Actinic Keratosis (AK) and Cutaneous Squamous Cell Carcinoma (cSCC)

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- I have no disclosures to reveal

Goals

- Epidemiology, pathogenesis, and clinical features of AK and cSCC
- Treatment modalities and management options
- cSCC: Advances in staging and prognostic assessment
- cSCC: Implications for treatment of advanced disease

AK

- Classic description: rough scaly papule on an erythematous base that develops in anatomic areas of high ultraviolet (UV) exposure
- Typically present in areas of highest solar damage in fair-skinned individuals
- Propensity for: head (esp scalp), ears, neck, dorsal aspects of arms and hands, lower extremities
- Overall, the rate in the United States is estimated to range from 11-26%; one source said 58 million in USA: 17%




AK – What is the issue?

- Estimates of the risk of progression of AK to SCC vary from less than 0.1% to 20%
- Limited follow-up in many studies makes precise prognosis difficult.
- Studies that have examined SCC histologically to look for adjacent contiguous AK have reported finding in more than 60% of cases
- Spontaneous regression rate of AKs highly variable, reported to be from 15% to 63% per year
- But AKs that spontaneously regress clinically reported to recur, with a recurrence rate estimated to be as high as 50% within the first year

Management – Procedural/In clinic

- Cryosurgery
- Chemical peel
- Curettage
- Photodynamic therapy
- Laser resurfacing

Management – Topical/At home

- 5-fluorouracil (5-FU) cream
- Diclofenac sodium gel
- Imiquimod cream
- Tirbanibulin ointment – KLYSIRI - microtubule inhibitor; 5 day course
- Ingenol mebutate – PICATO - withdrawn 10/2020

Cutaneous squamous cell carcinoma

Incidence, risk factors, diagnosis, and staging

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Boston, Massachusetts, and Washington, District of Columbia

Learning objectives
After completing this learning activity, participants should be able to describe the incidence of cSCC and define factors that are independently associated with poor outcomes on multivariate analysis of cSCC; outline the various staging systems for cSCC, the features that upstage a cSCC, and the rate of local recurrence, metastatic disease, and disease specific death at each stage; and identify aggressive cSCC that require further work-up and treatment.

Disclosures
Editors
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Cutaneous squamous cell carcinoma (cSCC), a malignant proliferation of cutaneous epithelium, represents 20% to 50% of skin cancers. Although the majority of cSCCs are successfully eradicated by surgical excision, a subset of cSCC possesses features associated with a higher likelihood of recurrence, metastasis, and death. The proper identification of these aggressive cSCCs can guide additional work-up and management. In the first article in this continuing medical education series, we discuss the incidence, recurrence rates, mortality rates, and risk factors associated with cSCC and review the staging systems used to stratify patients

[redacted]

Cutaneous squamous cell carcinoma

Management of advanced and high-stage tumors

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Boston, Massachusetts, and Washington, District of Columbia

Learning objectives
After completing this learning activity, participants should be able to evaluate evidence-based literature concerning cSCC preventive therapies; discuss general indications for Mohs surgery in the setting of cSCC; and work up high-risk cSCC and arrive at potential treatment options.

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While the majority of cutaneous squamous cell carcinomas (cSCCs) can be treated surgically, the additional work-up and treatments indicated for high-risk cSCC remain undefined. In recent years, improvements in tumor staging systems have allowed for the more accurate stratification of tumors into high- and low-risk categories. This insight, along with the publication of cSCC guidelines, brings us closer to the development of a consensus approach. The second article in this continuing medical education series addresses in question and answer format the most common questions related to advanced and high-stage cSCCs, with a simplified flowchart. The questions include the following: 1) Does my patient have high-risk cSCC?; 2) What is the next step for patients with cSCC and palpable lymphadenopathy?; 3) In patients with no clinically evident lymphadenopathy, who are candidates for lymph node staging?; 4) What forms of radiologic imaging can help detect subclinical lymph node metastases?; 5) What is the role of sentinel lymph node biopsy in cSCC?;

Guidelines of care for the management of cutaneous squamous cell carcinoma

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Chicago and Schaumburg, Illinois; Denver, Colorado; Rochester, Minnesota; Cleveland, Rootstown, Burton, and Columbus, Ohio; Rochester and New York, New York; Sacramento, San Francisco, Yorba Linda, and Stanford, California; Kissimmee and Tampa, Florida; Philadelphia, Pennsylvania; Towson and Danville, Maryland; Phoenix, Arizona; Birmingham, Alabama; and Ann Arbor, Michigan.

Cutaneous squamous cell carcinoma (cSCC) is the second most common form of human cancer and has an increasing annual incidence. Although most cSCC is cured with office-based therapy, advanced cSCC poses a significant risk for morbidity, impact on quality of life, and death. This document provides evidence-based recommendations for the management of patients with cSCC. Topics addressed include biopsy techniques and histopathologic assessment, tumor staging, surgical and nonsurgical management, follow-up and prevention of recurrence, and management of advanced disease. The primary focus of these recommendations is on evaluation and management of primary cSCC and localized disease, but where relevant, applicability to recurrent cSCC is noted, as is general information on the management of patients with metastatic disease. (J Am Acad Dermatol 2018;78:560-78.)

Non-melanoma skin cancer (NMSC)

- 3.3 million people per year in the United States, BCCs comprise of 80% of these cancers
- Not regularly recorded in cancer registries, making it difficult to determine accurate incidence rates in large populations.
- 2012: total number of NMSC in US population estimated to be 5.4 million; total number of people treated estimated at 3.3 million

Squamous Cell Carcinoma (SCC)

- Cutaneous squamous cell carcinoma (cSCC)
- cSCC 20% of skin malignancies, estimated annual incidence of 700,000
- Second most common skin cancer type also the second most common malignancy type
- Many cSCCs small low-risk cancers easily treated in physicians' offices by minor surgical procedures, some cSCCs can become problematic

Squamous Cell Carcinoma (SCC)

- Significant morbidity and cosmetic deformity can occur
- Metastases and death can ensue if the progression of cSCC is not halted
- 2012 estimate (Karia, et al): 5604 to 12,572 people developed nodal metastases and 3932 to 8791 people died from cSCC in the United States that year.
- “Rodney Dangerfield of skin cancer”

Squamous Cell Carcinoma (SCC)

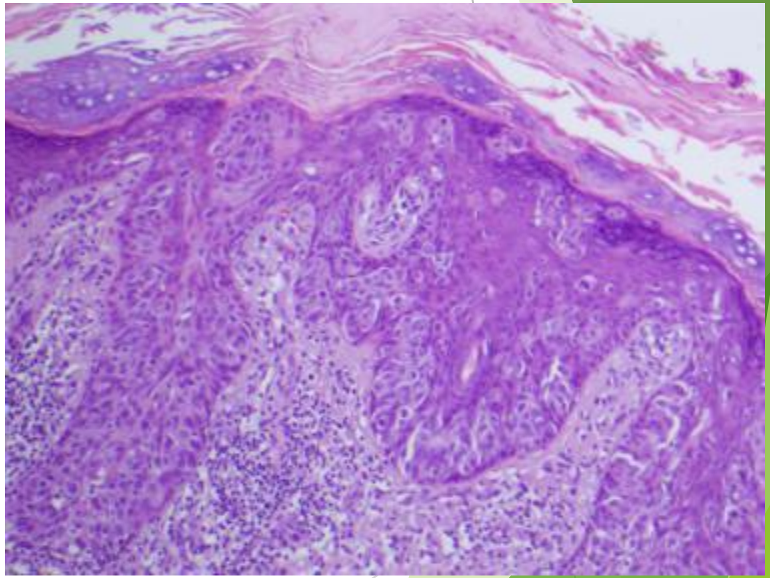
- Similar to BCC
- Often Actinic Keratosis (AK) precursor
- Most occur on head, neck, and extremities - anatomic areas that receive the maximum amount of sunlight
- Most common in light-skin persons of western European descent
- Man to woman ratio of 3:1
- Incidence increases with age in both genders.
- Causes: also greater UV exposure as a consequence of ozone depletion, greater sun-seeking behavior and exposure, increased longevity of the population, etc

Pathogenesis and Etiology

- Molecular risk:
  - TP53, CDKN2A, Ras, NOTCH1
- Risk factors
  - Light skin (Fitzpatrick skin types I-III), age, male sex, exposure to sunlight or other ultraviolet radiation
  - Immunosuppression – solid organ transplants, 65-250 x, heart and lung > renal
  - Human papillomavirus (HPV) – 16, 18; 8, 9, 15 in transplants
  - Chronic scarring conditions, e.g. Marjolin's ulcer
  - Familial cancer syndromes
  - Environmental exposures – arsenic, ionizing radiation

SCC types – “Low risk”

- In situ – Bowen’s disease



SCC types

- Invasive

SCC types

- Keratoacanthoma

SCC types – "Higher risk"

- Adenoid/adenosquamous
- Spindle cell
- Desmoplastic

Diagnosis

- Biopsy
  - Shave
  - Punch?

Clinical Risk Factors for Aggressive Tumor Behavior—"High Risk" Cutaneous SCC

- Location – area H, dorsal hands, genitalia, mucous membranes
- Size - > 2 cm local recurrence doubles, metastasis triples
- Depth - > 4mm and/or through subQ fat, > 6 mm lip, >10 mm anywhere
- Poorly Defined Borders
- Rapid Growth
- Histologic Differentiation – poor differentiation
- Histologic Subtype
- Perineural Invasion

Clinical Risk Factors for Aggressive Tumor Behavior—“High Risk” Cutaneous SCC

- Neurological Symptoms and Signs
- Recurrence
- Scar Carcinoma (Marjolin Ulcer)
- Immunosuppression – overall >12% met
- History of Radiation Treatment

TABLE 2. Five-Year Recurrence and Metastatic Rates for Primary and Locally Recurrent cSCC as a Percentage of Determinate Cases*

Treatment Modality	*Local Recurrence Rate*	*Metastatic Rate*
Primary tumors of the skin (all modalities), %	N/A	5.2
Cryotherapy	N/A	N/A
ED&C	3.7	N/A
Surgical excision	8.1	N/A
Radiation therapy	10.0	N/A
Non-Mohs modalities	7.9	N/A
Mohs micrographic surgery	3.1	N/A
Non-sun-exposed skin/scar carcinoma (all modalities), %	N/A	37.9
Primary tumors of the lip (all modalities)	N/A	13.7
Non-Mohs modalities	10.5	N/A
Mohs micrographic surgery	2.3	N/A
Primary tumors of the ear (all modalities)	N/A	11.0
Non-Mohs modalities	18.7	N/A
Mohs micrographic surgery	5.3	N/A
Locally recurrent tumors (all modalities), %	N/A	30.3
Surgical excision	23.3	N/A
Mohs micrographic surgery	10.0	N/A
Recurrent tumors of the skin (all modalities), %	N/A	25.1
Recurrent tumors of the ear (all modalities), %	N/A	45.0
Recurrent tumors of the lip (all modalities), %	N/A	31.5

*Adapted from Rowe DE, et al. J Am Acad Dermatol. 1992; 26(6):976–90. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

N/A, data not available.

TABLE 3. Risk Factors Associated With Local Recurrence and Metastasis of cSCC

Tumor characteristics
Any cSCC in high-risk sites: central face, periocular region, eyelid, eyebrow, nose, perioral, lip (cutaneous and vermilion), chin, mandible, ear, preauricular, postauricular, and temple
cSCC >1-cm diameter in intermediate-risk sites: cheeks, forehead, scalp, and neck
cSCC >2-cm diameter in any site
Poorly defined borders
cSCC exhibiting rapid growth
Neurologic symptoms
Locally recurrent cSCC after primary therapy
Histology
Depth >4 mm
Poorly differentiated
Aggressive histologic patterns: adenoid (acantholytic), desmoplastic, or spindle-cell cSCC, and invasive Bowen disease carcinoma
Perineural or vascular invasion
Host factors
Sites or previous radiation therapy
Exogenous immunosuppression (medications)
Endogenous immunosuppression (lymphoproliferative disorder, HIV)
Arising in scars or chronic wounds
Arising in sites of chronic inflammation
Genetic propensity for cSCC: XP

Goals of SCC treatment

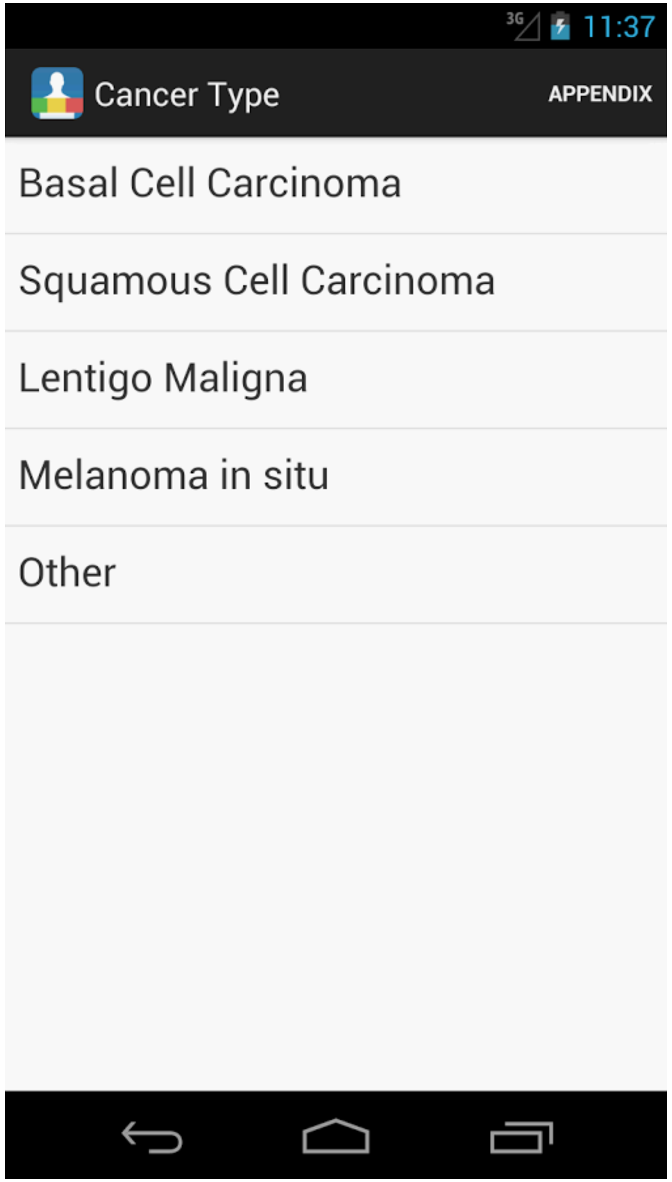
- (1) to completely extirpate the tumor
- (2) to minimize the risk of recurrence and metastasis
- (3) to restore normal function after treatment
- (4) to provide the best possible aesthetic outcome

Treatment options

- Curettage and Electrodesiccation (C and D, ED & C) – small, low risk, < 1 cm trunk, arms, legs; beware of Bowen's disease
- Cryotherapy – similar to above
- Standard Surgical Excision (SSE) –
  - well-circumscribed tumors < 2 cm not on the ears, lips, eyelids, nose, or scalp and do not invade the fat - margins of 4 to 6mm; > 2 cm, 9 mm or greater

Treatment options

- Mohs Micrographic Surgery (MMS)



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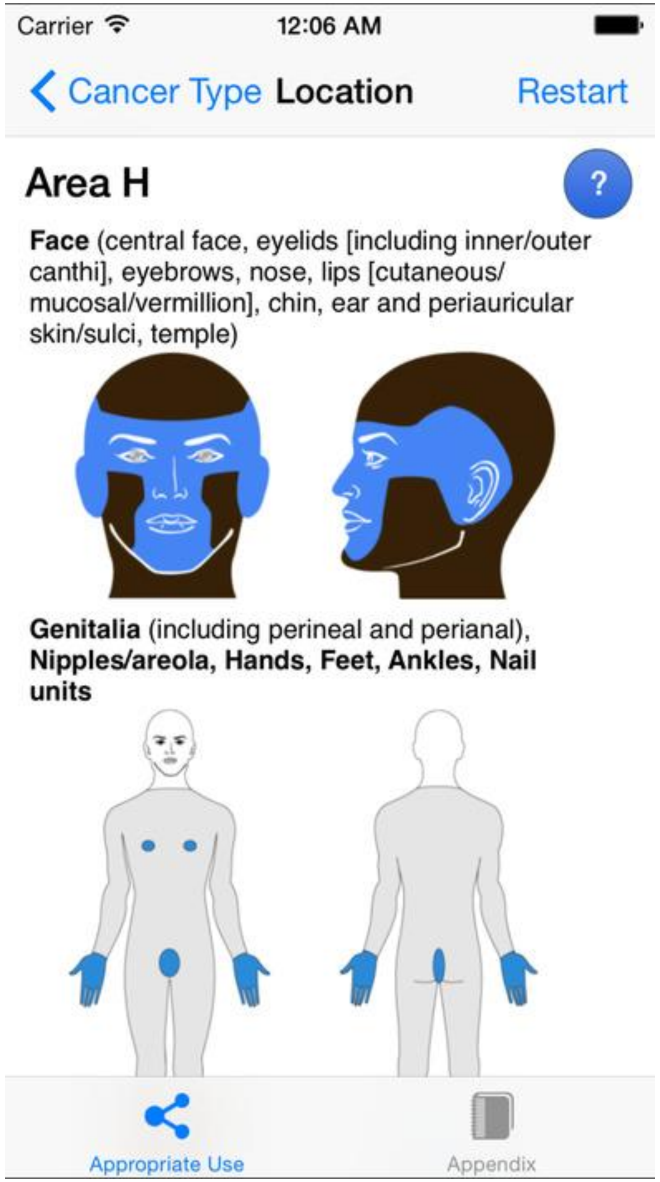
Cancer Type
APPENDIX
Basal Cell Carcinoma
Squamous Cell Carcinoma
Lentigo Maligna
Melanoma in situ
Other



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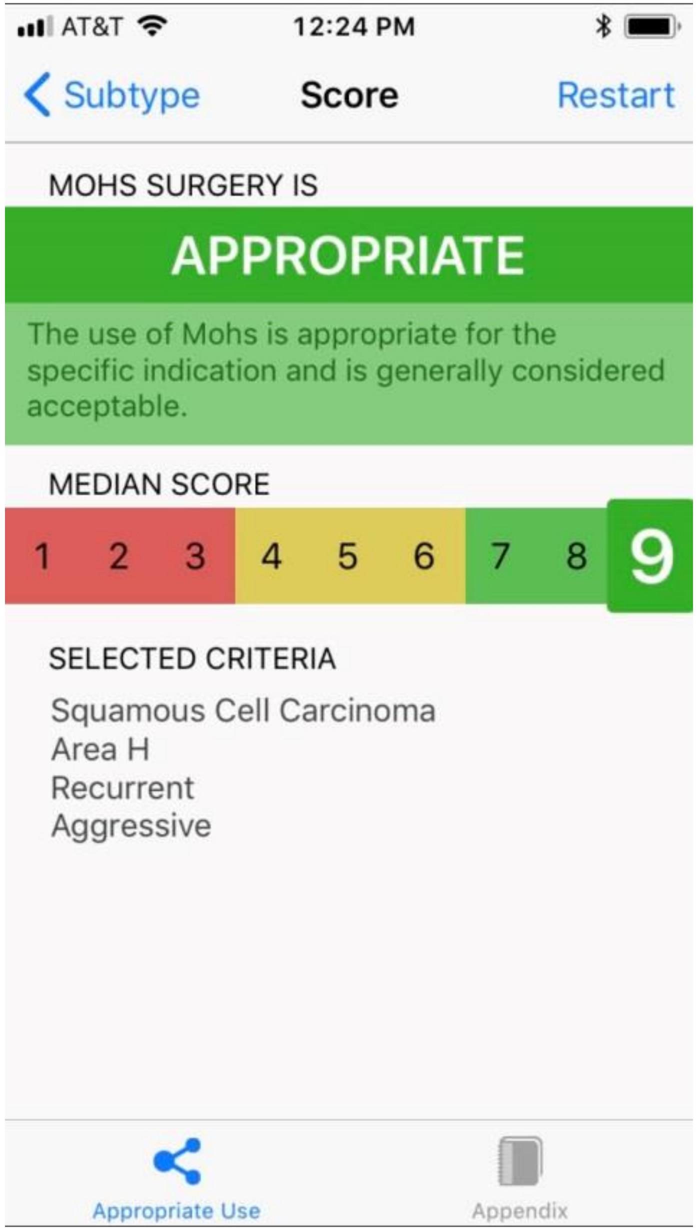
Cancer Type
Location
Restart
Area H
?
Face (central face, eyelids [including inner/outer canthi], eyebrows, nose, lips [cutaneous/mucosal/vermillion], chin, ear and periauricular skin/sulci, temple)
Genitalia (including perineal and perianal), **Nipples/areola, Hands, Feet, Ankles, Nail units**
Appropriate Use
Appendix

11:37
Area
APPENDIX
Area H
Area M
Area L
Trunk, Extremities (excluding pretibial surface, hands, feet, nail units, and ankles)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MOHS SURGERY IS
APPROPRIATE
The use of Mohs is appropriate for the specific indication and is generally considered acceptable.
MEDIAN SCORE
1 2 3 4 5 6 7 8 9
SELECTED CRITERIA
Squamous Cell Carcinoma
Area H
Recurrent
Aggressive
Appropriate Use
Appendix

TABLE 4. Appropriate Use Criteria for the Treatment of cSCC by Mohs Micrographic Surgery[110]			
*Tumor Type**	*Area H*	*Area M*	*Area L*
Primary cSCC with no high-risk† features healthy patients	Mohs appropriate	Mohs appropriate	Mohs appropriate (if >2.0 cm)‡
Primary SCC with no high-risk† features immunocompromised patients	Mohs appropriate	Mohs appropriate	Mohs appropriate (if >1 cm)‡
Verrucous cSCC healthy and immunocompromised patients	Mohs appropriate	Not assessed	Not assessed
SCC, KA type healthy patients	Mohs appropriate	Mohs appropriate	Mohs appropriate (if >1.0 cm)‡
cSCC, KA type immunocompromised patients	Mohs appropriate	Mohs appropriate	Mohs appropriate (if >0.5 cm)
cSCCIS/Bowen disease carcinoma healthy patients	Mohs appropriate	Mohs appropriate	Mohs appropriate (if >2.0 cm)‡
cSCCIS/Bowen disease carcinoma immunocompromised	Mohs appropriate	Mohs appropriate	Mohs appropriate (if >1.0 cm)‡
Recurrent cSCC (all types) or other high-risk features† healthy or immunocompromised patients	Mohs appropriate	Mohs appropriate	Mohs appropriate‡§
Aggressive (high risk) cSCC† healthy and immunocompromised patients	Mohs appropriate	Mohs appropriate	Mohs appropriate

Area H: central face, ears, genitalia, hands, feet, pretibial.

Area M: cheeks, forehead, scalp, neck.

Area L: trunk, extremities except hands, feet, pretibial.

*Tumor type excludes actinic keratosis and cSCCis–non-Bowen disease type.

†Aggressive cSCC indicates tumors with high-risk histologic features including the following: sclerosing, basosquamous, small cell, poorly or undifferentiated, spindle cell, pagetoid, infiltrating, KA (centrofacial), single cell, clear cell, lymphoepithelial, sarcomatoid, Breslow depth 2 mm or greater and Clark level IV or greater.

‡Mohs surgery is indicated for any size tumor with special patient features including the following: previous radiated skin, genetic syndromes, osteomyelitis, a history of aggressive-behaving tumors, chronic ulcer, inflammation, and traumatic scar.

§Except for cSCCis–Bowen disease type (Bowen disease carcinoma) ≤2.0 cm.

Treatment options

- Radiation therapy
  - Electron beam
  - Brachytherapy
- Topical therapies – not approved in US
  - 5-fluorouracil
  - Imiquimod
- Photodynamic therapy (PDT) – approved for AK's, multiple studies for cSCC, mostly in situ

Table II. Topical therapies for cutaneous squamous cell carcinoma chemoprevention and treatment

Therapy	Indications	Frequency of application	Mechanism of action	Adverse effects	Level of evidence*
Topical retinoids[47-50]	Ineffective at preventing cSCC according to VA randomized chemoprevention trial,[50] but other studies show decrease in AK count	N/A	Induces apoptosis of tumor cells; downregulate proliferative keratins K6 and K16	Burning, irritation, erythema, and dermatitis	IB
5-fluorouracil[80,81]	Approved by the FDA in 1970 for treatment of AKs; off-label use: treatment of cSCC in situ	AK: 0.5% cream: apply once daily for up to 4 weeks; 5% cream: apply twice daily for 2-4 weeks cSCC in situ: 5% cream: apply twice daily for 3 to 6 weeks; treatment can be continued for ≤10-12 weeks	Pyrimidine analogue: cytotoxic metabolites are incorporated into DNA and RNA, inducing cell cycle arrest and apoptosis	Erythema, shallow erosions, pruritus, dermatitis, burning sensation, and photosensitivity	AK: IA; cSCC in situ: IB
Imiquimod[82,83]	Approved by the FDA for the treatment of AKs; not practical for treatment of field disease because can have significant side effects when applied to large surface areas	AK: Aldara†—apply 2 times/ week × 16 weeks Zyclara†—treatment consists of 2 cycles (14 days each) separated by 1 rest period (14 days) with no treatment	Induces, synthesizes, and releases cytokines, thereby inducing secretion of interferon-gamma by naïve T cells	Local reactions: erythema, discomfort, erosion, and dyschromia Systemic symptoms: flu-like symptoms, dizziness, headache, and, rarely, urinary retention	AK: IA; cSCC in situ: IB
Ingenol mebutate[84]	Treatment of AKs	Face or scalp: apply 0.015% gel once daily to affected area for 3 consecutive days Trunk or extremities: apply 0.05% gel once daily to affected area for 2 consecutive days	Multiple mechanisms of action, including direct cell death and protein kinase C—mediated inflammatory response	Severe allergic reactions; herpes zoster; eye pain; periorbital edema; headache; mild to moderate erythema, scaling, and dryness	AK: IB
Diclofenac[85]	Treatment of AKs	Apply 3% gel to lesion area twice daily for 60-90 days	Nonsteroidal antiinflammatory drug that reduces the production of prostaglandins by inhibiting inducible cyclooxygenase-2	Pruritus, rash, desquamation, elevated liver function tests, flu-like symptoms, and headache	IB
Photodynamic therapy[53-56]	Treatment of AKs	Various protocols	Exogenous photosensitizer and light source induces a porphyria; neoplastic cells accumulate more porphyrins than normal cells	Erythema, blistering, desquamation, and discomfort	IB

AK, Actinic keratosis; *FDA*, US Food and Drug Administration; *cSCC*, squamous cell carcinoma; *N/A*, not applicable; *VA*, Veterans Affairs.

*Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

†Aldara, 3M Health Care Limited, Loughborough, England; Zyclara, Valeant Pharmaceuticals North America LLC, Bridgewater, NJ.

Classification

- The American Joint Committee on Cancer's (AJCC) most recent staging system, AJCC-8, published in October 2016, uses tumor diameter $\geq$2 cm as the distinguishing factor between T1 and T2 tumors
- High-risk features in AJCC-8 staging, which result in upstaging to T3, include tumor diameter $\geq$4 cm, minor bone erosion, invasion of nerves 0.1 mm in caliber or in subcutis, or deep invasion ($\geq$6 mm or beyond the subcutaneous fat)
- T4 is reserved for major bone involvement or skull base invasion

Table I. American Joint Committee on Cancer (AJCC) cutaneous SCC staging system for tumors of the head and neck skin 8th edition

T category	T criteria	N category	N criteria for pathologic N	M category	M criteria
TX	Primary tumor cannot be identified	NX	Regional lymph nodes cannot be assessed	M0	No distant metastasis
Tis	Carcinoma in situ	N0	No regional lymph node metastasis	M1	Distant metastasis
T1	Tumor <2 cm in greatest dimension	N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE^{-}*		
T2	Tumor ≥2 cm but <4 cm in greatest dimension	N2	Metastasis in a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE^{+}; or >3 cm but not >6 cm in greatest dimension and ENE^{-}; or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE^{-}; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE^{-}		
T3	Tumor ≥4 cm in clinical diameter OR minor bone erosion OR perineural invasion OR deep invasion†	N2a	Metastasis in single ipsilateral or contralateral node ≤3 cm in greatest dimension and ENE^{+}; or in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE^{-}		
T4	Tumor with gross cortical bone/marrow, skull base invasion, and/or skull base foramen invasion	N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE^{-}		
T4a	Tumor with gross cortical bone/marrow invasion	N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE^{-}		
T4b	Tumor with skull base invasion and/or skull base foramen involvement	N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE^{-}; or in a single ipsilateral node >3 cm in greatest dimension and ENE^{+}; or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE^{+}		
		N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE^{-}		
		N3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE^{+}; or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE^{+}		

Classification

- The Brigham and Women's Hospital (BWH) staging system contains a high-risk T2b category, which requires the presence of $\geq$2 risk factors and includes only about 5% of cSCCs but accounts for 72% of nodal metastases and 83% of deaths from cSCC

Table II. Brigham and Women's Hospital tumor staging system

Stage	No. of high-risk factors*
T1	0
T2a	1
T2b	2-3
T3	≥4

*Brigham and Women's Hospital high-risk factors include tumor diameter ≥2 cm, poorly differentiated histology, perineural invasion ≥0.1 mm, or tumor invasion beyond the subcutaneous fat (excluding bone invasion which automatically upgrades tumor to Brigham and Women's Hospital stage T3).

NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Squamous Cell Skin Cancer

Version 2.2022 — May 2, 2022

NCCN.org

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

Continue

CLINICAL PRESENTATION	WORKUP	DIAGNOSIS	RISK STATUS	

CLINICAL PRESENTATION

Lesion suspicious for skin cancer[a] →

WORKUP

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

→

DIAGNOSIS

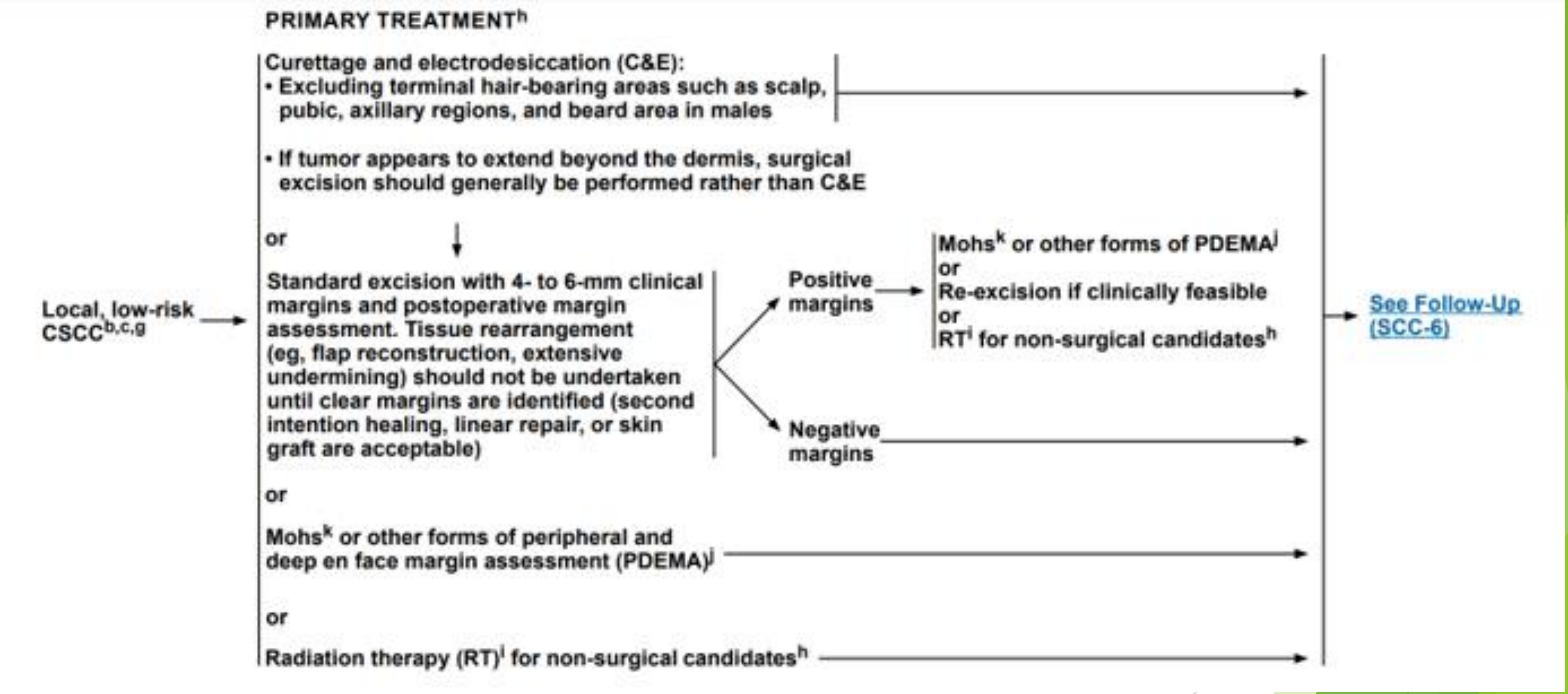
Cutaneous squamous cell cancer (CSCC) confirmed[f]

RISK STATUS

- Local
  - Low risk[c] → See Primary Treatment (SCC-2)
  - High risk/Very high risk[c] → See Primary Treatment (SCC-3)
- Clinically or radiographically concerning regional lymph nodes → See Clinical Staging and Preoperative Assessment (SCC-4)
- or
- Distant metastatic disease → See Regional recurrence or distant metastases (SCC-6)

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

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


PRIMARY TREATMENT[h]
Local, low-risk CSCC[b,c,g]
Curettage and electrodesiccation (C&E):
• Excluding terminal hair-bearing areas such as scalp, pubic, axillary regions, and beard area in males
• If tumor appears to extend beyond the dermis, surgical excision should generally be performed rather than C&E
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[k] or other forms of PDEMA[j]
or
Re-excision if clinically feasible
or
RT[i] for non-surgical candidates[h]
Negative margins
or
Mohs[k] or other forms of peripheral and deep en face margin assessment (PDEMA)[j]
or
Radiation therapy (RT)[i] for non-surgical candidates[h]
See Follow-Up (SCC-6)

PRIMARY TREATMENT[h]

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

- **Mohs[k] or other forms of PDEMA (preferred for very high risk)[j,n,o,p,u]**
  - **Positive margins** → Multidisciplinary consultation to discuss options:
    - Re-resect, if feasible
    - RT[i] ± systemic therapy[r]
    - Systemic therapy if curative RT not feasible[l]
  - **Negative margins** → If extensive perineural, large, or named nerve involvement, or if other poor prognostic features:[b,s] Recommend multidisciplinary consultation and Consider adjuvant RT[i,t]

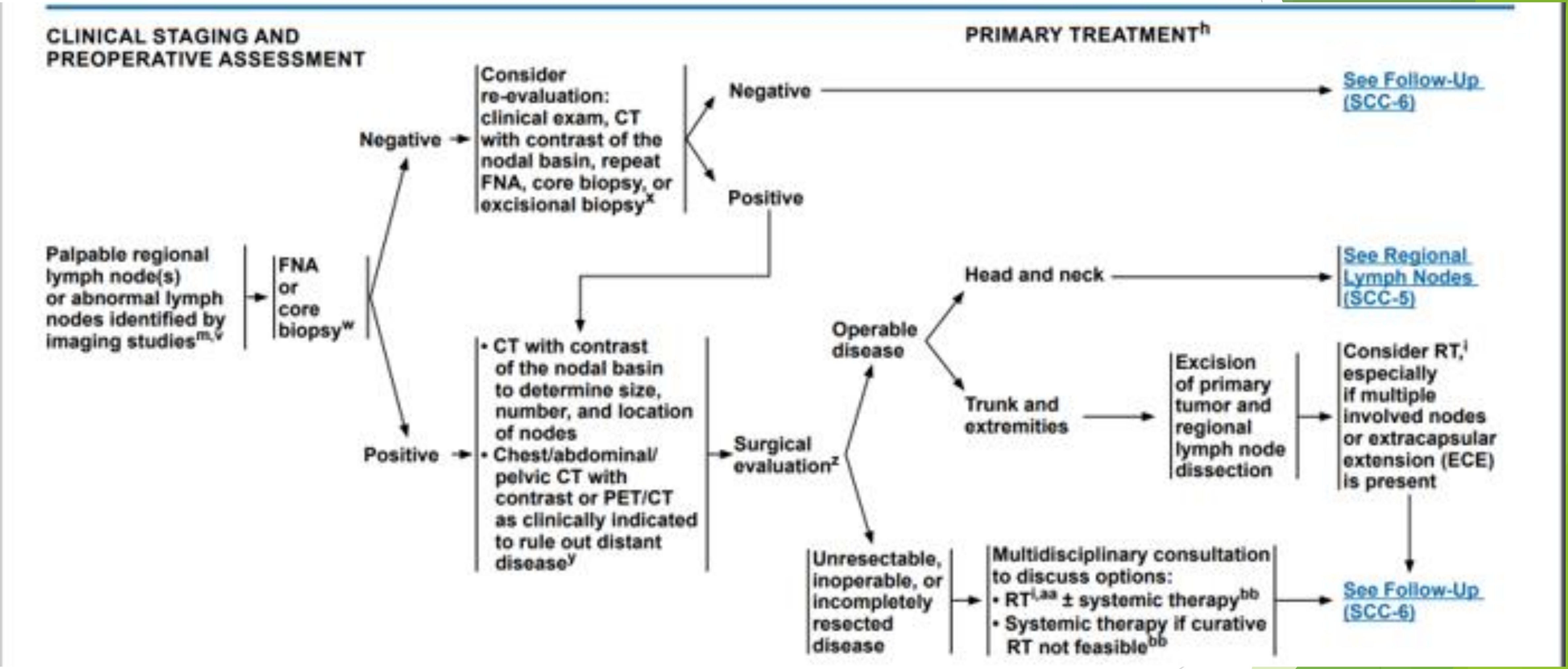
or

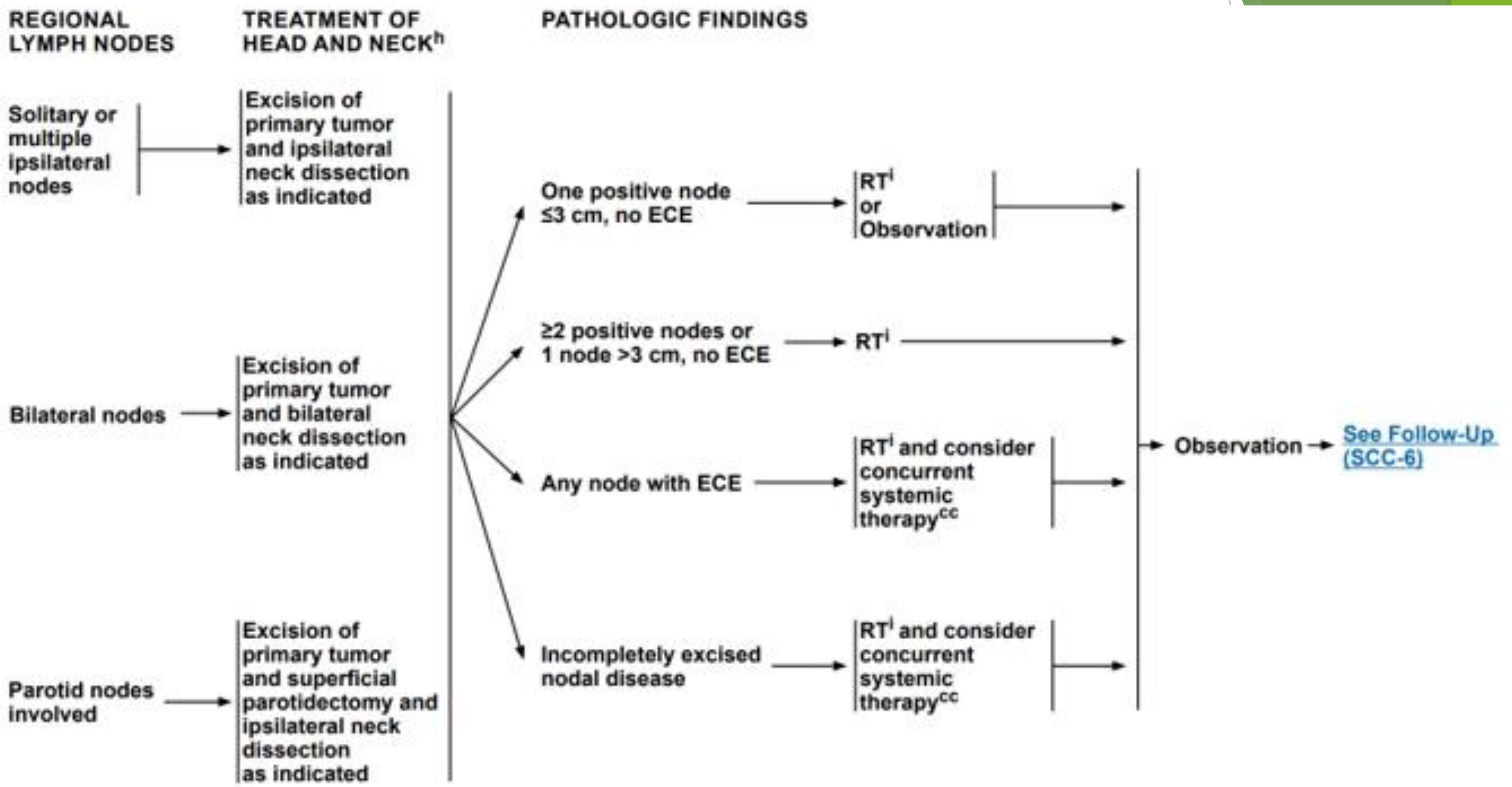
- **Standard excision with wider surgical margins[q] and postoperative margin assessment[n,o] and second intention healing, linear repair, or skin graft**
  - **Negative margins** → If extensive perineural, large, or named nerve involvement, or if other poor prognostic features:[b,s] Recommend multidisciplinary consultation and Consider adjuvant RT[i,t]
  - **Positive margins** → Mohs[k] or other forms of PDEMA[j] if feasible or Standard re-excision if PDEMA[j] not feasible → If residual disease is present, and further surgery is not feasible, consider multidisciplinary consultation to discuss options:
    - RT[i] ± systemic therapy[r]
    - Systemic therapy if curative RT not feasible[l]

or

- **For non-surgical candidates:**
  - RT[i] ± systemic therapy[r]
  - Systemic therapy if curative RT not feasible[l]

→ See Follow-Up (SCC-6)


CLINICAL STAGING AND PREOPERATIVE ASSESSMENT
PRIMARY TREATMENT[h]
Palpable regional lymph node(s) or abnormal lymph nodes identified by imaging studies[m,v]
FNA or core biopsy[w]
Negative
Consider re-evaluation: clinical exam, CT with contrast of the nodal basin, repeat FNA, core biopsy, or excisional biopsy[x]
Negative
See Follow-Up (SCC-6)
Positive
Positive
• CT with contrast of the nodal basin to determine size, number, and location of nodes
• Chest/abdominal/ pelvic CT with contrast or PET/CT as clinically indicated to rule out distant disease[y]
Surgical evaluation[z]
Operable disease
Head and neck
See Regional Lymph Nodes (SCC-5)
Trunk and extremities
Excision of primary tumor and regional lymph node dissection
Consider RT,[i] especially if multiple involved nodes or extracapsular extension (ECE) is present
Unresectable, inoperable, or incompletely resected disease
Multidisciplinary consultation to discuss options:
• RT[i,aa] ± systemic therapy[bb]
• Systemic therapy if curative RT not feasible[bb]
See Follow-Up (SCC-6)


REGIONAL LYMPH NODES
TREATMENT OF HEAD AND NECK[h]
PATHOLOGIC FINDINGS
Solitary or multiple ipsilateral nodes
Excision of primary tumor and ipsilateral neck dissection as indicated
Bilateral nodes
Excision of primary tumor and bilateral neck dissection as indicated
Parotid nodes involved
Excision of primary tumor and superficial parotidectomy and ipsilateral neck dissection as indicated
One positive node ≤3 cm, no ECE
RT[i] or Observation
≥2 positive nodes or 1 node >3 cm, no ECE
RT[i]
Any node with ECE
RT[i] and consider concurrent systemic therapy[cc]
Incompletely excised nodal disease
RT[i] and consider concurrent systemic therapy[cc]
Observation
See Follow-Up (SCC-6)

FOLLOW-UP

Local disease:

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

Regional disease:

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

Local recurrence[g] → See Primary Treatment for Local Disease (SCC-3)

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

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

[aa] Consider palliative RT/surgery for symptomatic sites. SBRT may also

Table 1: Systemic Therapy Options for Use with RT		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Cisplatin[2] • Clinical trial[3,4]	• None	• EGFR inhibitors (eg, cetuximab)[2] • Cisplatin + 5-FU[2] • Carboplatin ± paclitaxel[2,5,6]

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

Table III. Oral and systemic agents for cutaneous squamous cell carcinoma chemoprevention

Therapy	Indications	Dosing	Mechanism of action	Adverse effects	Level of evidence*
Nicotinamide[66-70]	Off-label use: decreases AKs and SCCs; can be used by anyone for chemoprophylaxis	500 mg PO BID	Amide form of vitamin B_3; enhances the repair of UV light—induced DNA damage; also reduces the level of immunosuppression induced by UV light	None reported; liver failure at high doses (>3 mg/d)	IB
Oral retinoids[58-64]	Off-label uses: cSCC prevention in xeroderma pigmentosum and organ transplant patients; consider in patients who develop 5-10 cSCCs per year; consider for patients on BRAF inhibitors with multiple cSCCs	High-dose isotretinoin (2 mg/kg/d); acitretin 10-30 mg PO daily	Natural or synthetic analogues of vitamin A; bind to specific nuclear receptors and involved in immunomodulation, induction of apoptosis, cell cycle control, inhibition of ornithine decarboxylase, and inhibition of cellular proliferation and keratinization	Dry skin and mucosa, alopecia, increased liver transaminases and triglycerides, decreased night vision, and teratogenicity	IB
Capecitabine[71-73]	Solid organ transplant recipients with multiple cSCCs	950 mg/m^2 on days 1-14 of a 21-day cycle along with 3 times weekly subcutaneous interferon alfa	Converted to active form, 5-FU, in the body	Fatigue, nausea, hand—foot syndrome, gout, and decreased renal function	III
Aspirin and NSAIDs[86]	Preventive effect shown in meta-analysis; however, unclear if benefits worth the potential adverse effects	Variable NSAIDs and dosing frequencies studied	Inhibits COX-2, which results in decreased inflammation and apoptosis of neoplastic cells	Gastrointestinal ulcers and bleeding, kidney failure, nausea, rash, headache, and dizziness	IA
Sirolimus[75-79]	Solid organ transplant recipients—studies show decreased risk of cSCC compared to calcineurin inhibitors	Varies	Inhibits the mammalian target of rapamycin, thereby reducing the growth and proliferation of tumor cells	Myelosuppression, hyperlipidemia, increased susceptibility to infection, peripheral edema, hypertension, headache, rash, and abdominal pain	IB

5-FU, 5-fluorouracil; *AK*, actinic keratosis; *BID*, twice daily; *COX-2*, cyclooxygenase-2; *cSCC*, cutaneous squamous cell carcinoma; *NSAID*, nonsteroidal antiinflammatory drug; *PO*, orally; *UV*, ultraviolet light.

*Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

THANK YOU!