



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

Version: 1.0.0.1

Protocol Posting Date: September 2022

CAP Laboratory Accreditation Program Protocol Required Use Date: March 2023

The changes included in this current protocol version do not affect the prior 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 (eg, following neoadjuvant therapy)
Cytologic specimens
Early-stage cutaneous squamous cell carcinomas (N-, and pT1 and pT2 cutaneous squamous cell carcinomas)
Non-squamous cell carcinomas of the skin

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

Tumor Type
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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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.

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### Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is “not applicable” or “cannot be determined.”
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with “+” and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

### 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 ie, all required elements must be in the synoptic portion of the report in the format defined above.

**Summary of Changes**

**v 1.0.0.1**

- Updated answer under Tumor Site question to “Specify site” along with associated metadata
- Updated pT category note and Explanatory ‘Note H’

RETIRED

**Reporting Template****Protocol Posting Date: September 2022****Select a single response unless otherwise indicated.****CASE SUMMARY: (CUTANEOUS SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK)****Standard(s): AJCC-UICC 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****Tumor Focality**

- Unifocal  
 Multifocal: \_\_\_\_\_  
 Cannot be determined: \_\_\_\_\_

**Multiple Primary Sites**

- Not applicable (no additional primary site(s) present)  
 Present: \_\_\_\_\_

*Please complete a separate checklist for each primary site if required as above.***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  
**+Additional Dimensions in Centimeters: \_\_\_\_\_ x \_\_\_\_\_ cm**  
 Cannot be determined (explain): \_\_\_\_\_

**Histologic Type (Note B)**

- Squamous cell carcinoma, not otherwise specified
- Keratoacanthoma
- Acantholytic squamous cell carcinoma
- Spindle cell squamous cell carcinoma
- Verrucous squamous cell carcinoma
- Adenosquamous carcinoma
- Clear cell squamous cell carcinoma
- Squamous cell carcinoma with sarcomatoid differentiation
- Squamous cell carcinoma with osteoclast-like giant cells
- Pseudovascular squamous cell carcinoma
- Lymphoepithelioma-like carcinoma
- Other (specify): \_\_\_\_\_

**Histologic Grade (Note C)**

- GX: Cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated
- Other (specify): \_\_\_\_\_
- Not applicable

**Tumor Depth of Invasion (DOI) (Note D)**

- Not applicable
- Specify depth in Millimeters (mm): \_\_\_\_\_ mm
- At least (mm): \_\_\_\_\_ mm
- Cannot be determined (explain): \_\_\_\_\_

**+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):** \_\_\_\_\_

**Lymphovascular Invasion**

- Not identified
- Present
- Cannot be determined: \_\_\_\_\_

**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: \_\_\_\_\_

**MARGINS (Note F)**

**Margin Status for Invasive Tumor**

All margins negative for invasive tumor

**+Distance from Invasive Tumor to Closest Margin**

*Specify in Millimeters (mm)*

Exact distance: \_\_\_\_\_ mm

Greater than: \_\_\_\_\_ mm

Less than 1 mm

Other (specify): \_\_\_\_\_

Cannot be determined: \_\_\_\_\_

**+Closest Margin(s) to Invasive Tumor**

Specify location(s) of closest margin(s): \_\_\_\_\_

Cannot be determined

**+Other Close Margin(s) to Invasive Tumor**

Specify location(s) and distance(s) of other close margin(s): \_\_\_\_\_

Cannot be determined

Invasive tumor present at margin

**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

**Margin Status for Noninvasive Tumor**

Not applicable

All margins negative for in situ disease

**+Distance from Noninvasive Tumor to Closest Margin**

*Specify in Millimeters (mm)*

Exact distance: \_\_\_\_\_ mm

Greater than: \_\_\_\_\_ mm

Less than 1 mm

Other (specify): \_\_\_\_\_

Cannot be determined: \_\_\_\_\_

**+Closest Margin(s) to Noninvasive Tumor**

Specify closest margin(s): \_\_\_\_\_

Cannot be determined

In situ disease present at margin

**Margin(s) Involved by Noninvasive Tumor (select all that apply)**

- Peripheral: \_\_\_\_\_
- Deep: \_\_\_\_\_
- Other (specify): \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_
- Other (specify): \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**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

**Laterality of Lymph Node(s) with Tumor**

- Ipsilateral (including midline): \_\_\_\_\_
- Contralateral: \_\_\_\_\_
- Bilateral: \_\_\_\_\_
- Cannot be determined: \_\_\_\_\_

**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: \_\_\_\_\_

**Extranodal Extension (ENE) (Note G)**

- Not identified
- Present
- Cannot be determined: \_\_\_\_\_
- Other (specify): \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**Number of Lymph Nodes Examined**

- Exact number (specify): \_\_\_\_\_
- At least (specify): \_\_\_\_\_
- Other (specify): \_\_\_\_\_
- Cannot be determined

**+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: \_\_\_\_\_

**PATHOLOGIC STAGE CLASSIFICATION (pTNM, 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.*

**TNM Descriptors (select all that apply)**

- Not applicable
- m (multiple primary tumors)
- r (recurrent)
- y (post-treatment)

**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)

**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: Greater than or equal to 4 risk factors or bone invasion

#### **ADDITIONAL FINDINGS**

##### **+Additional Findings (select all that apply)**

None identified

Immunosuppressed status (specify cause, if known): \_\_\_\_\_

Other (specify): \_\_\_\_\_

#### **SPECIAL STUDIES**

*Biomarkers tested may be included in the section below. Pending biomarker studies may be listed in the Comments section of this report.*

##### **Biomarkers Tested (may repeat for up to 10 biomarkers)**

**+Specify Test and Result:** \_\_\_\_\_

#### **COMMENTS**

**Comment(s):** \_\_\_\_\_

## Explanatory Notes

### A. Scope of Guidelines

The reporting of cutaneous squamous cell carcinoma of head and neck is facilitated by the provision of a case summary illustrating the features required for comprehensive patient care. However, there are many cases in which the individual practicalities of applying such a case summary may not be straightforward. Common examples include finding the prescribed number of lymph nodes, trying to determine the levels of the radical neck dissection, and determining if isolated tumor cells in a lymph node represent metastatic disease. Case summaries have evolved to include clinical, radiographic, morphologic, immunohistochemical, and molecular results in an effort to guide clinical management. Adjuvant and neoadjuvant therapy can significantly alter histologic findings, making accurate classification an increasingly complex and demanding task. This protocol tries to remain simple while still incorporating important pathologic features as proposed by the American Joint Committee on Cancer (AJCC) cancer staging manual, the World Health Organization (WHO) classification of tumors, the TNM classification<sup>1</sup>, the American College of Surgeons Commission on Cancer, and the International Union on Cancer (UICC). This protocol is to be used as a guide and resource, an adjunct to diagnosing and managing cancers of the oral cavity in a standardized manner. It should not be used as a substitute for dissection or grossing techniques and does not give histologic parameters to reach the diagnosis. Subjectivity is always a factor, and elements listed are not meant to be arbitrary but are meant to provide uniformity of reporting across all the disciplines that use the information. It is a foundation of practical information that will help to meet the requirements of daily practice to benefit both clinicians and patients alike.

### References

1. Gress DM, Edge SB, Greene FL, et al. Principles of cancer staging. In: Amin MB, ed. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017.

### B. Histologic Subtypes

The World Health Organization (WHO) classification<sup>1</sup> of squamous cell carcinomas of the skin is shown below:

Squamous cell carcinoma, not otherwise specified

Keratoacanthoma

Acantholytic squamous cell carcinoma

Spindle cell squamous cell carcinoma

Verrucous squamous cell carcinoma

Adenosquamous carcinoma

Clear cell squamous cell carcinoma

Other (uncommon) variants

Squamous cell carcinoma with sarcomatoid differentiation

Squamous cell carcinoma with osteoclast-like giant cells

Pseudovascular squamous cell carcinoma

Lymphoepithelioma-like carcinoma

### References

1. Elder DR, Massi D, Scolyer RA, Willemze R, editors. World Health Organization Classification of Skin Tumours. 4th ed. Lyon: IARC.

### C. Histologic Grade

Grading of cutaneous squamous cell carcinoma is not standardized. Classically, tumors graded qualitatively using 4 tiers as follows:<sup>1</sup>

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<sup>2</sup> 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<sup>3,4</sup> despite limited data showing weak to moderate interobserver concordance.<sup>5</sup>

From a management perspective, grade is typically reduced to two tiers with poorly differentiated tumors (Grades 3 and 4) constituting the high risk category<sup>3</sup>. 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.<sup>6</sup> Of note, it is this grade of tumors that appears to show the highest interobserver variability.<sup>5</sup>

The application of grading to variant morphologies in cutaneous squamous cell carcinoma is not well studied, though some variants (i.e. keratoacanthoma, verrucous squamous cell carcinoma) have a well-established intrinsic biologic behavior.<sup>4</sup> It is thus reasonable to use the “not applicable” category when a variant morphology comprises the bulk of the tumor.

#### References

1. Tumors of the surface epithelium. In: McKee PH, Calonje E, Brenn T, Lazar AJ, Billings SD. 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, Antoniadis 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.<sup>1,2,3</sup> 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. The upper point of reference is 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,<sup>1</sup> 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.<sup>2</sup> 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.<sup>3,4</sup> 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.<sup>1</sup> 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.<sup>2</sup>

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.<sup>3</sup> However, only a single prospective study using Mohs technique was the basis for these guidelines.<sup>4</sup> 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.<sup>5</sup>

#### 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. NCCN clinical practice guidelines in oncology (NCCN Guidelines®) squamous cell skin cancer. 2018 11/08/2018.
4. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. *Journal of American Academic Dermatology*. 1992;27(2 Pt 1):241–248.
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. Lymph Nodes

Lymph node status, specifically size, number and extranodal extension have been noted to represent adverse prognosticators.<sup>1,2</sup> 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.<sup>3,4</sup>

### 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. TNM and Stage Groupings

The TNM staging system for cutaneous squamous cell carcinoma of the head and neck of the American Joint Committee on Cancer (AJCC) is recommended.<sup>1</sup> 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.

### T Category Considerations

#### High-Risk Features for Primary (T) Tumor Staging<sup>1</sup>

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 AJCC 7.<sup>2</sup> Compared to AJCC 8, BWH had higher specificity and positive predictive value for identifying cases at risk for metastasis or death.<sup>3</sup> 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%).<sup>4</sup>

T0	In situ SCC
T1	0 high-risk factors*
T2a	1 high-risk factor*
T2b	2-3 high-risk factors*
T3	Greater than or equal 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 T3
- Poorly differentiated histology
- Perineural invasion of nerve(s) greater than or equal 0.1 mm in caliber

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