Protocol for the Examination of Specimens from Patients with Cutaneous Carcinoma of the Head and Neck

Version: 1.2.0.0
Protocol Posting Date: April 2026

CAP Laboratory Accreditation Program Protocol Required Use Date: January 2027
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes wide local excisions and craniofacial resections
Tumor Type	**Description**
Carcinoma	Includes ONLY N+, and pT3 and pT4 cutaneous squamous cell carcinoma including squamous cell carcinomas of dry vermillion lip and commissure

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens
Early-stage cutaneous squamous cell carcinomas (N-, and pT1 and pT2 cutaneous squamous cell carcinomas)
Other keratinocytic / epidermal carcinomas and appendageal carcinomas of the skin

The following tumor types should NOT be reported using this protocol:

Tumor Type
Merkel cell carcinoma (consider the Merkel Cell Carcinoma protocol)
Squamous cell carcinomas of the vulva (consider the Vulva protocol)
Squamous cell carcinomas of the penis (consider the Penis protocol)
Squamous cell carcinomas of other cutaneous sites (no current protocol)

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Glossary:
Author: Expert who is designated by the chair of the Cancer Committee.
Expert Panel Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements
Synoptic reporting with core and conditional data elements for designated specimen types* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with "+". Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under Accreditation Checklists.
A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.
**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

Synoptic Reporting
All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location
- Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 1.2.0.0

- Update to protocol name to remove “Squamous Cell” from title
- Addition of the Tumor Bed Margin Status section
- Removal of the ADDITIONAL FINDINGS section
- Removal of Explanatory Note A “Scope of Guidelines”

Reporting Template

Protocol Posting Date: April 2026
Select a single response unless otherwise indicated.
CASE SUMMARY: (CUTANEOUS CARCINOMA OF THE HEAD AND NECK)
Standard(s): AJCC 8

SPECIMEN (Note A)

Procedure (select all that apply)
___ Excision, ellipse
___ Excision, wide
___ Excision, other (specify): _____
___ Re-excision, ellipse
___ Re-excision, wide
___ Re-excision, other (specify): _____
___ Lymphadenectomy, sentinel node(s)
___ Lymphadenectomy, regional nodes (specify): _____
___ Other (specify): _____
___ Not specified

TUMOR

Multiple Primary Sites (required only if applicable)#
 # Please complete a separate checklist for each primary site if required as above.
___ Not applicable (no additional primary site(s) present)
___ Present: _____

Tumor Focality
___ Unifocal
___ Multifocal: _____
___ Cannot be determined (explain): _____

Tumor Site
___ Specify site: _____
___ Not specified

Tumor Laterality (select all that apply)
___ Right
___ Left
___ Midline
___ Not specified

Tumor Size
___ Greatest dimension in Centimeters (cm): _____ cm
___ Cannot be determined (explain): _____

Histologic Type (Note B)
This protocol can be used to report basal cell and appendageal carcinoma. Please complete a separate protocol for each separate primary tumor as applicable.

Squamous cell carcinomas
___ Squamous cell carcinoma, NOS
___ Verrucous squamous cell carcinoma
___ Acantholytic squamous cell carcinoma
___ Lymphoepithelial carcinoma
___ Clear cell squamous cell carcinoma
___ Spindle cell squamous cell carcinoma
___ Squamous cell carcinoma with sarcomatoid differentiation
Other
___ Basal cell carcinoma (specify subtype, if known): _____
___ Appendageal carcinoma (specify subtype, if known): _____
___ Other (specify): _____

+Histologic Type Comment: _____

Histologic Grade (Note C)
___ G1: Well-differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated
___ Other (specify): _____
___ GX: Cannot be assessed
___ Not applicable

Tumor Depth of Invasion (DOI) (Note D)
___ Specify depth in Millimeters (mm): _____ mm
___ At least in Millimeters (mm): _____ mm
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Anatomic Level
___ Not applicable
___ I (carcinoma in situ)
___ II (carcinoma present in but does not fill and expand papillary dermis)
___ III (carcinoma fills and expands papillary dermis)
___ IV (carcinoma invades reticular dermis)
___ V (carcinoma invades subcutaneum)

Tumor Extent (specify other structures involved) (required only if pT defined elements are applicable): _____

Lymphatic and / or Vascular Invasion
___ Not identified

___ Present: _____
___ Cannot be determined (explain): _____

Perineural Invasion (Note E)
___ Not identified
___ Present
___ Less than 0.1 mm in caliber
 # Location of the involved nerve deep to the dermis serves as a surrogate for this size cut-off and qualifies as greater than or equal to 0.1 mm.
___ Greater than or equal to 0.1 mm in caliber#
___ Specify: _____
___ Cannot be determined (explain): _____

+Tumor Comment: _____

MARGINS (Note F)

Specimen Margin Status for Invasive Tumor
___ All specimen margins negative for invasive tumor
+Distance from Invasive Tumor to Closest Specimen Margin
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
+Closest Specimen Margin(s) to Invasive Tumor
___ Specify location(s) of closest specimen margin(s): _____
___ Cannot be determined: _____
+Other Close Specimen Margin(s) to Invasive Tumor
___ Specify location(s) and distance(s) of other close specimen margin(s): _____
___ Cannot be determined: _____
___ Invasive tumor present at specimen margin(s)
Specimen Margin(s) Involved by Invasive Tumor (select all that apply)
___ Peripheral: _____
___ Deep: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

Specimen Margin Status for Non-invasive Tumor
___ All specimen margins negative for non-invasive tumor
+Distance from Non-invasive Tumor to Closest Specimen Margin
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm

___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
+Closest Specimen Margin(s) to Non-invasive Tumor
___ Specify closest specimen margin(s): _____
___ Cannot be determined: _____
___ In situ disease present at specimen margin
Specimen Margin(s) Involved by Non-invasive Tumor (select all that apply)
___ Peripheral: _____
___ Deep: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

+Tumor Bed Margin Status (separately submitted)
___ Tumor bed margins assessed

+Tumor Bed Margin Orientation
___ Oriented to true margin surface
___ Unoriented to true margin surface
___ Cannot be determined: _____

+Tumor Bed Margin Status for Invasive Tumor
___ All tumor bed margins negative for invasive tumor
+Distance from Invasive Tumor to True Margin Surface (pertinent to oriented specimens which are sectioned perpendicularly)
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
___ Invasive tumor present at tumor bed margin(s)
Tumor Bed Margin(s) Involved by Invasive Tumor (per part labeling)
___ Specify involved tumor bed margin(s): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined: _____

+Tumor Bed Margin Status for Non-invasive Tumor
___ All tumor bed margins negative for in situ disease
+Distance from Non-invasive Tumor to True Margin Surface (pertinent to oriented specimens which are sectioned perpendicularly)
Specify in Millimeters (mm)
___ Exact distance: _____ mm

___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
___ In situ disease present at tumor bed margin
Tumor Bed Margin(s) Involved by Non-invasive Tumor (per part labeling)
___ Specify involved tumor bed margin(s): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES (Note G)

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)
Number of Lymph Nodes with Tumor
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Laterality of Lymph Node(s) with Tumor
___ Ipsilateral (including midline): _____
___ Contralateral: _____
___ Bilateral: _____
___ Cannot be determined (explain): _____
Size of Largest Nodal Metastatic Deposit
Specify in Centimeters (cm)
___ Exact size (specify): _____ cm
___ At least (specify): _____ cm
___ Greater than: _____ cm
___ Less than: _____ cm
___ Other (specify): _____
___ Cannot be determined (explain): _____

Extranodal Extension (ENE) (Note G)
___ Not identified
___ Present
___ Cannot be determined (explain): _____
___ Other (specify): _____

___ Cannot be determined (explain): _____

Number of Lymph Nodes Examined
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)
___ Not applicable
___ Lung: _____
___ Bone: _____
___ Brain: _____
___ Liver: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

pTNM CLASSIFICATION (AJCC 8th Edition) (Note H)
Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Prior Procedure Classification
In general, CAP cancer protocol case summaries are intended to guide reporting on the specimen that the pathologist is evaluating at that time. However, cutaneous squamous cell carcinoma cases frequently include multiple procedures. Because of this, a prior procedure that was performed may affect the pathologic classification of the tumor. In order to represent this appropriately in the pathology report, information from prior procedures may be incorporated into the assignment of pathologic classification if it is available. When information from a prior procedure is included in this report, details of that procedure should be documented in the report as well.
___ No information from a prior procedure is included in the classification assigned in this report
___ Classification assigned in this report includes information from a prior procedure (explain):
_____

Modified Classification (required only if applicable) (select all that apply)
___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category
___ pT not assigned (cannot be determined based on available pathological information)
___ pTis: Carcinoma in situ
___ pT1: Tumor smaller than or equal to 2 cm in greatest dimension
___ pT2: Tumor larger than 2 cm, but smaller than or equal to 4 cm in greatest dimension
 # Deep invasion is defined as invasion beyond the subcutaneous fat (i.e., to underlying microanatomic landmarks such as fascia, muscle, perichondrium, and / or periosteum) or greater than 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.

___ pT3: Tumor larger than 4 cm in maximum dimension or minor bone erosion or perineural invasion or deep invasion#

pT4: Tumor with gross cortical bone / marrow, skull base invasion and / or skull base foramen invasion

___ pT4a: Tumor with gross cortical bone / marrow invasion

___ pT4b: Tumor with skull base invasion and / or skull base foramen involvement

___ pT4 (subcategory cannot be determined)

T Suffix (required only if applicable)

___ Not applicable

___ (m) multiple primary synchronous tumors in a single organ

pN Category#

 # 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 ENE should be recorded as ENE(−) or ENE(+).

___ pN not assigned (no nodes submitted or found)

___ pN not assigned (cannot be determined based on available pathological information)

___ pN0: No regional lymph node metastasis

___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)

pN2: 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(-)

___ pN2a: 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(-)

___ pN2b: Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)

___ pN2c: Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)

___ pN2 (subcategory cannot be determined)

pN3: 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(+)

___ pN3a: Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)

___ pN3b: 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(+)

___ pN3 (subcategory cannot be determined)

pM Category (required only if confirmed pathologically)

___ Not applicable - pM cannot be determined from the submitted specimen(s)

___ pM1: Distant metastasis

Brigham and Women's (BWH) Tumor Classification System (Note H)

+High-risk Factors (select all that apply)

___ Tumor diameter greater than or equal to 2 cm

___ Poorly differentiated histology

___ Perineural invasion greater than or equal to 0.1 mm in caliber
___ Tumor invasion beyond subcutaneous fat (excluding bone invasion, which upgrades tumor to BWH stage T3)

+BWH Tumor Classification
___ T1: 0 high-risk factor
___ T2a: 1 high-risk factor
___ T2b: 2-3 high-risk factors
___ T3: 4 risk factors or bone invasion

SPECIAL STUDIES

For reporting molecular testing and other cancer biomarker testing results, the CAP Head and Neck Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.

COMMENTS

Comment(s): _____

Explanatory Notes

A. Specimen

Optimal pathologic evaluation of squamous cell carcinomas requires complete excision that incorporates the entire lesion removed intact.[1,2] While the type of biopsy may be depend on the anatomic location and size of the lesion, such as shave, punch, incisional or excisional,[1] the curative surgical excision is aimed at complete removal of the tumor along with surrounding tumor-free skin and soft tissue to ensure adequate risk-adapted safety margin.[2] For scalp and forehead tumors lacking bone invasion, the excision often includes aponeurosis/galea, while the underlying periosteum is typically spared.[2,3] En-bloc excision may be necessary in patients with multiple closely clustered tumors,[2] and may include portion of underlying bone, if bone involvement is suspected or noted by imaging studies. The use of intraoperative frozen sections for margin control is a common practice,[2,3] and may be in the form of standard excision or Mohs micrographic surgery. In rare instances, curettage and electrodesiccation may be used as an alternative treatment strategy for small low-risk keratinocytic carcinomas.[4] However, margin status cannot evaluated in such specimens; and, determination of tumor thickness may also be precluded due to tissue fragmentation and tangential processing of tissue fragments.

References

1. Alexander J Stratigos AJ, Garbe C, Dessinioti C, et al. European consensus-based interdisciplinary guideline for invasive cutaneous squamous cell carcinoma. Part 1: Diagnostics and prevention-Update 2023. *Eur J Cancer.* 2023 Nov: 193:113251.
2. Alexander J Stratigos AJ, Garbe C, Dessinioti C, et al. European consensus-based interdisciplinary guideline for invasive cutaneous squamous cell carcinoma: Part 2. Treatment-Update 2023. *Eur J Cancer*. 2023 Nov: 193:113252.
3. SFORL work group; Durbec M, Couloigner V, Tronche S, et al. Guidelines of the French Society of Otorhinolaryngology (SFORL), short version. Extension assessment and principles of resection in cutaneous head and neck tumors. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2014 Dec;131(6):375-383.
4. Yakish K, Graham J, Hossler EW. Efficacy of curettage alone for invasive cutaneous squamous cell carcinoma: A retrospective cohort study. *J Am Acad Dermatol.* 2017 Sep;77(3):582-584.

B. Histologic Subtypes

The World Health Organization (WHO) classification[1] of epidermal and appendageal carcinomas of the skin is shown below:

Squamous cell carcinomas
- Verrucous squamous cell carcinoma
- Acantholytic squamous cell carcinoma
- Lymphoepithelial carcinoma
- Clear cell squamous cell carcinoma
- Spindle cell squamous cell carcinoma
- Squamous cell carcinoma with sarcomatoid differentiation

Basal cell carcinomas
- Superficial basal cell carcinoma
- Nodular basal cell carcinoma
- Micronodular basal cell carcinoma
- Infiltrating basal cell carcinoma

Sclerosing/morphoeic basal cell carcinoma
Basosquamous carcinoma
Basal cell carcinoma with sarcomatoid differentiation
Basal cell carcinoma with adnexal differentiation
Fibroepithelial basal cell carcinoma

Malignant apocrine and eccrine tumors
Adnexal adenocarcinoma, NOS
Microcystic adnexal carcinoma
Cribriform tumor (previously carcinoma)
Porocarcinoma
NUT carcinoma
Malignant neoplasms arising from spiradenoma, cylindroma, or spiradenocylindroma
Malignant mixed tumor
Hidradenocarcinoma
Endocrine mucin-producing sweat gland carcinoma
Mucinous carcinoma
Digital papillary adenocarcinoma
Adenoid cystic carcinoma
Apocrine carcinoma
Squamoid ductal eccrine carcinoma
Syringocystadenocarcinoma papilliferum
Secretory carcinoma
Signet-ring cell/histiocytoid carcinoma

Malignant tumors with follicular differentiation
Proliferating trichilemmal tumor
Pilomatrical carcinoma
Trichoblastic carcinoma/carcinosarcoma
Trichilemmal carcinoma

Malignant tumors with sebaceous differentiation
Sebaceous carcinoma

References

1. WHO Classification of Tumours Editorial Board. *Skin tumours* [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2023 [cited 2026 Jan. 22]. (WHO classification of tumours series, 5th ed.; vol. 12). Available from: https://tumourclassification.iarc.who.int/chapters/64

C. Histologic Grade

Grading of cutaneous squamous cell carcinoma is not standardized. Classically, tumors graded qualitatively using 4 tiers as follows:[1]

Grade 1: *Well-differentiated* tumors are characterized by squamous epithelium that frequently shows easily recognizable and often abundant keratinization. Intercellular bridges are readily apparent. There is minimal pleomorphism, and mitotic figures are mainly basally located.

Grade 2: *Moderately differentiated* tumors show more structural disorganization in which squamous epithelial derivation is less obvious. Nuclear and cytoplasmic pleomorphism are more pronounced, and mitotic figures may be numerous. Keratin formation is typically limited to keratin pearls, horn cysts, and scattered individually keratinized cells.

Grade 3: In *poorly differentiated* tumors it may be difficult to establish squamous differentiation, usually by identification of rare intercellular bridges or small foci of keratinization.

Grade 4: Used to denote anaplastic or *undifferentiated* tumors.

Broders classification of histologic grading[2] is a popular alternative single parameter quantitative grading system often utilized as well and is summarized as follows:

Grade 1 Less than 25% is undifferentiated
Grade 2 Greater than or equal to 25% but less than 50% is undifferentiated
Grade 3 Greater than or equal to 50% but less than 75% is undifferentiated
Grade 4 Greater than or equal to 75% is undifferentiated

Grade has remained a key independent prognosticator in cutaneous squamous cell carcinoma[3,4] despite limited data showing weak to moderate interobserver concordance.[5]

From a management perspective, grade is typically reduced to two tiers, with poorly differentiated tumors (Grades 3 and 4) constituting the high-risk category.[3] However, limited evidence suggests that even moderately differentiated tumors (Grade 2) may show a higher risk for subclinical spread requiring more layers of clearance by Mohs micrographic surgery.[6] Of note, it is this grade of tumors that appears to show the highest interobserver variability.[5]

The application of grading to subtypes in cutaneous squamous cell carcinoma is not well studied, though some subtypes (i.e., verrucous squamous cell carcinoma) have a well-established intrinsic biologic behavior.[4] It is thus reasonable to use the “not applicable” category when a subtype comprises the bulk of the tumor.

References

1. McKee PH, Calonje E, Brenn T, Lazar AJ, Billings SD. Tumors of the surface epithelium. In: *McKee's Pathology of the Skin with Clinical Correlations*. 5th ed. Philadelphia, PA: Elsevier Mosby; 2020.
2. Broders AC. Squamous cell epithelioma of the lip. *J Am Med Assoc* 1920; 74: 656-64.
3. Prezzano JC, Scott GA, Lambert Smith F, Mannava KA, Ibrahim SF. Concordance of Squamous Cell Carcinoma Histologic Grading Among Dermatopathologists and Mohs Surgeons. *Dermatol Surg.* 2021 Nov 1;47(11):1433-1437.
4. Kyrgidis A, Tzellos TG, Kechagias N, Patrikidou A, Xirou P, Kitikidou K, Bourlidou E, Vahtsevanos K, Antoniades K. Cutaneous squamous cell carcinoma (SCC) of the head and neck: risk factors of overall and recurrence-free survival. *Eur J Cancer*. 2010 Jun;46(9):1563-72.
5. Lohmann CM, Solomon AR. Clinicopathologic variants of cutaneous squamous cell carcinoma. *Adv Anat Pathol.* 2001;8(1):27-36.

6. Eversman A, Tracey EH, Michalik D, Rodriguez M, Varra V, Briskin IN, Vidimos AT, Poblete-Lopez CM. Moderate differentiation is a risk factor for extensive subclinical spread of cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 2021 Dec;85(6):1606-1608.

D. Tumor Thickness/Depth of Invasion

While tumor thickness (Breslow)/depth of invasion (DOI) are key risk factors for nodal disease on univariate and multivariate analysis,[1,2,3] both terms are often interchangeable, but as per AJCC 8th edition, whenever possible, DOI, as measured from the granular layer of the adjacent normal epidermis to the base of the tumor is recommended for determining T status. This DOI is measured at a right angle to the adjacent normal skin, with the upper point of reference the granular layer of the epidermis of the adjacent uninvolved epidermis. The lower reference point is the deepest point of tumor invasion (i.e., the leading edge of a single mass or an isolated group of cells deep to the main mass).

If the tumor is transected by the deep margin of the specimen, the thickness may be indicated as "at least __ mm" with a comment explaining the limitation of thickness assessment.

Anatomic (Clark) levels are defined as follows:

I Intraepidermal tumor only
II Tumor present in but does not fill and expand papillary dermis
III Tumor fills and expands papillary dermis
IV Tumor invades into reticular dermis
V Tumor invades subcutis

References

1. Saito Y, Fujikawa H, Takatsuka S, Abe R, Takenouchi T. Risk factors for lymph node metastasis in cutaneous squamous cell carcinoma: a long-term retrospective study of Japanese patients. *Int J Clin Oncol*. 2021 Mar;26(3):606-612.
2. Schmitz L, Kanitakis J. Histological classification of cutaneous squamous cell carcinomas with different severity. *J Eur Acad Dermatol Venereol*. 2019 Dec;33 Suppl 8:11-15.
3. Thompson AK, Kelley BF, Prokop LJ, Murad MH, Baum CL. Risk Factors for Cutaneous Squamous Cell Carcinoma Recurrence, Metastasis, and Disease-Specific Death: A Systematic Review and Meta-analysis. *JAMA Dermatol*. 2016 Apr;152(4):419-28.

E. Perineural Invasion

While perineural invasion in cutaneous squamous cell carcinoma is an independent poor prognosticator,[1] evidence suggests that a more nuanced approach to this parameter allows for improved stratification of patients. Size, location with respect to tumor, anatomic depth, number, and even microscopic extent (circumferential vs focal) are key features to consider.[2] Of these, the diameter of involved nerve is more studied and a diameter of greater than or equal to 0.1 mm is included in the definition of "deep invasion" in pT status.[3,4] Location of the involved nerve deep to the dermis serves as a surrogate for this size cut-off and can be used even in the absence of a reticle or ocular micrometer to help assign a pT category. In other words, the size of involved nerves deep to the dermis can be classified as greater than or equal to 0.1 mm.

References

1. Zhang J, Wang Y, Wijaya WA, Liang Z, Chen J.J. Efficacy and prognostic factors of adjuvant radiotherapy for cutaneous squamous cell carcinoma: A systematic review and meta-analysis. *Eur Acad Dermatol Venereol*. 2021 Sep;35(9):1777-1787.
2. Totonchy MB, McNiff JM, Suozzi KC, Leffell DJ, Christensen SR. A Histopathologic Scoring System for Perineural Invasion Correlates with Adverse Outcomes in Patients with Cutaneous Squamous Cell Carcinoma. *Dermatol Surg*. 2021 Apr 1;47(4):445-451.
3. Ross AS, Whalen FM, Elenitsas R, Xu X, Troxel AB, Schmults CD. Diameter of involved nerves predicts outcomes in cutaneous squamous cell carcinoma with perineural invasion: an investigator-blinded retrospective cohort study. *Dermatol Surg*. 2009 Dec;35(12):1859-66.
4. Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy GF, Qureshi AA, Schmults CD. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. *J Clin Oncol*. 2014 Feb 1;32(4):327-34.

F. Margins

Margin status emerges as a key adverse prognosticator on meta-analysis and is a critical factor to consider for consideration of adjuvant radiotherapy and is thus a required reporting element.[1] If the specimen is oriented or can be oriented based on anatomic landmarks, the position of margins involved by tumor should be indicated. Although a comment on margins is necessary only for wide local excisions or formal resections, it is commonly employed in many (dermato)pathology laboratories on all specimens and has been advocated as part of a standard diagnostic template.[2]

Distance of tumor to margins is not well studied in cutaneous squamous cell carcinomas and is thus currently not required. Nonetheless reporting of this parameter is highly recommended to maintain equivalence of reporting standards with mucosal counterparts. Current NCCN guidelines recommend gross clearance of 4-6 mm for tumors less than 2.0 cm, and wider (without specifying) on larger advanced stage tumors under the purview of this protocol.[3] However, only a single prospective study using Mohs technique was the basis for these guidelines.[4] Equivalence to margin distances for wide local excision/resection let alone microscopic margin distances is not established in these guidelines. However, for head and neck sites limited evidence does suggest some prognostic value at a cutoff of 5 mm on univariate analysis.[5]

References

1. Zhang J, Wang Y, Wijaya WA, Liang Z, Chen J.J. Efficacy and prognostic factors of adjuvant radiotherapy for cutaneous squamous cell carcinoma: A systematic review and meta-analysis. *Eur Acad Dermatol Venereol*. 2021 Sep;35(9):1777-1787.
2. Khanna M, Fortier-Riberdy G, Dinehart SM, Smoller B. Histopathologic evaluation of cutaneous squamous cell carcinoma: results of a survey among dermatopathologists. *J Am Acad Dermatol*. 2003;48(5):721-726.
3. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *J Am Acad Dermatol*. 1992;27(2 Pt 1):241–248.
4. Schmults CD, Blitzblau R, Aasi SZ, et al. NCCN Guidelines® Insights: Squamous Cell Skin Cancer, Version 1.2022. *J Natl Compr Canc Netw*. 2021 Dec;19(12):1382-1394. doi: 10.6004/jnccn.2021.0059. PMID: 34902824.
5. Phillips TJ, Harris BN, Moore MG, Farwell DG, Bewley AF. Pathological margins and advanced cutaneous squamous cell carcinoma of the head and neck. *J Otolaryngol Head Neck Surg*. 2019 Oct 25;48(1):55.

G. Regional Lymph Nodes

Lymph node status, specifically size, number and extranodal extension have been noted to represent adverse prognosticators.[1,2] As such they have been incorporated into AJCC N categorization in a fashion similar to that of human papillomavirus (HPV) unrelated mucosal HNSCC. But while these parameters are impactful, the actual performance of this adaptation of mucosal HNSCC N classification system cutaneous HNSCC has been shown to be suboptimal.[3,4]

References

1. Amit M, Liu C, Gleber-Netto FO, Kini S, Tam S, Benov A, Aashiq M, El-Naggar AK, Moreno AC, Rosenthal DI, Glisson BS, Ferrarotto R, Wong MK, Migden MR, Baruch EN, Li G, Khanna A, Goepfert RP, Nagarajan P, Weber RS, Myers JN, Gross ND. Inclusion of extranodal extension in the lymph node classification of cutaneous squamous cell carcinoma of the head and neck. *Cancer*. 2021 Apr 15;127(8):1238-1245.
2. Varra V, Woody NM, Reddy C, Joshi NP, Geiger J, Adelstein DJ, Burkey BB, Scharpf J, Prendes B, Lamarre ED, Lorenz R, Gastman B, Manyam BV, Koyfman SA. Suboptimal Outcomes in Cutaneous Squamous Cell Cancer of the Head and Neck with Nodal Metastases. *Anticancer Res*. 2018 Oct;38(10):5825-5830.
3. Luk PP, Ebrahimi A, Veness MJ, McDowell L, Magarey M, Gao K, Palme CE, Clark JR, Gupta R. Prognostic value of the 8th edition American Joint Commission Cancer nodal staging system for patients with head and neck cutaneous squamous cell carcinoma: A multi-institutional study. *Head Neck*. 2021 Feb;43(2):558-567.
4. Watts F, Palme CE, Porceddu S, Sundaresan P, Clark JR, Gupta R. Clinician perspectives on the factors influencing prognostic stratification by the American Joint Commission on Cancer Head and Neck Cutaneous Squamous Cell Carcinoma Staging. *Surgery.* 2021 Nov;170(5):1467-1473. doi: 10.1016/j.surg.2021.04.019. Epub 2021 Jun 12.

H. pTNM Classification

The TNM staging system for cutaneous squamous cell carcinoma of the head and neck of the American Joint Committee on Cancer (AJCC) is recommended.[1] By AJCC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor and depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor cannot be resected for any reason and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

<u>T Category Considerations</u>

High-Risk Features for Primary (T) Tumor Staging[1]

Deep invasion: Invasion beyond the subcutaneous fat or >6 mm in depth. Extension into microanatomic landmarks such as fascia, muscle, perichondrium, and/or periosteum underlying subcutaneous fat qualify as deep invasion.

Perineural invasion for T3 classification: 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.

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y", "r", and "a" prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

The "m" suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The "y" prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination.

The "y" categorization is not an estimate of tumor prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy).

The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the "r" prefix: rTNM.

The "a" prefix designates the stage determined at autopsy: aTNM.

Brigham and Women's Hospital (BWH) Tumor Staging

The Brigham and Women's Hospital (BWH) system is an alternative tumor classification system. Prior analysis from a single institution cohort demonstrated that the BWH staging system offers improved distinctiveness, homogeneity, and monotonicity over the AJCC 7th edition staging system.[2] Compared to the AJCC 8th edition staging system, BWH had higher specificity and positive predictive value for identifying cases at risk for metastasis or death.[3] A systematic review of sentinel node biopsy in CSCC demonstrated that BWH T2b/T3 tumors have a high risk of sentinel node positivity (29.4%).[4]

pT0	In situ SCC
pT1	0 high-risk factors*
pT2a	1 high-risk factor*
pT2b	2-3 high-risk factors*
pT3	4 risk factors* or bone invasion

*BWH staging high-risk features:

- Clinical tumor diameter greater than or equal 2 cm
- Tumor invasion beyond subcutaneous fat, excluding bone invasion, which upgrades tumor to stage pT3
- Poorly differentiated histology
- Perineural invasion of nerve(s) greater than or equal 0.1 mm in caliber

References

1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.

2. Karia PS, Jambusaria-Pahlajani A, Harrington DP, Murphy GF, Qureshi AA, Schmults CD. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital tumor staging for cutaneous squamous cell carcinoma. *J Clin Oncol*. 2014;32(4):327-334.
3. Ruiz ES, Karia PS, Besaw R, Schmults, CD. Performance of the American Joint Committee on Cancer Staging Manual, 8th Edition vs the Brigham and Women's Hospital Tumor Classification System for Cutaneous Squamous Cell Carcinoma. *JAMA Dermatol*. 2019;155(7):819-825.
4. Schmitt AR, Brewer JD, Bordeaux JS, Baum CL. Staging for cutaneous squamous cell carcinoma as a predictor of sentinel lymph node biopsy results: meta-analysis of American Joint Committee on Cancer criteria and a proposed alternative system. *JAMA Dermatol*. 2014;150(1):19-24.