
In the Name of God

Squamous cell skin cancer

Principles of treatment

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Risk Stratification/ Staging system

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Squamous Cell Skin Cancer

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Discussion

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(+).

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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

Risk Stratification/ Staging system

- NCCN: *Risk Stratification*

- AJCC 7th edition:
- NCCN: More accurate to define high risk groups among patients with clinically localized disease(T1/T2)

- AJCC 8th edition: T stage?

Squamous cell skin cancer

- **Local**

1. Low risk
2. High risk/ very high risk

- **Extensive disease**
- Clinically / radiographically concerning regional lymph nodes
- Distant metastases
- Deep structural involvement(bone), perineural disease, deep soft tissue

Risk Stratification

- Risk group: based on the highest risk factor present
- High-risk group: increased risk of local recurrence
- Very high-risk: increased risk of local recurrence & distant metastasis
- ***Size/ location*** :
- pre-operative clinical tumor diameter
- If clinical evaluation of incisional bx suggests that microstaging is inadequate, consider narrow margin excisional biopsy

Risk Stratification

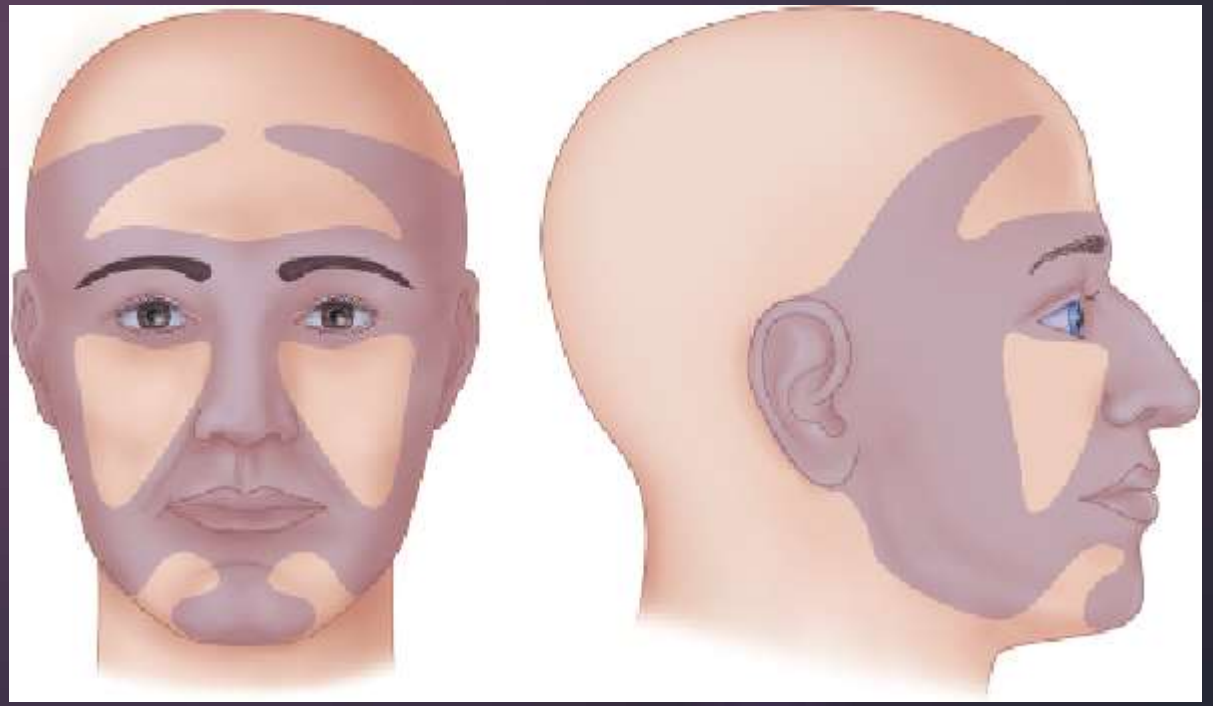
- **Size**

  - various size in different data

  - Most recent data: tumors > 2 cm are at high risk of metastases & poorer DSS

Risk Stratification

- ***location:***
- ***High risk***: head & neck, hands, feet, pretibial,anogenital (independent of size)
- Genitalia area & mucosal surfaces & ears : greater risk of metastases
- (so called mask area of the face/1983)
- ***Low risk***: trunk and extremities



Risk Stratification

- cSCC < 2 cm : extrapolation data from BCC
- 27 years retrospective review of 5755 BCC:
- High risk site: mask area
- Increased recurrence : High risk location & >6 mm in diameter
- Moderate risk location > 10 mm

MMS/ CCPDMA versus standard excision or C&E

Risk Stratification

- **NCCN:**

- **High risk:**

1. Tumors in low risk area & size ≥ 20mm
2. Tumors in moderate risk area & size ≥10mm
3. Tumors in high risk area with any size

Risk Stratification

- ***Primary versus recurrent disease***

  - Higher risk of recurrence and metastasis for recurrent versus primary disease has been extensively documented in the literature

Risk Stratification

- ***Immunosuppresion***

- Increasing the risk of cSCC development
- Associated with poorer outcome(recurrence, metastasis, death)

- Multiple lesion/ high grade disease/ deep tissue spread/ PNI & LVI / HPV infection

Risk Stratification

- ***Neurologic symptoms***

  - Clinical symptoms: up to 40 % of patients
  - Pain. Burning, stinging, anesthesia, paresthesia, facial paralysis, diplopia, blurred vision
  - Any suggestion of neurologic involvement: high risk category
  - Increased recurrence/ metastasis/ poor outcome

Risk Stratification

- ***Site of prior RT/ chronic inflammatory process***

- Primary cSSCs arising in area previously irradiated for unrelated condition
- All recurrent tumors irrespective of prior RT: high risk
- data from Studies:
  - prior RT for unrelated (frequently benign) conditions: risk factor for NMSC
  - Increased risk of metastasis for lesion arising in the setting of chronic scarring or inflammation

Risk Stratification

- ***Pathologic risk factor***
  - Degree of differentiation
  - Histology
  - Depth
  - PNI
  - LVI/VI

Risk Stratification

- ***Multiple SCCs***
- Immunosuppressed patients (solid organ transplant, lymphoma, CLL, drug induced immunosuppression, HIV)

- Rare genetic disorder:

Albinism/ xeroderma pigmentosum/

Close follow up and patients education is recommended

Risk Stratification

- Narrow excision margins due to anatomic/functional constrains: increased recurrences
- Complete margin assessment such as with mohs/PDEMA is recommended for optimal tumor clearance & maximal tissue conservation

- Tumors <6 mm in size, without high/ very high risk features: other treatment modalities can be considered if at least 4 mm clinically tumor free margins can be obtained

Risk Stratification

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	(-)	(-)	(+)

Local treatment for SCC

- ***The primary goals of treatment of CSCC:***

- Most effective & efficient means: Surgical approaches

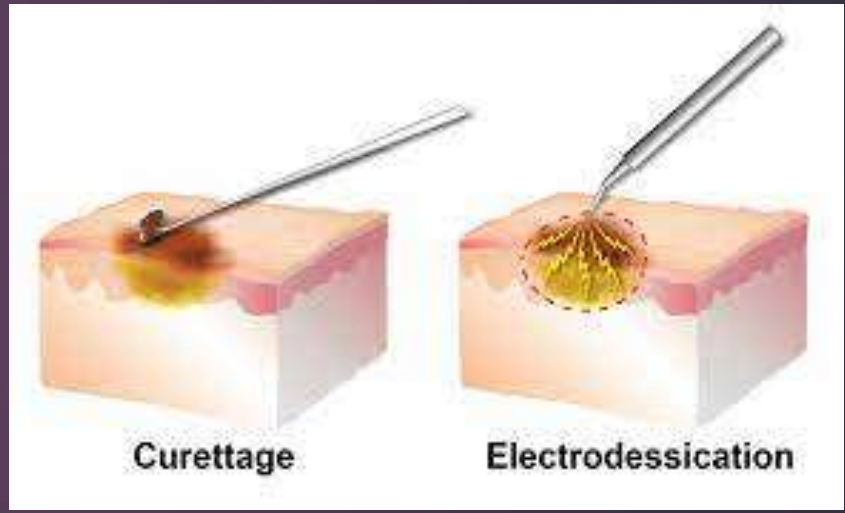
- Complete removal of the tumor & the maximal preservation of function & cosmesis

- All treatment decisions should be customized:

- Individual case & patient `s preference

Local treatment for SCC

- ***Curettage and electrodesiccation(C&E)***
  - Up to 3 cycle may be performed in a session
  - Fast & cost-effective for superficial lesion
  - Margin assessment is not possible
  - Cure rate : 95-96% (low risk patients)



Curettage and electrodesiccation(C&E)

- ***NCCN:***

- Low risk tumors with three caveats
- Should not be used to treat areas with terminal hair growth(scalp,pubic or axillary)
- Should not be used to Beard area in males due to the risk that a tumor extending down follicular structures might not be adequately removed
- If the subcutaneous layer is reached during the course of C&E, the surgical excision should generally be performed instead.
- If C&E has been performed based on the low risk tumor, biopsy should be reviewed

Excision with postoperative margin assessment

- Standard surgical excision followed by post operative margin assessment
- Well circumscribed cSCC less than 2 cm: excision with 4mm margin(complete removal 95%)
- Low risk lesion > 2cm : 6 mm margin (complete removal 95%)
- high risk lesion margins:
- Less than 1 cm:4 mm
- 1-1.9 cm: 6 mm
- ≥ 2 cm: 9 mm

Superficial therapies

- Should be reserved for SCC in situ
- Topical / cryotherapy/ photodynamic therapy
- ***Topical***
- ***Imiquimod***: high rates of initial clearance(70-100%) and low rates of recurrences
- Side effects: inflammatory skin reaction(erythema, pruritis, pain,,)
- Discontinuation after lesion clearance has not been shown to lead to recurrence

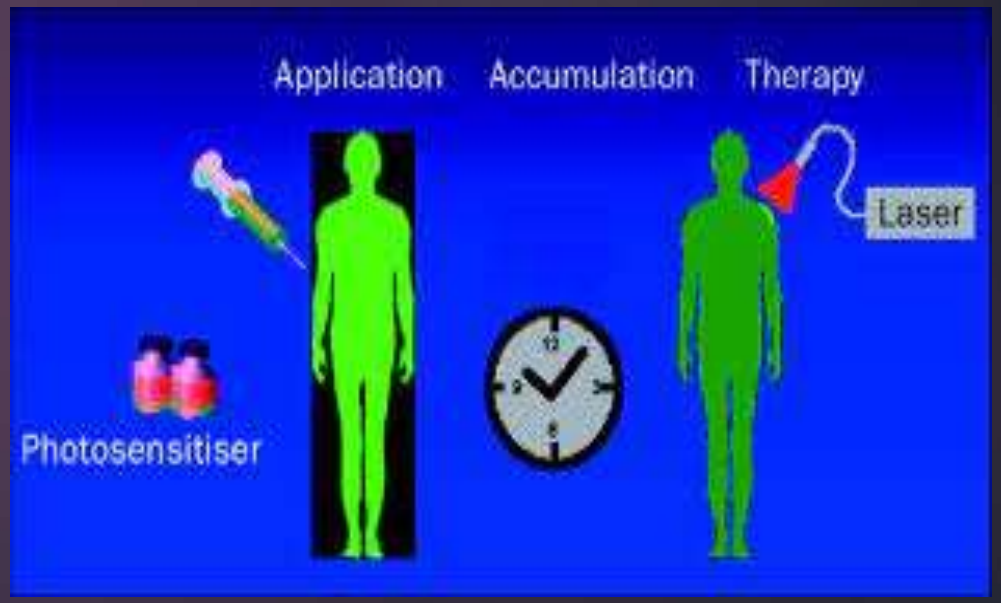
- ***5FU:*** lower clearance rate than imiquimod and vary widly(27-93%)
- inflammatory skin reaction: ulceration, erosion…

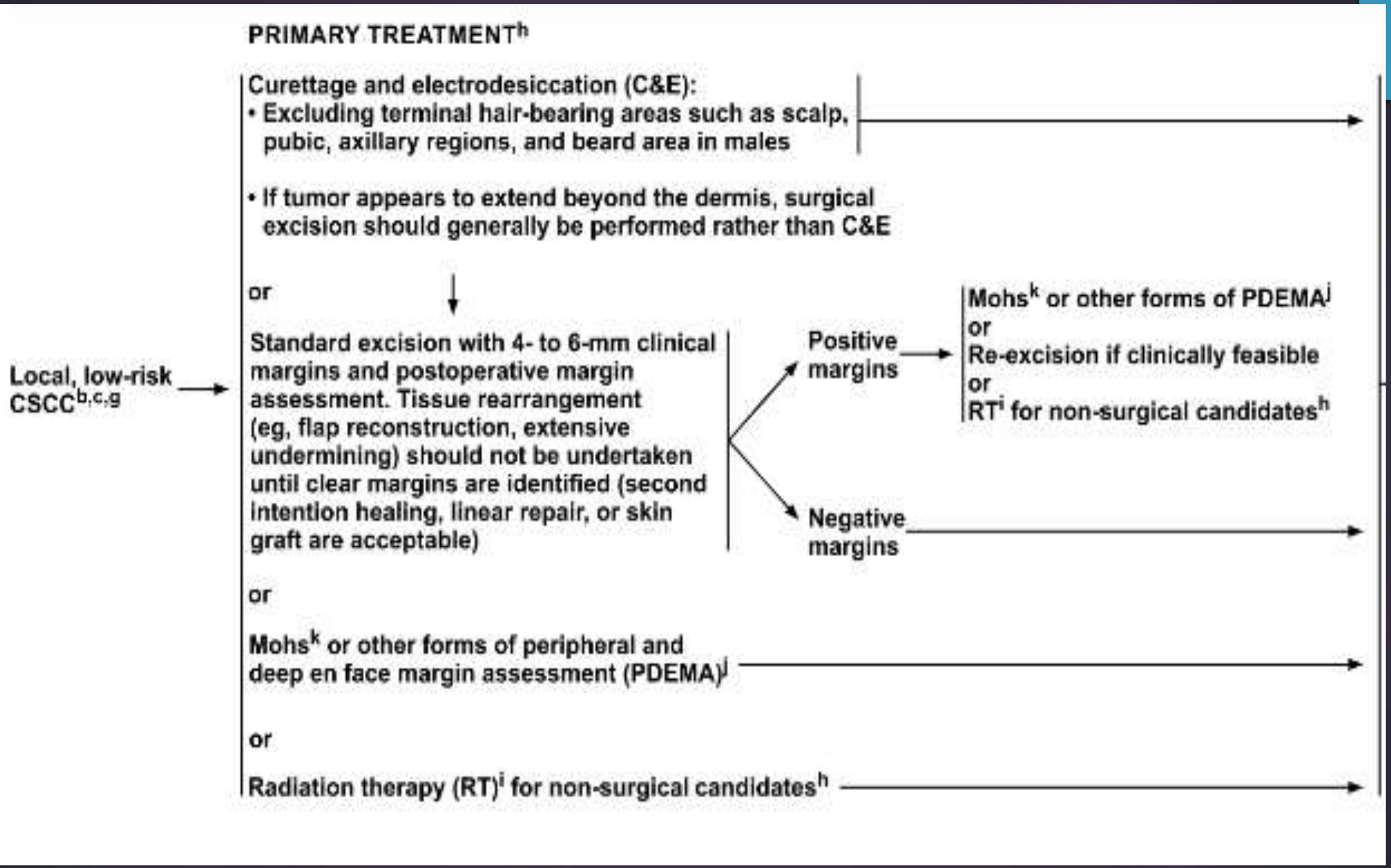
Superficial therapies

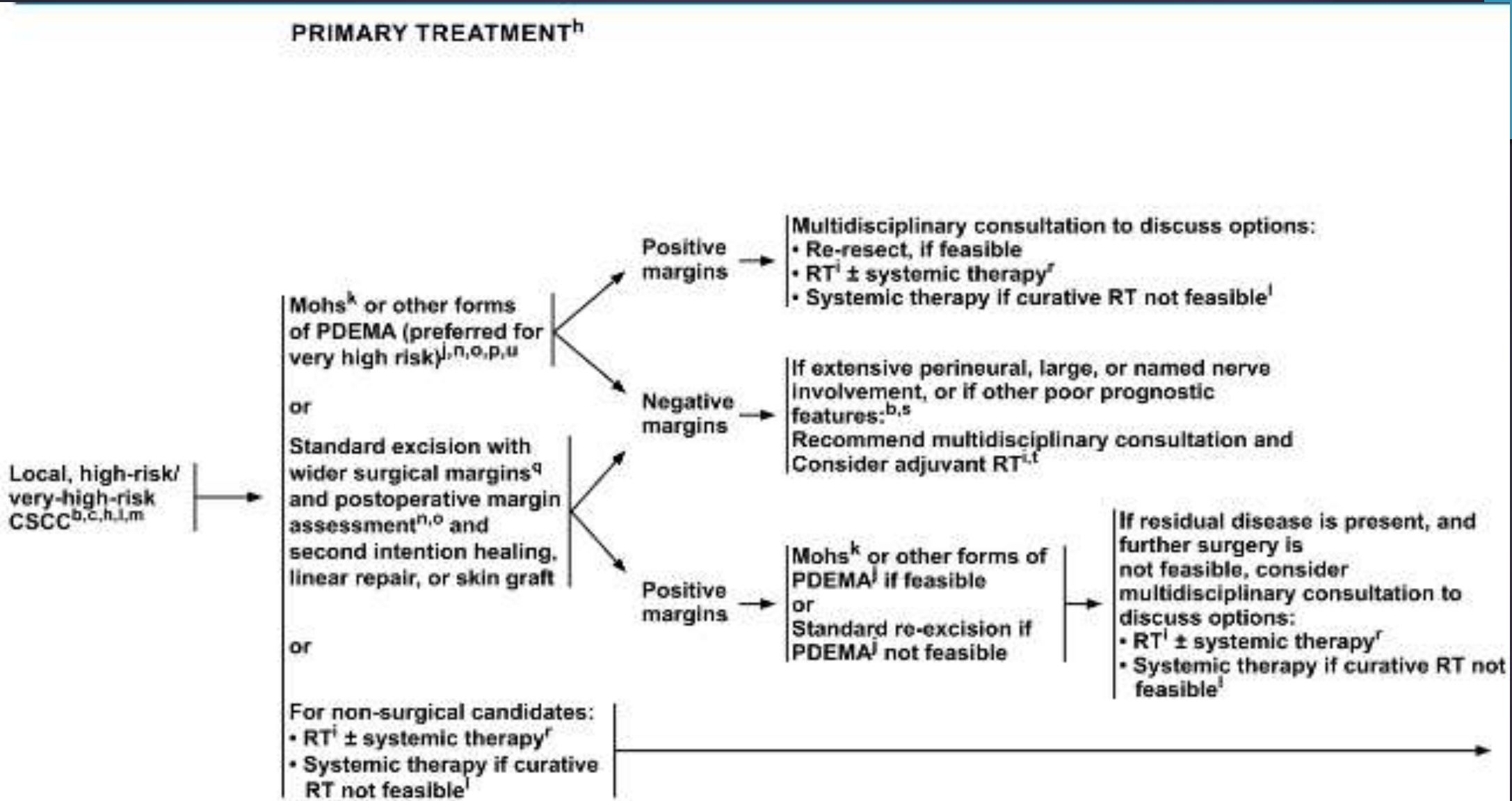
- ***Cryosurgery/ cryotherapy***
  - Recurrence rates of 0-4 % for invasive SCC
  - Recurrence rates of 1-13 % for SCC insitu(retrospective data)
  - Recurrence rates of 0-50 % for SCC insitu(prospective data)
  - Variation in patients selection, variable follow up, different teqniques
  - Adverse effect: edema, blistering, scabbing, ulceration, loss of pigment, pain, scarring and infection
  - pain and time to healing is greater than C&E
  - Poorer cosmetic outcome rather than 5Fu

Photodynamic therapy

- Involves the application of a photosensitizing agent on the skin followed by irradiation with a light source
- Methyl aminolevulinate(MAL) & 5-aminolevulinic acid(ALA)
- Insitu lesion: complete clearance 52-98%
- greater risk of Skin reaction than 5FU??
- MAL is no longer produced in US




PRIMARY TREATMENT[h]
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
Local, low-risk CSCC[b,c,g]
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]


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]
or
Standard excision with wider surgical margins[q] and postoperative margin assessment[n,o] and second intention healing, linear repair, or skin graft
or
For non-surgical candidates:
• RT[i] ± systemic therapy[r]
• Systemic therapy if curative RT not feasible[l]
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]
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]


Thank you
for your
attention