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

Protocol applies to cutaneous squamous cell carcinoma (CSCC), cutaneous carcinoma (CC), basal cell carcinoma (BCC) of the head and neck, and all other nonmelanoma skin carcinomas of the head and neck (NMSC) (except Merkel cell carcinoma [MCC]). Anatomic site of external vermilion lip is included (and is excluded from Oral Cavity). This protocol does not apply to squamous cell carcinoma arising from other organ sites such as the eyelid, perianal region, penis, vulva, or cutaneous squamous cell carcinoma and basal cell carcinoma of the skin outside the head and neck.

Based on:

AJCC/UICC TNM, 8th edition
CAP Cancer Protocol RETIRED June 30, 2017
AAPA Macroscopic Examination Template Version 2.0
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Revision History:

None

Summary of Changes:

This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual. The CAP protocol for squamous cell carcinoma of the skin was retired on June 30, 2017.

Procedures Covered in this Protocol:

- Biopsy
- Excision
- Re-Excision
- Lymphadenectomy

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The purpose of the Protocols is to support Laboratory Personnel engaged in the macroscopic examination of cancer resection specimens. The Protocols are based on specified relevant source documents, drafted by pathologists' assistant experts, and supported by information provided by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC). These Protocols are intended to serve patients by ensuring that the macroscopic examination of cancer resection specimens is compliant with CAP Cancer Protocols, the AJCC Cancer Staging Manual, and provide optimization of the pre-analytic steps necessary to promote appropriate molecular studies.

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Molecular Considerations:

While the link is not well established, HPV infection has been associated with cutaneous squamous cell carcinoma. Some strains that have been linked to increased SCC development include HPV-36, in the case of epidermodysplasia verruciformis, and HPV-8 in immunocompetent patients.

Increased expression and mutation of *TP53* have been observed in squamous cell carcinoma in situ. Allelic deletion of one or more chromosome 9q markers has also been detected in occasional lesions.

While most basal cell carcinomas are treated by surgical excision, the use of Hedgehog Inhibitors (HHI) in cases that have a known Patched-1 (PTCH1) and Smoothen (SMO) gene mutation may help patients with rare advanced or metastatic cases. Treatment with vismodegib or sonidegib (HHIs) may also reduce the size of a primary lesion to decrease surgical scarring size during excision.

These tests can be performed on formalin-fixed, paraffin embedded tissue sections. The macroscopic description should provide the fixative used. 10% neutral buffered formalin is the preferred fixative. It is recommended that the duration of fixation be provided as well.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol:**

  - Biopsy (punch, shave, other)
  - Excision (shave removal, saucerization, ellipse, wide, other)
  - Re-excision (ellipse, wide, other)
  - Lymphadenectomy (sentinel nodes, regional nodes)

- **Specimen Size and Extent of Resection:**

  - Biopsy: measure in three dimensions.
  - Excision: measure skin surface in two dimensions and maximum depth.
  - Re-excision: measure skin surface in two dimensions and maximum depth.
  - Lymphadenectomy:
    - Sentinel – measure each node in three dimensions.
    - Regional – count and provide a range in size.

- **Specimen Integrity and Adequacy:**

  Note if defects to the margin or epithelium are present. Describe the anatomic location of the defect from the tumor and relevant margins. If defects involve the tumor and serve to hinder assessment of the final surgical margin, consultation with the surgeon for clarification should be considered, as well as differentially inking the margins in areas affected by defects as this may assist in creating a post-surgical treatment plan.

TUMOR ("T" of TNM)

- **Tumor Size and Focality:**

  - State if unifocal, multifocal or cannot be determined.
  - Provide three dimensions of each tumor/tumor bed. *

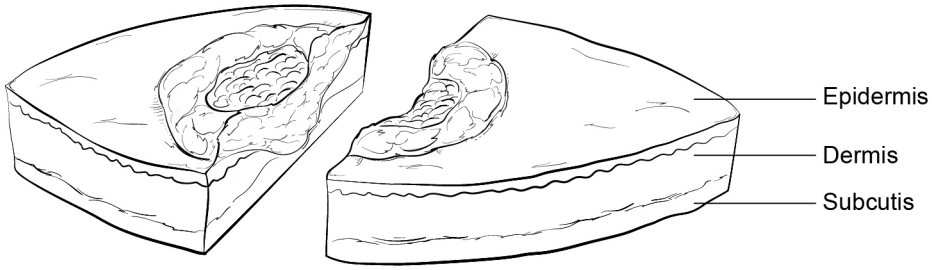
  *Tumors greater than 4 cm are high-risk and define primary tumors as T3.

- **Tumor Site(s):**

  - Specify tumor site on skin if known.
  - If multiple tumors are present, list individual sites and distance apart from one another.

- **Tumor Depth of Invasion and Relationship to Attached Organs/Structures:**

  - The thickness of the tumor (Breslow) may be an indicator of a high-risk tumor and may upstage the tumor to T3 if invasion is beyond the subcutaneous fat or greater than 0.6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor). Indicate if the tumor is confined to the epidermis, extends into the subcutaneous tissue, or transects at the deep resection margin.
  - Depth of tumor invasion, as measured by Breslow millimeter depth and tissue level depth correlates with metastatic potential.
  - Describe if the tumor invades into attached underlying organs / structures, (mucosa, muscle, cartilage or bone). *(Figure 1)*



This type of lesion is crusted, raised, papular, and centrally ulcerating.

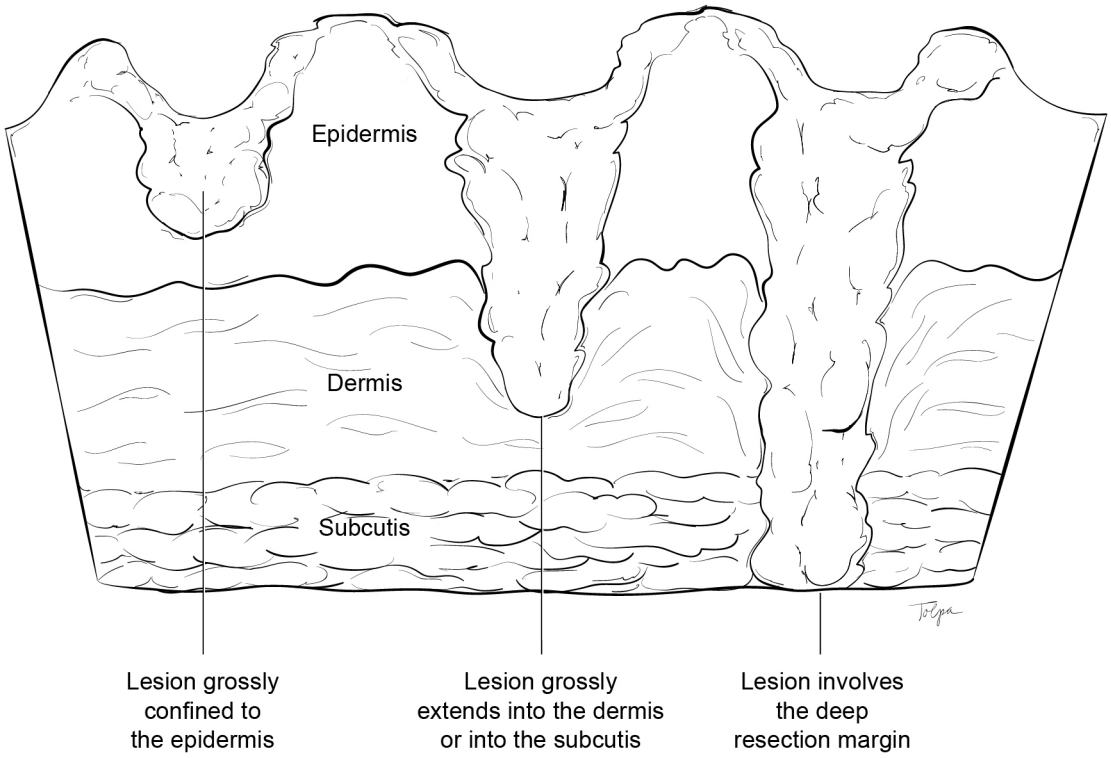


Figure 1: Cutaneous Carcinoma Depth of Invasion

Definition of Primary Tumor (pT): *(Figure 2)*

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
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
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 involvement
pT4a	Tumor with gross cortical bone/marrow invasion
pT4b	Tumor with skull base invasion and/or skull base foramen involvement

*Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression.

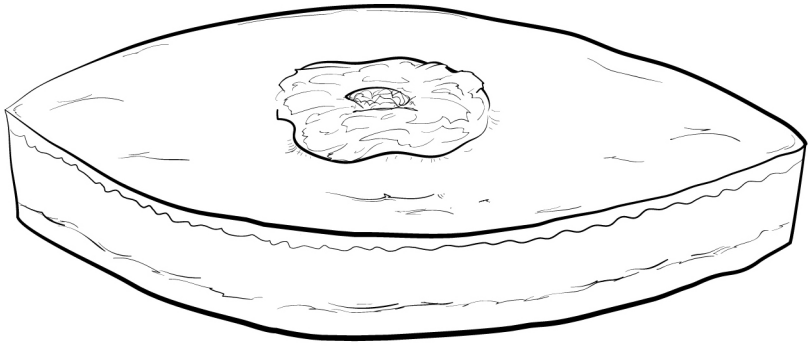
High risk macroscopic features include anatomic site, tumor size (>4 cm), depth of invasion (DOI) beyond the subcutaneous fat or equal to or greater than 6 mm, perineural invasion, and/or minor bone erosion.

Brigham and Women's Hospital (BWH) Tumor Staging for Cutaneous Squamous Cell Carcinoma

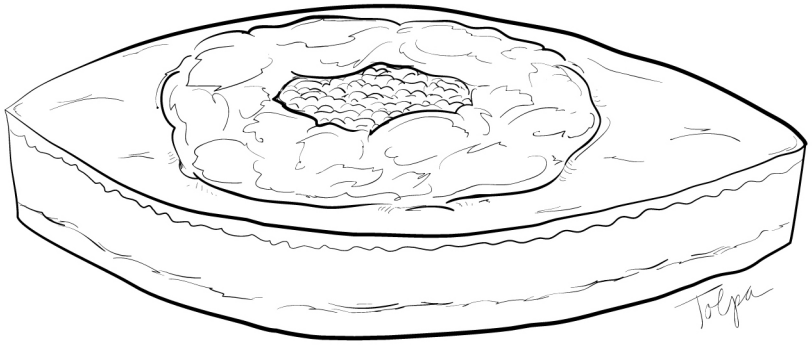
T0	In situ SCC
T1	0 risk factors*
T2a	1 risk factor*
T2b	2-3 risk factors*
T3	4 risk factors* or bone invasion

*BWH staging high-risk features:

- Clinical tumor diameter ≥2 cm
- Tumor invasion beyond subcutaneous fat
- Poorly differentiated histology
- Perineural invasion of nerve(s) ≥0.1 mm in caliber



T1: Tumor smaller than or equal to 2 cm in greatest dimension



T2: Tumor larger than 2 cm, but smaller than or equal to 4 cm in greatest dimension

Figure 2: T1 and T2 Criteria for Cutaneous Carcinoma of the Head and Neck

***TNM Descriptors**:*

pT: The designation "T" refers to 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.

pT(m)NM: For multiple primary tumors, the T score is modified, with the suffix "(m)" recorded in parentheses following the pT indicator (pT indicating primary tumor). Each tumor should be assessed independently of the others. Variability in histologic features should be considered with adequate sampling performed to either assure or exclude histologic variability. With regard to the T score, for staging purposes, the pT score is established based on the primary tumor showing the greatest degree of invasion.

ypTMN: If multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy) has been utilized the T score will be modified with the prefix "y". The "y" categorization is not an estimate of tumor prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy). Rather, the extent of tumor actually present at the time of examination must be disclosed. If neoadjuvant therapy renders macroscopic examination of tumor involvement inconclusive, dissection methods should be considered, which allow for mapping of the treated area, emphasizing the areas of potential deepest invasion.

rTNM: The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval.

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

Residual Tumor (R) Category

The absence or presence of residual tumor at the primary tumor site after treatment is denoted by the symbol R. The R categories for the primary tumor site are as follows:

R	R Definition
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor at the primary cancer site or regional nodal sites

- **Margins:**
  - If the specimen is oriented or is an excision, the distance of tumor/tumor bed from closest peripheral and deep margins should be reported in mm.
  - State if the peripheral and deep margins are macroscopically involved by tumor/tumor bed.
  - Although necessary for only oriented or excisional biopsies, the position of the tumor/tumor bed to peripheral and deep margins is advocated as part of a standard practice for all specimens.

LYMPH NODES ("N" of TNM)

When deep invasion and metastasis occurs, local and regional lymph nodes are the most common sites of metastasis. Nodal metastasis usually occurs in an orderly manner, initially in a single node, which expands in size. Eventually, multiple nodes become involved with metastasis. Metastatic disease may spread to secondary nodal basins, including contralateral nodes when advanced. Although uncommon, nodal metastases may bypass a primary nodal basin.

Definition of Regional Lymph Node

Pathological N (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
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 nodes, none larger than 6 cm in greatest dimension, ENE(-) *or* metastases in multiple ipsilateral lymph node(s), none larger than 6 cm and ENE(-)
pN2a	Metastasis in a single ipsilateral lymph 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(-)
pN3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); *or* 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(+)
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(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+).

Extranodal extension (ENE) is defined as extension through the lymph node capsule into the surrounding connective tissue, with or without stromal reaction.

Lymph Node Sampling:

For assessment of pathological node status (pN), a selective neck dissection often is required and ordinarily should include 10 or more nodes. A comprehensive (radical or modified radical neck dissection) ordinarily will include 15 or more lymph nodes.

- Count lymph nodes identified.
- Specify site of lymph nodes identified.
- Measure lymph node in three dimensions or provide a range in size of greatest dimension if multiple.
- Describe the cut surface of the identified lymph nodes.

For macroscopically positive lymph nodes:

- Give a precise size of the lymph node and tumor implant.
- Representative sampling of these lymph nodes is adequate.
- Sample areas where extranodal extension is seen or cannot be excluded.

For small lymph nodes or macroscopically negative larger lymph nodes:

- Submit small lymph nodes in toto.
- Section larger lymph nodes at 2 mm intervals.
- Submit the entire capsule of the lymph node for possible extranodal extension.
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- If the lymph node is large but macroscopically negative, submit sequentially so that a size calculation can be established.
- Take steps to ensure that an accurate lymph node count can be rendered.

METASTASIS ("M" of TNM)

Definition of Distant Metastasis (pM)

pM Category	pM Criteria
M0	No distant metastasis
pM1	Distant metastasis

When applicable indicate whether distant metastasis is identified and specify the site.

Distant metastases are staged primarily by the presence (M1) or absence (M0) of metastases in distant organs or sites outside of the regional lymph nodes. After metastasizing to lymph nodes, cutaneous squamous cell carcinoma may spread to visceral sites, including lung.

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