Protocol for the Examination of Specimens From Patients With Squamous Cell Carcinoma of the Skin

Protocol applies to invasive squamous cell carcinomas of the skin. Squamous cell carcinomas of the eyelid, vulva, and penis are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2013

Procedures

- Biopsy
- Excision
- Re-excision
- Lymph node examination

Authors

Priya Rao, MD*
Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California
Bonnie L. Balzer, MD, PhD, FCAP
Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California
Alexander J. Lazar, MD, PhD, FCAP
Departments of Pathology and Dermatology, The University of Texas MD Anderson Cancer Center, Houston, Texas
Nanette J. Liegeois, MD, PhD
Department of Dermatology, Johns Hopkins Medicine, Baltimore, Maryland
Jennifer M. McNiff, MD, FASCP
Departments of Dermatology and Pathology, Yale University School of Medicine, New Haven, Connecticut
Paul Nghiem, MD, PhD
Division of Dermatology, University of Washington Medical Center, Seattle, Washington
Victor G. Prieto, MD, PhD, FACP
Departments of Pathology and Dermatology, MD Anderson Cancer Center, University of Texas, Houston, Texas
M. Timothy Smith, MD
Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, South Carolina
Bruce Robert Smoller, MD, FCAP
Department of Pathology, University of Arkansas for Medical Sciences, Little Rock, Arkansas
Mark R. Wick, MD, FCAP
Department of Pathology, University of Virginia Health System, Charlottesville, Virginia
David Frishberg, MD, FCAP†
Department of Pathology, Cedars-Sinai Medical Center, Los Angeles, California
For the Members of the Cancer Committee, College of American Pathologists

* Denotes primary author. † Denotes senior author. All other contributing authors are listed alphabetically.

Previous contributors (Carcinoma of the skin): Mark R. Wick, MD; Carolyn Compton, MD, PhD; Lyn Duncan, MD; Harley A. Haynes, MD; Gregg M. Menaker, MD; Nicholas E. O'Connor, MD

The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the "Surgical Pathology Cancer Case Summary" portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

The inclusion of a product name or service in a CAP publication should not be construed as an endorsement of such product or service, nor is failure to include the name of a product or service to be construed as disapproval.

CAP Squamous Cell Carcinoma Protocol Revision History

Version Code
The definition of version code can be found at www.cap.org/cancerprotocols.

Version: SquamousCell 3.1.0.2

The following changes have been made since the June 2012 release.

Biopsy, Excision, Re-excision, Lymphadenectomy

Pathologic Staging (pTNM)

Primary Tumor (pT)
The definition of pT4 was updated, as follows:
___ pT4: Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

Important Note
This protocol supersedes some elements of the previous College of American Pathologists carcinoma of the skin protocol,[1] last revised in 2005, which was optional for squamous cell carcinomas. This new protocol is required only for tumors >2 cm in greatest dimension (which are automatically at least pT2 lesions) and is applicable to squamous cell carcinoma only.

Currently, most cancer registrars do not routinely report cutaneous squamous cell carcinomas. Nevertheless, there is an evolving standard of practice in dermatopathology to report invasive squamous carcinomas in a templated manner (see especially Khanna et al[2]); this protocol is intended to be helpful in developing such templates.

Important changes include:

- Assignment of pT2 has been changed to reflect a combination of size and "high risk factors" (see note F).
- pT3 and PT4 categories have been re-defined, and are assigned on the basis of invasion of specific structures (see note F).
- Nodal involvement (previous pN1) has been subdivided into N1, N2, and N3, based on number, size, and site (ipsilateral, contralateral, bilateral) of involved nodes (see note F).

Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

SQUAMOUS CELL CARCINOMA OF THE SKIN: Biopsy, Excision, Re-excision, Lymphadenectomy

Note: Use of case summary is optional for tumors ≤2 cm.

Select a single response unless otherwise indicated.

Procedure
___ Biopsy, punch
___ Biopsy, shave
___ Biopsy, other (specify): _____
___ 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 Site (Note A)
Specify, if known: _____
___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see "Comment")

Histologic Type (select all that apply) (Note B)
___ Squamous cell carcinoma (SCC)
+ ___ Acantholytic SCC
+ ___ Spindle cell (sarcomatoid) SCC
+ ___ Verrucous SCC
+ ___ Pseudovascular SCC
+ ___ Adenosquamous carcinoma
+ ___ Squamous cell carcinoma, type not otherwise specified
+ ___ Other (specify): _____

Histologic Grade (Note C)
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Maximum Tumor Thickness (Note D)
___ Not applicable
Thickness: ___ mm
Thickness: at least ___ mm (see "Comment") (Note C)

Anatomic Level (Note D)
___ 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)

Margins (select all that apply) (Note E)

Peripheral Margins
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
+ Distance of invasive carcinoma from closest peripheral margin: ___ mm
+ Specify location(s), if possible: _____
___ Involved by invasive carcinoma
Specify location(s), if possible: _____
___ Uninvolved by carcinoma in situ
+ Distance of carcinoma in situ from closest peripheral margin: ___ mm
+ Specify location(s), if possible: _____
___ Involved by carcinoma in situ
Specify location(s), if possible: _____

Deep Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
+ Distance of invasive carcinoma from margin: ___ mm
+ Specify location(s), if possible: _____
___ Involved by invasive carcinoma
Specify location(s), if possible: _____

Lymph-Vascular Invasion (Note D)
___ Not identified
___ Present
___ Indeterminate

Perineural Invasion (Note D)
___ Not identified
___ Present
___ Indeterminate

Lymph Nodes (Note F)
___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved By Metastatic Carcinoma
Specify: ____
___ Number cannot be determined (explain): _____

+ Size of largest metastatic focus: ___ cm

+ Extranodal extension:
+ ___ Present
+ ___ Not identified

Pathologic Staging (pTNM) (Note F)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ
___ pT1: Tumor 2 cm or less in greatest dimension with fewer than two high-risk features
___ pT2: Tumor greater than 2 cm in greatest dimension with or without one additional high-risk feature, or any size with two or more high-risk features
___ pT3: Tumor with invasion of maxilla, mandible, orbit, or temporal bone
___ pT4: Tumor with invasion of skeleton (axial or appendicular) or perineural invasion of skull base

Regional Lymph Nodes (pN)
___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
___ pN2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
___ pN2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension.
___ pN3: Metastasis in a lymph node, more than 6 cm in greatest dimension

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
+ Specify site(s), if known: _____

+ Additional Pathologic Findings
+ Specify: _____

+ Comment(s)

Explanatory Notes

A. Anatomic Site
Primary site on ear or hair-bearing lip is considered a "high-risk factor" in the American Joint Committee on Cancer (AJCC) seventh edition staging system that may be used in upstaging a tumor from pT1 to pT2.[3]

B. Histologic Subtypes
The World Health Organization (WHO) classification[4] of squamous cell carcinomas of the skin is shown below:

Spindle-cell (sarcomatoid) squamous cell carcinoma (SCC)
Acantholytic SCC
Verrucous SCC
SCC with horn formation
Lymphoepithelial SCC

Variants not included in the WHO classification include:

Papillary SCC
Clear cell SCC
Small cell SCC
Posttraumatic (eg, Marjolin ulcer)
Metaplastic (carcinosarcomatous) SCC
Paget disease
Mammary Paget disease
Extramammary Paget disease
Adnexal carcinomas
Keratoacanthoma

C. Histologic Grade
Histologic grades are as follows[5]:

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 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.

An alternative oft-cited system is Broders' 1932 classification of histologic grading,[6] summarized as follows:

Grade 1	75% or more of the lesion is well differentiated
Grade 2	50% to 75% of the lesion is well differentiated

Grade 3 25% to 50% of the lesion is well differentiated
Grade 4 Less than 25% of the lesion is well differentiated

D. High-Risk Histologic Features
In addition to anatomic site and poor differentiation (high grade), the presence of certain high-risk histologic features may be used in upstaging a tumor from pT1 to pT2 (see note E). These include tumor thickness, anatomic level, presence of perineural invasion, and presence of lymph-vascular invasion.[3]

Maximum tumor thickness (Breslow) is measured with a calibrated ocular micrometer at a right angle to the adjacent normal skin. The upper point of reference is the granular layer of the epidermis of the overlying skin or, if the lesion is ulcerated, the base of the ulcer. The lower reference point is the deepest point of tumor invasion (ie, 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

In addition to the "high-risk" factors listed above, a number of other prognostic features not specifically employed for the seventh edition AJCC staging system have been reported[7-10] and include: inflammatory response; association with actinic keratosis; association with human papillomavirus (HPV); association with Bowen's disease; acantholytic, basaloid, small cell, signet ring, desmoplastic, or spindle cell histological subtypes; and follicular SCC.

E. Margins
If the specimen is oriented, the position of peripheral margins involved by tumor should be indicated. Although a comment on margins is necessary only for excisional biopsies or formal resections, it is commonly employed in many dermatopathology laboratories on all specimens and has been advocated as part of a standard diagnostic template.[2] Measurements of distance from tumor to margins need not be routinely reported but may be done so in special circumstances and/or when requested by the treating physician.

F. TNM and Stage Groupings
The TNM staging system for squamous cell carcinoma of the skin of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is recommended.[3] By AJCC/UICC 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

Clinical:	Primary site on ear or hair-bearing lip
Histologic:	>2 mm thickness
	Clark level IV/V
	Perineural invasion
	Poor differentiation

Stage Groupings

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

[#] M0 is defined as no distant metastasis.

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 (ie, 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 (ie, 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.

Additional Descriptors

Residual Tumor (R)

Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.[6]

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

References

1. Wick MR, Compton CC. Protocol for the examination of specimens from patients with carcinomas of the skin, excluding eyelid, vulva, and penis. *Arch Pathol Lab Med.* 2001;125(9):1169-1173.
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. Cutaneous squamous cell carcinoma and other cutaneous carcinomas. In: Edge SB, Byrd DR, Carducci MA, Compton CC, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2009.
4. LeBoit PE, Burg G, Weedon D, Sarasin A, eds. *World Health Organization Classification of Tumours*: *Pathology and Genetics of Skin Tumours.* Geneva, Switzerland: WHO Press; 2006:49-93.
5. Brenn T and McKee PH. Tumors of the surface epithelium. In: McKee PH, Calonje E, GRanter SR. *Pathology of the Skin with Clinical Correlations.* 3rd ed. Philadeplphia, PA: Elsevier Mosby; 2005.
6. Lohmann CM, Solomon AR. Clinicopathologic variants of cutaneous squamous cell carcinoma. *Adv Anat Pathol*. 2001;8(1):27-36
7. Petter G, Haustein UF. Histologic subtyping and malignancy assessment of cutaneous squamous cell carcinoma. *Dermatol Surg.* 2000;26(6):521-530.
8. Smoller BR. Squamous cell carcinoma: from precursor lesions to high-risk variants. *Mod Pathol*. 2006;19(suppl 2):S88-92.
9. Cassarino DS, Derienzo DP, Barr RJ. Cutaneous squamous cell carcinoma: a comprehensive clinicopathologic classification--part one. *J Cutan Pathol*. 2006;33(3):191-206.
10. Cassarino DS, Derienzo DP, Barr RJ. Cutaneous squamous cell carcinoma: a comprehensive clinicopathologic classification--part two. *J Cutan Pathol*. 2006;33(4):261-279.