.[152] While a meta-analysis by Mainville et al considers that oral nicotinamide is an effective preventative option for healthy patients and those with organ transplants, two other clinical trials concluded that AK rate was not significantly reduced in immunocompromised patients.[153-155]

Treatment of Actinic Keratoses

Cryotherapy has been used to treat AK for many decades, despite lack of prospective randomized trials comparing them with non-treatment. Large prospective randomized trials in patients with AKs (N > 100) have shown that each of the following therapies provides better complete clearance rates compared with placebo: topical 5-fluorouracil (5-FU) with or without calcipotriol,[156-161] topical imiquimod,[162-165] topical tirbanibulin,[166] and photodynamic therapy (PDT).[167-175] Prospective randomized trials have reported pair-wise comparisons of the above treatments, but results are not consistent. These comparisons include PDT versus cryotherapy,[167,169,172,176-178] imiquimod,[179,180] 5-FU,[181-183] or ingenol mebutate[184-186]; cryotherapy versus 5-FU or imiquimod[187-189]; and 5-FU versus imiquimod[190] or ingenol mebutate.[191,192] Meta-analyses of randomized trials have attempted to determine an order of preference for these treatments.[193-196]

The NCCN Panel currently assigns a preference for 5-FU based on data from a randomized trial that reported the cumulative probability of remaining free from disease progression was significantly higher for 5-FU (74.7%) than imiquimod (53.9%), MAL-PDT (37.7%), or ingenol mebutate (28.9%).[197] The longest duration for CSCC prophylaxis has been demonstrated with the combination of 5-FU and calcipotriol.[161] It was demonstrated that more participants who received topical calcipotriol plus 5-FU for AK remained disease-free over the >1500-day period compared to those receiving petroleum jelly-based skin product plus 5-FU.[198] Moreover, significantly fewer participants in the test cohort developed CSCC on the treated face and scalp within 3 years (7% vs. 28% in control group; hazard ratio, 0.215; $P = .032$).[198]

Topical tirbanibulin is a recommended treatment for AK based on results from two identically designed double-blind phase III trials in which patients received either tirbanibulin or vehicle ointment for the treatment of AKs on the face or scalp. In both trials, complete clearance by day 57 occurred in significantly more patients in the tirbanibulin group compared to the vehicle group (trial 1: 44% vs. 5%; $P < .001$; trial 2: 54% vs. 13%; $P < .001$).[166]

The utility of topical diclofenac is less clear, as efficacy results vary across large randomized trials, with some studies reporting no significant difference between diclofenac/hyaluronan and hyaluronan alone.[160,199-201] Diclofenac/hyaluronan has also been shown to be inferior to MAL-PDT and to 5-FU for the treatment of AKs.[202,203] The Panel therefore assigns category 2B for diclofenac in this setting.

Fewer high-quality data are available regarding the efficacy and safety of other treatments that are sometimes used and may be considered for treating AKs: chemical peels (trichloroacetic acid) and ablative skin resurfacing (eg, dermabrasion, laser).[204-211] These studies have all confirmed that chemical peel or laser resurfacing significantly reduced

AKs, although in some studies they were less effective than PDT or 5-FU. The use of chemical peels and ablative skin resurfacing varies widely across NCCN institutions.

AK on the lip, known as actinic cheilitis, may require a different approach. Prospective studies on the treatment of actinic cheilitis are limited. Therapies tested include surgical vermilionectomy, lip shave, electrodessication, laser vermilion ablation, laser resurfacing, 5-FU, laser + 5-FU, trichloroacetic acid (TCA) chemical peel, PDT, PDT + imiquimod, and diclofenac.[212-223] The NCCN Panel considers ablative laser vermilionectomy to be of value as a primary treatment option for extensive actinic cheilitis.

Retrospective studies, meta-analyses, and a small open-label phase II trial have shown that imiquimod was effective for treating patients with SCC in situ, with high rates of initial clearance (70%–100%) and low rates of recurrence.[224-228] One small double-blind randomized trial showed that imiquimod led to the resolution of 73% of lesions compared to 0% with vehicle control ($P < .001$).[229] Clearance rates with 5-FU tend to be lower than those for topical imiquimod and vary widely, ranging from 27% to 92%.[225,228,230-232] Toxicities are similar between imiquimod and 5-FU, being primarily inflammatory skin reactions such as severe eczematous reactions, ulceration, and erosions.[225,231,232]

PDT with photosensitizing agents including methyl aminolevulinate (MAL) and 5-aminolevulinic acid (ALA) or porfimer sodium is another option for superficial SCC. MAL is no longer produced in the United States. For SCC in situ, rates of initial complete clearance following PDT range between 52% and 98%.[231,233-244] Durable complete response rates range from 48% to 89%.[231-236,238-242,244,245] It has been shown that differences in PDT techniques can cause significant differences in clearance rate for SCC in situ.[234,242] Furthermore, results from randomized trials showed fewer treatments required for complete clearance and higher durable complete response rates with PDT versus cryotherapy.[232,246] Compared to 5-FU, PDT was also associated with higher rates of initial complete clearance and higher durable complete response rates.[231,232] Data suggest that 5-FU may be associated with lower risk of adverse events compared with PDT or cryotherapy, but it is unclear whether risk of toxicity differs between cryotherapy and PDT.[231,232,246]

Hyperkeratotic AKs pretreatment may include topical tazarotene, curettage, or topical keratolytics such as topical urea, lactic acid, and salicylic acid prior to treatment with 5-FU with or without calcipotriol, imiquimod, or tirbanibulin. The development of AKs may also be reduced by oral retinoid (eg acitretin, isotretinoin) treatment; however, there are significant side effects especially in patients with childbearing potential and the benefits are limited to the time of treatment.[247] Another treatment that may be considered for severe refractory disease after progression on oral retinoids is low-dose oral capecitabine, which was investigated in a small cohort of patients with transplants with varying side effects.[248,249]

Cryotherapy has been used for many years as a fast and cost-effective means for removal of SCCs. Prospective and retrospective studies, including large meta-analyses, have shown recurrence rates of 0% to 4% for invasive SCCs treated with cryotherapy.[34,250-253] For SCC in situ, recurrence rates range from 1% to 13% in retrospective studies[144,145,253,254] and 0% to 50% in prospective studies.[143,232,246,252,255] One prospective study reported that patients were much more likely to experience pain with cryotherapy compared with C&E, and time to complete healing was also significantly longer with cryotherapy.[143] Cryotherapy may also be associated with poorer cosmetic outcomes compared with topical 5-FU.[232]

Treatment Modalities for Local SCC

Curettage and Electrodesiccation

Curettage and electrodesiccation (C&E) is a fast and cost-effective technique for superficial lesions; however, it does not allow histologic margin assessment. Retrospective and observational data with long-term follow-up (>5 year) indicate that cure rates are between 95% to 100% for patients with primary CSCC lesions treated with C&E.[34,256-258] These estimates are largely based on patients with low-risk SCC, 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.[259,260]

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

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

Peripheral and deep en face margin assessment (PDEMA), or complete margin assessment, is a term used for a subset of surgical techniques for high-quality histologic visualization and interpretation of the margin surface or surgically excised tissue. Mohs micrographic surgery is the most common utilized PDEMA technique. Mohs procedures are particularly successful in non-metastatic basal and squamous cell skin cancers where tissue-sparing and precision microscopic control of margins is a priority and has been associated with lower recurrence rates.[261,262] While PDEMA is a team procedure that requires the participation of physicians from multiple disciplines, Mohs physicians serve as both the surgeon and pathologist requiring highly specialized training. Efforts have been extended to generate consensus recommendations to offer Mohs surgeons guidance and promote standardization to make data aggregate from multicenter clinical trials possible.[263]

Mohs is a primary treatment option for low-risk CSCC and high-risk CSCC, as well as the preferred surgical technique for very-high-risk CSCC because it allows intraoperative analysis of 100% of the excision margin. Additionally, Mohs is a treatment option for patients with locally advanced CSCC (laCSCC) following a multidisciplinary discussion to consider neoadjuvant systemic therapy and/or participation in a clinical trial. An extensive meta-analysis of studies with long-term follow-up (≥5 years) reported local recurrence rates of 3.1% for primary CSCCs and 10% for recurrences treated with Mohs.[34] Moreover, local recurrence rates have been reported to be significantly less likely with Mohs compared to standard excision.[264,265] Cure rates for Mohs depended on tumor diameter (<2 vs. ≥2 cm: 98.1% vs. 74.8%) and differentiation (well vs. poorly differentiated: 97.0% vs. 67.4%). For each of these subgroups, cure rates for Mohs were higher than for treatment with non-Mohs modalities.[34]

Retrospective and prospective observational studies of localized primary SCCs treated with Mohs reported local recurrence rates of 1.2% to 4.1% and rates of metastases between 0% and 6.3%.[256,257,266-279] Compared with primary tumors, rates of local recurrence or metastasis after Mohs are higher for recurrent tumors (previously treated with a non-Mohs modality).[90,268] For recurrent CSCCs treated with Mohs, subsequent local reported recurrences occurred 5.9% to 7.7%; metastasis 0% to 10%.[266-272] Other risk factors associated with recurrence after Mohs include larger subclinical extension and more Mohs stages required for clearance.[268] CSCC with PNI is associated with elevated rates of recurrence (6.8%–32.3%) in studies that occasionally include BCC as well as treatment by RT.[117,136,138,280-282] Risk factors associated with metastasis after Mohs include: size >2 cm, Clark's level (metastatic CSCC are more likely to be deeper – Clark level III–V), poor differentiation, location in areas of prior radiation, small tumor nests and infiltrative tumor strands, single-cell infiltration, PNI, and acantholysis.[90]

It is not uncommon to find discrepancies between pathology results from preoperative biopsy or initial debulking compared with frozen sections taken during Mohs.[283-285] When Mohs with marginal assessment is being performed and the preoperative biopsy is considered insufficient for providing all the staging information required to properly treat the tumor, submission of the central specimen for pathologic evaluation with paraffin sections is recommended. If invasion to the parotid fascia is noted, superficial parotidectomy may be indicated.

Excision with PDEMA (via permanent or frozen section) is acceptable as an alternative to Mohs provided that it includes a complete margin assessment of en face peripheral and horizontal deep margins coupled with close communication between pathologists and surgeons regarding where within the tumor bed further resection is needed. These subsequent specimens must also be processed, and results communicated via the PDEMA method. Low recurrence rates (0%–1%), and specifically lower recurrence rates when compared directly to standard excision,[286] have been reported where histologically clear margins are achieved.[287] It is important to note that truly histologically negative margins are not necessarily achieved by frozen sectioning alone, without PDEMA. Studies have reported that for CSCC tumors with negative margins upon frozen sectioning, permanent paraffin section analysis indicates positive margins in 10% to 20%.[284,285,288-290] These discrepancies may be due to unrepresentative sampling of the margins, and instances of frozen sections in which permanent section showed positive margins have reported much higher recurrence rates.[290] Overall, the descriptive term PDEMA underscores the Panel's belief that complete assessment of all tissue margins is the key to optimal tumor removal for high-risk tumors. Such effort at local control is particularly important in SCC because one third of deaths occur from local disease alone. Mohs or other forms of PDEMA are also recommended in case of positive margins after standard excision for low-risk CSCC.

Shave Removal

Shave removal, the shaving of epidermal or dermal lesion, is a sharp removal by transverse bowl-shaped slicing to remove epidermal and dermal lesions, without including fat, and does not require suture closure.[291] Like C&E, there is concern for inaccurate margin status assessment with shave removal.[292] However, it is a recommended technique for low-risk BCCs located in the trunk or extremities. Shave removal studies have reported 0.5% to 30% rate of recurrence over a 3- to 5-year follow-up, multiple tumors treated in single visits, and a risk for misdiagnosis of only 1% of patients.[291-294] Shave removal is a primary treatment option for low-risk CSCC when the tumor does not extend beyond the dermis.

Standard Excision with Postoperative Margin Assessment

A common therapeutic option for CSCC is standard surgical excision followed by postoperative pathologic evaluation of margins. Retrospective analyses and prospective observational studies have reported rates of recurrence or metastasis ranging from 0% and 14%, with most studies reporting rates of 6% or lower.[34,91,121,131,256,257,271,276,295-299] Distant metastasis was rarely observed, and rates of regional metastasis were highly variable across studies, ranging from 0% to 13%.[121,131,276,295,299,300] One large meta-analysis found that recurrence rates were lower for primary versus recurrent tumors, both with follow-up of <5 years (5.7% vs. 17.3%) and with longer follow-up (8.1% vs. 23.3%).[34] Incomplete excisions can depend on lesion location, thickness, PNI, invasion into the deep fascia, differentiation, surgeons' skills, and primary versus recurrent tumors,[268,301-303] among other factors.[276,295,304-311]

The clinical margins chosen by the NCCN Panel for the primary treatment of low-risk CSCC are based on the work of Brodland and colleagues.[312] Their analysis indicated that for well-circumscribed CSCC lesions <2 cm in diameter, excision with 4-mm clinical margins should result in complete removal in more than 95% of CSCCs. For low-risk lesions >2 cm in diameter, results indicated that 6-mm margins would be needed to achieve histologically clear margins in 95% of instances.

The NCCN Panel also recommends standard excision as the primary treatment for high-risk/very-high-risk CSCC when Mohs micrographic surgery (Mohs) and other forms of PDEMA are not available, however, wider surgical margins than those recommended for low-risk lesions must be taken and increased recurrence rates should be expected. Standard excision with wider margins is also a recommended treatment option for laCSCC following consideration of neoadjuvant cemiplimab and/or clinical trial after a multidisciplinary discussion to assess the most favorable treatment course.

According to Brodland et al, for CSCCs in high-risk locations (scalp, ears, eyelids, nose, lips) or with other high-risk features (histologic grade ≥2, invasion of subcutaneous tissue), lesions with a diameter <1 cm, 1 to 1.9 cm, and ≥2 cm would require margins of at least 4 mm, 6 mm, and 9 mm, respectively.[312] Other retrospective analyses of CSCCs removed with Mohs further support that larger excision margins are needed to consistently achieve clear margins as tumor diameter increases and when other risk factors are present.[268,272,301,313] Currently, European Guidelines recommend standard excisions with 6 to 10 mm peripheral clinical margins for high-risk to very-high-risk CSCCs.[314-317] Appropriate margins should be determined case by case based on tumor- and patient-specific factors.

Whenever standard excision is utilized, any peripheral rim of erythema around a SCC must be included in what is assumed to be the tumor. For patients with positive margins from surgical excision and postoperative margin assessment, re-excision often yields clean margins, and in many instances, the re-excision specimen contains no tumor cells.[121,131,296,318-320] Re-excision with postoperative margin assessment is therefore among the recommended treatment options for positive margins after standard excision of low-risk high-risk/very-high-risk, very-high-risk, and laCSCC. In any case, tissue rearrangement should not be undertaken until clear margins are identified.

Radiation Therapy

Radiation as Primary Therapy

Although surgery is the mainstay of local treatment for SCC, patient preference and other factors may lead to the choice of RT as primary therapy. The NCCN Panel noted that the determination of the appropriateness of RT should be performed together with a radiation oncologist. Patients may receive RT if they are considered nonsurgical candidates due to comorbidities, extent of disease, risk of functional or cosmetic defects, or inability to clear disease with surgery through a

multidisciplinary discussion for low-risk, high-risk/very-high-risk, very-high-risk, and locally advanced CSCC. In the laCSCC setting, RT may be administered with or without additional systemic therapy. A large meta-analysis reported 5-year recurrence rates of 6.7% and 10% after RT of primary and recurrent SCC, respectively.[34] Subsequent retrospective analyses of patients with primary CSCCs have reported a large range of recurrence rates, from 2.8% to 42%, the latter for patients with locally advanced disease (size >2 cm or deeply invasive).[256,321-327] The risk of recurrence appears to increase with increasing lesion size and T-stage.[324,326,328] A few small studies (n < 20) have reported that for CSCCs that have been previously treated and recurred, treatment with RT results in 16.7% recurrence.[323,326]

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%.[254,325,326,329-331]

Adjuvant Radiation

For low-risk CSCC, the NCCN Panel recommends adjuvant RT for non-surgical candidates in case of positive margins after definitive surgery. For high-risk/very-high-risk and very-high-risk CSCC, the NCCN Panel recommends adjuvant RT as a treatment option for patients with positive margins, if resection is not feasible, after a multidisciplinary consultation Adjuvant RT can also be considered for patients with negative margins and extensive perineural, large or named nerved involvement or if the CSCC has other poor prognostic features. Adjuvant RT may also be considered for patients with laCSCC and positive margins with or without systemic therapy. Similarly, it is a treatment that can be considered for high-risk/very-high-risk, very-high-risk, CSCC and laCSCC with negative margins if there is extensive perineural, large or named nerve involvement, or other poor prognostic features. [332]

It has been shown that adjuvant RT improved locoregional control and survival outcomes for patients with positive margins after surgery or other high-risk features for recurrence.[332-337] However, RT in the progressive disease is usually not curative so every effort should be taken to obtain a clear surgical margin prior to RT initiation.[281] The outcome benefit of adjuvant RT following resection of CSCC with negative margins has been estimated to be approximately 50% reduction in local and nodal recurrence risks,[338] despite older inconclusive data.[337,339,340] Other retrospective studies combined results for patients treated with other modalities (eg, Mohs/standard excision alone, RT alone, chemotherapy), patients with other types of skin cancer (BCC and metatypical BCC), patients with LN metastases, and a mix of patients with primary and recurrent skin lesions, with and without positive margins.[116,138,336,341-343] These studies suggest that postoperative RT for patients with high-staged CSCC may improve local and regional control and disease-free survival (DFS), but a survival benefit has not been demonstrated.

Radiotherapy Safety & Administration

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

Large cohort and population-based studies (N > 1000) have shown that rates of NMSCs are significantly higher in those who received prior RT (either for a benign condition or for cancer) compared with those who have no history of therapeutic RT exposure.[344-347] In patients who developed NMSC after prior RT, most NMSC lesions occurred within the radiation field, with elevated risk of NMSC confined to the site of RT exposure. The risk of NMSC was particularly high in patients who received therapeutic RT early in life.

RT can result in poor cosmetic outcomes, including telangiectasia, changes in skin pigmentation, and fibrosis. More serious long-term complications include non-healing ulcers (especially for SCC in situ[254,329,330]); soft tissue, cartilage, bone, or brain necrosis; decreased sensation; and cataracts (for lesions in the periorbital region).[326,328,329,331,348-350]

Specifics about the application of RT, including total doses, treatment duration, and contraindications, are described under *Principles of Radiation Therapy* in the algorithm; however, appropriateness of RT treatment should be determined together with a radiation oncologist. Additional information can be found in the ASTRO Guideline on Definitive and Postoperative Radiation Therapy for Basal and Squamous Cell Cancers of the Skin.[351] RT is contraindicated in patients with genetic conditions predisposing to irradiation-related skin cancer (eg, basal cell nevus syndrome [Gorlin syndrome][352-356] and DNA-repair disorders such as Fanconi's anemia, xeroderma pigmentosum), and relatively contraindicated in patients with connective tissue diseases (eg, lupus, scleroderma).[357-359] Given higher rates of poor cosmesis and complications with increasing cumulative radiation dose,[328,348,360] reirradiation should not be routinely utilized for recurrent disease within a prior radiation field. Protracted fractionation is associated with improved cosmetic results,[348,350,361] and should be utilized for poorly vascularized or cartilaginous areas. Retrospective studies have found that for patients with CSCC and PNI, progressive disease tends to occur along involved nerves.[116,362,363] The NCCN Panel recommends including the course of the local nerves proximally for extensive PNI, clinically evident PNI, or involvement of named nerves (particularly in the head and neck region).

A variety of external beam options have been shown to be effective for treating CSCC and have similar cosmetic/safety results.[328,348,361,364-366] Isotope-based brachytherapy can be an effective treatment for certain sites of disease, particularly on the head and neck.[367-373] A retrospective multicentric analysis of 1676 carcinomas of the skin of the nose and nasal vestibule yielded a local control rate of 93% with a minimum follow-up of 2 years. It was determined in this study that local control depended on tumor size (diameter <2 cm: 96%, 2–3.9 cm: 88%, ≥4 cm: 81%) and tumor site (external surface of the nose: 94%, vestibule: 75%).[372]

On the other hand, there are insufficient long-term efficacy and safety data to support the routine use of electronic surface brachytherapy.[374,375] Electronic brachytherapy (EB) uses electrically generated x-rays, which are not regulated by the Nuclear Regulatory Commission. One of the apparent advantages of EB devices is the decreased shielding requirements and the portability of the units, however, this may lead to EB use in settings unfamiliar with the hazards of therapeutic radiation delivery.[376] The American Association of Physicists in Medicine (AAPM) task group 152 has provided guidelines for proper and safe EB use including having an authorized medical physicist (AMP) physically present from the initiation through the duration of all treatments involving an EB unit. The AMP is responsible for output calibration, quality assurance, training and treatment planning.[376] Furthermore, training and educational requirements for those administering EB vary considerably from state to state, and users should consult their local radiation safety committee to confirm appropriate compliance. The American Brachytherapy Society (ABS) has published a consensus statement for electronic brachytherapy, noting a paucity of long-term clinical outcome data and lack of comparison to surgery or standard radiotherapy techniques.[377] Particularly concerning is the absence of standardized dosimetry (in comparison to high dose rate [HDR] brachytherapy and external beam radiotherapy) to ensure adequate target coverage, skin surface dose, and plan quality assurance. The ABS, therefore, recommends that "EB treatment should be performed on clinical registry or trial at this time". The American Academy of Dermatology (AAD) has published a Position Statement: "The AAD believes additional

research is needed on electronic surface brachytherapy particularly on long term outcomes". The AAD acknowledges concerns regarding aggressive marketing to dermatologists with a focus on revenue streams, potentially undermining quality of care and patient safety. The AAD also cautions dermatologists to be mindful of the Stark physician self-referral law. Recently, image guidance current procedural terminology (CPT) codes have been used for the delivery of EB, despite a lack of evidence demonstrating a benefit in clinical outcomes with image guidance. We do not support the use of image guidance with EB currently. In conclusion, EB should only be performed by Radiation Oncologists with Medical Physics support, on registry or clinical trial, with appropriate safeguards, and in adherence with all State and Federal regulations. Further research is needed regarding dose deposition and long-term clinical outcomes.

Sentinel Lymph Node Biopsy

The NCCN Panel recommends consideration of sentinel lymph node biopsy (SLNB) during treatment planning prior to primary treatment when the disease is recurrent or has multiple high-risk features for high-risk/very-high-risk CSCC where surgery or RT has a high likelihood of cure as well as for very-high-risk CSCC with significant risk of extensive local recurrence, nodal or in-transit metastasis. Studies have reported sub-clinical nodal metastases in 7% to 21% of patients with high-risk non-anogenital CSCC who underwent SLNB.[76,86,114,115,378-384] Although small sample sizes and low rates of SLN positivity limit assessment of prognostic factors, a few studies suggest that risk factors for SLNB positivity include tumor diameter and thickness, LVI, PNI, and the presence of multiple high-risk factors.[76,114,115,382,385]

Several studies reported that among patients with localized SCC and a negative SLNB, nodal metastases were later detected in 2% to 15% of patients.[76,86,114,115,379-381,383,386] In addition to false negatives, some studies documented patients with a negative SLNB who developed local recurrences or metastases outside of the previously biopsied LN basin.[86,115,379] For positive SLNB, multidisciplinary discussion is recommended after obtaining radiologic staging of the neck, chest, abdomen, and pelvis if not yet completed. In the absence of metastatic disease consider completion lymphadenectomy of the affected nodal basin. If surgery is not an option due to patient preference or poor performance status, then consider radiation therapy. Following neck dissection, see *Very-high-risk CSCC* in the algorithm for additional recommendations. It has been shown that despite receiving completion lymph node dissection, patients with a positive SLN had higher rates of postoperative recurrence/metastases, ranging from 33% to 45%,[114,115,379,382] and were also more likely to die from SCC, with significantly lower 3-year DSS rates compared to patients who have a negative SLN.[86,115,382] Therefore, although SLNB may have prognostic value, it is unclear whether SLNB followed by completion lymph node dissection or adjuvant RT improve patient outcomes.

Regional Lymph Node Involvement in SCC

Regional nodal involvement significantly increases the risk of recurrence and mortality.[36,85,97] Nodal metastasis also commonly coincides with other adverse histopathologic findings such as LVI, poor differentiation, and PNI.[11,74,75,82,85,90,92,97,390] About 60% to 82% of patients with nodal disease show involvement in the parotid gland, while cervical neck node disease without parotid invasion is observed in 18% to 41% of patients.[391]

Workup for Suspicion of Regional Lymph Node Involvement

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

Treatment of SCC with Regional Lymph Node Involvement

The NCCN Panel recommends resection of regional disease over RT or chemotherapy. RT with or without concurrent systemic therapy is reserved for patients who are not surgical candidates. Most studies of patients with regional involvement CSCC focus on treatment of parotid and/or cervical nodes either with surgery alone (parotidectomy and/or neck dissection) or surgery plus adjuvant RT. Some studies included patients receiving concomitant chemotherapy[56,392-398] or patients who received RT alone.[96,397,399-401] For studies where the majority of patients receive surgery plus adjuvant RT, recurrence rates are 20% to 35% and estimates of 5-year DFS and DSS are 59% to 83% and 63% to 83%, respectively.[56,57,392,393,395-397,399,401-406] Many studies support that adjuvant RT improved local regional control, DFS, and OS compared with surgery or RT alone.[392,393,396,397,399,401-403,406] In contrast, other studies found no significant association between adjuvant RT and improved disease outcomes.[56,392,404,405] There may be subsets of patients who derive more clinical benefit from adjuvant RT than other patients; however, it is difficult to identify such patients. Results vary for all of the prognostic factors frequently considered such as immunosuppression, primary tumor size, LVI, PNI, differentiation, and features of the regional disease such extranodal extension (ENE) and number of involved nodes.[56,57,392,393,395,396,399,401,403,406,407]

Several staging systems have been proposed for regional CSCC, as shown in Table 1. O'Brien proposed a staging system that separates parotid involvement from neck LN involvement based on multivariate analysis showing improved local control for P1 compared with P2/P3.[408] Multivariate analyses of survival and locoregional control have yielded favorable[394,399,401,406] as well as discordant results[57,394,403] regarding the prognostic value of O'Brien P-stage. O'Brien also showed that survival was significantly better for patients with N0/N1 compared with N2.[408] Two studies supported this result,[57,406] but several others did not.[399,401,403] According to the AJCC 7th edition, N1 disease with no ENE had a 5-year cure rate of 92%.[116] N2 disease with immunosuppression, in particular patients with transplants or those with hematologic malignancies, on the other hand, had a 5-year survival of 52%, in contrast to 72% for patients who are immunocompetent.[409] The AJCC 7th edition staging does not separate parotid from cervical lymph node involvement and includes both 3-cm and 6-cm cutoffs for largest lymph node dimension.[410] Forest et al found that lymph node size was related to ENE, and that 6-cm cutoff and 3-cm cutoff groups performed similarly.[392] Risk stratification per the NCCN Guidelines takes into account both ENE[403,411,412] and margin status after resection[394,401,403,408,411] as prognostic factors for recurrence and survival. The updated AJCC staging system also includes ENE as a criterion for determining N-stage.[133] It should be noted that there are studies that showed no significant association between outcomes and ENE or margin status.[394,396]

The NCCN-recommended and preferred treatment for CSCC with lymph node involvement is excision of the primary tumor and regional lymph node dissection for all surgical candidates. Patients treated with dissection of nodes in the trunk and extremities should consider adjuvant RT of the nodal bed, especially if multiple nodes are involved or if ENE is present. For patients with nodal metastasis to the head and neck, the extent of surgery should depend on the number, location, and size of affected nodes. Postoperative adjuvant treatment should depend on the pathologic findings after surgery—namely the extent of resection, number of positive

nodes, and presence or absence of ENE. Patients with ENE or incompletely excised nodes should receive adjuvant RT and also consider concurrent systemic therapy depending on individual toxicity tolerance. Patients with inoperable nodal disease should be treated with RT of the nodal bed and consider concurrent systemic therapy. Multidisciplinary consultation is recommended for these patients and should consider the systemic therapies used to treat head and neck squamous cell carcinomas as indicated in the NCCN Guidelines for Head and Neck Cancers. For symptomatic sites, palliative RT or surgery should be considered. Stereotactic body radiation (SBRT) may be appropriate in select patients.

Satellitosis/In-transit Metastasis

Satellitosis or in-transit metastasis (S-ITM) is a clinically significant risk factor for the recurrence and defined by the presence of dermal lesions between the primary tumor and lymphatic nodal basins.[413] Due to S-ITMs rarity and therefore scarcity of data, neither the AJCC 8th edition[414] nor the Brigham Women's Hospital (BWH) staging system[74,75] include it as a CSCC risk factor. The NCCN Panel has strived to delineate treatment planning imaging options as well as primary treatment after a multidisciplinary discussion based on whether the tissue sampling confirmed S-ITM is operable, unresectable, or incompletely resected. Despite these steps S-ITM remains a challenge when encountered in the clinical setting.[415]

Recurrence and Metastasis

Metastatic CSCC is rare, estimated at 1.9% to 2.7% of all CSCC, with nodal metastases and distant metastatic disease estimated at 3.7% and 0.4%, respectively.[11,82] For the management of local tumor recurrence or new regional disease, the Algorithm directs clinicians to follow the appropriate pathways for primary treatment. Complicated high-risk tumors, regional recurrence, or the development of distant metastases should be managed by a multidisciplinary tumor board. The NCCN Panel encourages participation in a clinical trial for patients with metastatic CSCC. Unfortunately, such trials are scarce. For symptomatic sites, palliative RT or surgery should be considered. SBRT may be appropriate in select patients. Under highly selective circumstances and in the context of multidisciplinary consultation, resection of limited metastases can be considered.

Systemic Therapy for Distant Metastatic Disease

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

Systemic Therapy Options

Very-high-risk CSCC with significant risk of extensive local recurrence, nodal, or in-transit metastasis treatment planning option includes cemiplimab-rwlc as a neoadjuvant therapy after multidisciplinary discussion if the tumor has rapid tumor growth, in-transit metastasis, lymphovascular invasion, is borderline resectable, or if surgery alone may not be curative or result in significant functional limitation. Systemic therapy is also an option that can be considered by a multidisciplinary team for patients with laCSCC. Locally advanced CSCC is defined as primary or recurrent extensive disease where surgery and/or RT may not result in a cure or would possibly produce significant functional impairment.[416]

Primary treatment for resectable laCSCC includes consideration of neoadjuvant cemiplimab-rwlc after multidisciplinary discussion. For patients with laCSCC who cannot undergo surgery due to comorbidities, extent of disease, risk of functional or cosmetic defect, or inability to clear disease with surgery, primary treatment consists of RT with or without systemic therapy or systemic therapy alone if curative RT is not feasible. These primary treatment options also apply to unresectable, inoperable, or incompletely resected palpable regional lymph nodes identified by imaging after a multidisciplinary consultation. Additional treatment for patients with positive margins after resection also includes RT with or without systemic therapy or systemic therapy alone if curative RT is not feasible. Treatment of regional lymph nodes of the head and neck also include RT and consideration of concurrent systemic therapy in certain circumstances. For patients with confirmed S-ITM, systemic therapy with or without RT is a therapeutic option unresectable or incompletely resected disease after a multidisciplinary discussion while neoadjuvant systemic therapy can be considered for operable disease.

For locoregional disease for which surgery or RT are unlikely to be curative, both cytotoxic and epidermal growth factor receptor (EFGR) inhibitor systemic therapy (monotherapy or combination) have been successfully used to reduce tumor load, which in some cases enabled complete resection or complete response with or without concurrent/subsequent RT.[417-421] In the absence of prospective comparative trial data, it is unclear whether systemic therapy provides additional clinical benefit when used postoperatively with RT. Small retrospective studies were unable to establish definitely that the addition of chemotherapy to postoperative RT significantly improved any disease-related outcome in patients with regional disease,[395,412,422-424] except for one study.[425] The emergence of anti-programmed cell death protein 1 (PD-1) inhibitors and robust clinical trial data have opened up novel treatment venues for patients with both locally advanced and metastatic CSCC not amenable to surgery and RT. It must be noted that the preferred recommendation for all of these settings is enrolment in a clinical trial.

The preferred systemic therapy for use with RT or surgery for regional recurrence following systemic treatment option recommended by the NCCN Panel is cisplatin.[426-429] EGFR inhibitors (eg, cetuximab,[420,428-436] erlotinib,[437] gefitinib,[421] panitumumab[438]) and carboplatin ± paclitaxel[389,426,428,439,440] are considered other recommended regimens while cisplatin + 5-FU[417,427,435,436,441] is a regimen useful in certain circumstances. Evidence supporting the efficacy of any of these regimens is mostly limited to case reports and small retrospective studies. In a small (N = 21) prospective phase II study in patients with locally advanced primary or nodal disease who received definitive RT with concurrent cisplatin or carboplatin, the overall complete response (CR) was reported to be 63%.[426] Efficacy and safety data for cisplatin, cetuximab, or carboplatin + paclitaxel in combination with RT can also be extrapolated from large randomized trials in patients with non-cutaneous head and neck cancers.[387-389] On the other hand, data from a rare, large (N = 321)

randomized trial in patients with CSCC of the head and neck testing RT ± carboplatin did not find an added benefit with carboplatin.[422]

The preferred systemic therapy options if curative RT or surgery is not feasible for locally advanced, recurrent, or metastatic disease for use alone without RT recommended by the NCCN Panel are cemiplimab-rwlc[442-445] and pembrolizumab.[446,447] Other recommended regimens for systemic therapy alone include nivolumab[448] or if the patients are ineligible for or progressed on checkpoint inhibitors and clinical trials carboplatin + paclitaxel ± cetuximab[449-453] and EGFR inhibitors (eg, cetuximab,[419,420,429,430,432,434,436,454,455] panitumumab,[438,456] gefinitib,[457] dacomitinib,[458] erlotinib[459]). Regimens that are useful in certain circumstances include neoadjuvant cemiplimab[445] or if the patients are ineligible for or progressed on checkpoint inhibitors and clinical trials, cisplatin ± 5-FU[417,419,427,429,436] and capecitabine.[460,461]

A phase II, multicenter, nonrandomized study for neoadjuvant cemiplimab-rwlc enrolled 79 patients with CSCC and showed a 51% pathologic complete response and 13% pathologic major response in the neoadjuvant setting.[445] Grade 3 or higher adverse events were only observed in 18% of patients. Therefore, the NCCN Panel recommends neoadjuvant cemiplimab-rwlc be discussed as a treatment option for patients whose disease is considered borderline resectable, unresectable, or in which surgery may carry a high morbidity.

Published data reported an objective response rate (ORR) of 44% to 54%, CR of 0% to 13%, and partial response (PR) of 31% to 50% to cemiplimab-rwlc in patients with locally advanced, recurrent, or metastatic CSCC.[442-444] Data from the phase II KEYNOTE-629 trial, which included patients with locally advanced, recurrent, or metastatic CSCC, reported an ORR of 34% to 50%, a CR of 4% to 17%, and a PR of 25% to 33% for patients treated with pembrolizumab.[446,447] An open label, single-arm, phase II study evaluated the safety and efficacy of nivolumab as a first-line systemic therapy in individuals with advanced CSCC (N = 24).[448] A best ORR of 58.3% was achieved, yet no complete responses were reported. The study also reported a median follow-up of 17.6 months, estimated median PFS and OS of 12.7 and 20.7 months, respectively. A median DOR was not reached. Preliminary data and the clinical experience of NCCN Panel members suggest that other anti–PD-1 inhibitors may also be effective in this setting. It was demonstrated in a retrospective study that patients receiving immunotherapy showed a statistically significant better survival compared to those treated with other systemic therapies (*P* =.034) [429]; the validity of this finding remains to be tested in prospective randomized studies. The use of immune checkpoint inhibitors might perhaps be extended to other indications, with early reports advocating its safety and efficacy concurrently with RT.[462]

In the case of EGFR inhibitors, all recommended regimens have been tested in small, single-arm phase II clinical trials among patients with CSCC nonamenable to surgery and RT. However, low rates of response were documented. Among 25 patients who received cetuximab, 8 PR's and 2 CR's were documented, with a disease control rate of 69%.[420] As for gefitinib, among 40 patients treated, the ORR was reported to be 16%, with an additional 35% achieving stable disease at 8 weeks.[457] In a smaller study of 16 patients with CSCC testing panitumumab, the best ORR (PR and CR) was 31%, with a further 6 patients achieving stable disease.[456] The response rates reported for 42 patients treated with dacomitinib were 2% CR, 26% PR, with a disease control rate of 86%.[458] The ORR for 39 patients treated with erlotinib was 10%, with a disease control rate of 71%.[459] Efficacy data for chemotherapeutic agents are not much better. In a systemic review of 60 patients with metastatic CSCC treated with cisplatin, the CR was reported to be 2%, with an ORR of 45% and median DFS of 14.6 months.[436] Data supporting carboplatin utility are even more limited, with most studies examining carboplatin combinations and not carboplatin monotherapy.[429,455]

Follow-up

It has been well-established that 13% to 50% of these patients will develop another SCC within 5 years.[463-465] This represents at least a 10-fold increase in risk compared to the general population.[464,465] 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.[73,464] Therefore, continued long-term surveillance of these patients is essential, as is patient education about sun protection and regular self-examination of the skin. Additionally, 70% to 80% of cutaneous SCC recurrences develop within 2 years of the initial therapy.[11,34,60,75,78] Therefore, close follow-up of these patients during this time period is critical.

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

Patients should also be monitored with regular physical exams including complete skin and regional lymph node examination. The frequency of follow-up should be adjusted based on risk (See *Follow-up* in the algorithm). For following disease, the imaging modality and targeted area should be at the discretion of the treating team based on the suspected extent of disease (ie, local, regional, metastatic). Histologic confirmation is often sufficient to diagnose local recurrence, but MRI with or without contrast can be considered to assess extent of local disease. For nodal or distant metastases, histologic analysis and/or other imaging modalities can be used for confirmation and to gauge extent of disease. In certain patients at high risk for multiple primary tumors, increased surveillance and consideration of prophylactic measures may be indicated. Follow-up with a dermatologist is strongly recommended if any of the following criteria are met: past or imminent solid organ, marrow, or stem cell transplant, one or more cutaneous melanomas in the past 5 years, or four or more nonmelanoma skin cancers in the past 5 years.

Care for Patients at High Risk of Developing Multiple SCCs

Treatment of SCC in Patients at High Risk

For individuals who rapidly develop multiple CSCC lesions, destructive techniques such as C&E and cryotherapy may be used. Some NCCN Panel members use a combination of shave removal to excise 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 patients at high risk with multiple lesions vary widely between NCCN Member Institutions and between practitioners at these institutions, and there is no standard language for describing these methods. Compared to the low-risk population, RT is used more frequently as an adjuvant therapy in patients at high risk and for PNI.[466] Satellite lesions and in-transit cutaneous metastases may occur more frequently and are more likely to progress in this population.[467,468]

Analyses of large populations of patients with organ transplants have found that the incidence of new skin cancers is linked to the duration and dose of immunosuppression.[469-471] Prospective randomized trials have shown that switching from other immunosuppressants to mTOR inhibitors reduces the risk of developing new CSCC lesions, particularly in patients with a history of one or more CSCCs.[472-480] When surgery is impractical due to high CSCC burden, oral capecitabine has been suggested in the transplantation setting, although toxicity is a concern.[249]

Prevention in Patients at High Risk

Treatment of precancers at first development can help prevent the development of subsequent invasive tumors. Prophylactic treatment may be needed for patients with a history of multiple lesions and/or extensive diffuse AK or field cancerization. Oral retinol and synthetic retinoids (eg, acitretin,[247] isotretinoin, etretinate) have been tested in prospective studies in patients at high risk for multiple AKs or SCCs, including patients with transplants.[481-486] patients with xeroderma pigmentosa,[487] or with psoriasis and PUVA (psoralen plus UV-A) exposure.[488] By comparison with placebo or with SCC incidence during treatment-free periods, data from these studies support that oral retinol and oral retinoids significantly reduce the incidence of new CSCCs in patients at very high risk for multiple lesions.[482-485,487,488] Outside of these very-high-risk groups, the effectiveness of retinol/retinoid therapy for prophylaxis is less clear.[489-491] Side effects may be significant and include mucocutaneous, such as cheilitis, excessive peeling of the skin, and hair disorders,[486] but musculoskeletal, vascular, hepatic triglyceride, and neurologic adverse events have also been reported.[485,487,490,492] In addition, these agents are teratogenic and must be used with extreme caution in individuals of child-bearing potential.[493]

The NCCN guidelines do *not* recommend topical retinoids as prophylactic treatment for patients at high risk for multiple AKs or CSCCs. Results of a large randomized trial in patients with a history of ≥2 BCCs/SCCs showed that prophylactic topical tretinoin (0.1%) did not reduce the development of new cutaneous BCCs or SCCs compared with vehicle control.[494] A double-blind randomized study showed that topical tazarotene had a chemo-preventative effect in only 6% of patients with basal cell nevus syndrome, a condition associated with frequent development of primary BCCs.[495]

Results from a randomized controlled study suggest that prophylactic nicotinamide may be effective at preventing the development of CSCC recurrence or metastases in patients at high risk.[152] 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) compared to placebo. During the subsequent 6 months off treatment, there was a trend toward increased rates of new SCCs for the nicotinamide arm compared with placebo (59% relative difference; P = .07). Although there are currently no clinical trial data directly comparing nicotinamide with oral retinoids for CSCC prophylaxis, nicotinamide has a much better safety profile. Further clinical research is needed to determine whether nicotinamide provides long-term clinical benefit for patients at risk of developing multiple NMSCs and AK lesions.

Patient Education for Patients at High Risk

Patient education is especially important for those at high risk for CSCC progression or recurrence. Treatment delay is associated with larger tumor size, larger defect size from surgical removal, and more Mohs layers taken to obtain clear margins.[107,496-499] 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.[500,501] Low education level is also associated with large NMSC tumor area at presentation.[502] Educational interventions and physician advice have been shown to increase the likelihood of patients undergoing a complete skin exam, and patients with more knowledge of skin cancer are more likely to get regular complete skin exams.[385,503,504]

Patient education should begin, in the case of patients with transplants at transplantation and at birth or diagnosis for patients with xeroderma pigmentosum. Education should include discussion of individual risk assessment and the need for stringent sun avoidance and protection methods. Regular sunscreen use can significantly reduce the rate of development of new AKs and CSCCs, and increases remission rates of AKs.[147-150] Knowledge of more than one method for UV protection is

associated with higher rates of using some form of protection,[505] as is awareness of susceptibility/risk and overall education level.[506,507]

Having a prior NMSC has proved to be insufficient motivation for altering patient behavior regarding UV protection and avoidance. Although those with prior NMSC are more likely to use sunscreen and to avoid sun exposure, adoption of preventative measures was low: only 54% used sunscreen, and 20% to 45% used other avoidance/protective methods.[508] Another cross-sectional study showed that tanning bed use was similar among those with and without prior NMSC.[509]

Randomized trials have shown that educational interventions can effect significant changes in use of solar protection in outdoor workers and patients with transplants.[504,510-515] While both extensive and repetitive education improve patient knowledge, repetitive education is needed to effect long-term change in patient behavior.[516] This is especially important for patients with transplants, as preoccupation with other medical concerns may make them unreceptive to skin cancer education.[517] For patients with transplants, an intervention including text messaging reminders was shown to be more effective at improving patient knowledge and changing sun protective behaviors compared with more traditional approaches.[518]

Monthly self-examination is recommended and should include all skin surfaces and LNs. Patients should be taught the proper method for systematic self-examination of the skin and lymph nodes. A randomized controlled trial has shown that educational intervention increased the frequency and sensitivity of self-examination of the skin among patients with transplants.[519] 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 occur weekly.

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

O'Brien 2002 Staging System[408]	
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[410]	
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[133]	
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[392]	
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 ENE(-)
Medium	1 LN+ >3 cm ENE(-) or ≥2 LN+ ENE(-)
High	≥1 LN+ ENE(+) or Incompletely excised disease

ENE(+), with extranodal extension; ENE(-), without extranodal extension; LN+, positive lymph node(s); SCC, squamous cell carcinoma.
[a]Pathologic criteria.

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