

Protocol for the Examination of Specimens from Patients with Carcinomas of the Lip and Oral Cavity

Protocol applies to all invasive carcinomas of the oral cavity, including lip and tongue. Mucosal malignant melanoma is included. Lymphomas and sarcomas are not included.

Based on AJCC/UICC TNM, 7th edition

Protocol web posting date: October 2009

Procedures

- Biopsy
- Resection

Authors

Mary S. Richardson, MD, DDS*

Department of Pathology, Medical University of South Carolina, Charleston, SC

Leon Barnes, MD

Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA

Diane L. Carlson, MD, FCAP

Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, NY

John Chan, MD, FCAP

Department of Pathology, Queen Elizabeth Hospital, Hong Kong

Gary Ellis, DDS

ARUP Laboratories, Salt Lake City, UT

Louis B. Harrison, MD

Department of Radiation Oncology, Beth Israel Medical Center, St. Luke's and Roosevelt Hospitals, New York, NY

Jennifer Leigh Hunt, MD, FCAP

Department of Pathology, Massachusetts General Hospital, Boston, MA

Jatin Shah, MD, FACS

Head and Neck Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

Lester D. R. Thompson, MD, FCAP

Department of Pathology, Southern California Permanente Medical Group, Woodland Hills, CA

Richard J. Zarbo, MD, DMD, FCAP

Department of Pathology, Henry Ford Health System, Detroit, MI

Bruce M. Wenig, MD, FCAP†

Department of Pathology and Laboratory Medicine, Beth Israel Medical Center, St. Luke's and Roosevelt Hospitals, New York, NY

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: Ben Z. Pilch, MD; Elizabeth Gillies, MD; John R. Houck Jr, MD; Kyung-Whan Min, MD; David Novis, MD; Jatin Shah, MD; Richard J. Zarbo, MD, DMD; Bruce M Wenig, MD

© 2009 College of American Pathologists (CAP). All rights reserved.

The College does not permit reproduction of any substantial portion of these protocols without its written authorization. The College hereby authorizes use of these protocols by physicians and other health care providers in reporting on surgical specimens, in teaching, and in carrying out medical research for nonprofit purposes. This authorization does not extend to reproduction or other use of any substantial portion of these protocols for commercial purposes without the written consent of the College.

The CAP also authorizes physicians and other health care practitioners to make modified versions of the Protocols solely for their individual use in reporting on surgical specimens for individual patients, teaching, and carrying out medical research for non-profit purposes.

The CAP further authorizes the following uses by physicians and other health care practitioners, in reporting on surgical specimens for individual patients, in teaching, and in carrying out medical research for non-profit purposes: (1) **Dictation** from the original or modified protocols for the purposes of creating a text-based patient record on paper, or in a word processing document; (2) **Copying** from the original or modified protocols into a text-based patient record on paper, or in a word processing document; (3) The use of a **computerized system** for items (1) and (2), provided that the Protocol data is stored intact as a single text-based document, and is not stored as multiple discrete data fields.

Other than uses (1), (2), and (3) above, the CAP does not authorize any use of the Protocols in electronic medical records systems, pathology informatics systems, cancer registry computer systems, computerized databases, mappings between coding works, or any computerized system without a written license from CAP. Applications for such a license should be addressed to the SNOMED Terminology Solutions division of the CAP.

Any public dissemination of the original or modified Protocols is prohibited without a written license from the CAP.

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 (Checklist)" 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 checklist 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.

Surgical Pathology Cancer Case Summary (Checklist)

Protocol web posting date: October 2009

LIP AND ORAL CAVITY: Incisional Biopsy, Excisional Biopsy, Resection

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)

- ☐ Vermilion border upper lip
- ☐ Vermilion border lower lip
- ☐ Mucosa of upper lip
- ☐ Mucosa of lower lip
- ☐ Commissure of lip
- ☐ Lateral border of tongue
- ☐ Ventral surface of tongue, not otherwise specified (NOS)
- ☐ Dorsal surface of tongue, NOS
- ☐ Anterior two-thirds of tongue, NOS
- ☐ Upper gingiva (gum)
- ☐ Lower gingiva (gum)
- ☐ Anterior floor of mouth
- ☐ Floor of mouth, NOS
- ☐ Hard palate
- ☐ Buccal mucosa (inner cheek)
- ☐ Vestibule of mouth
 - ☐ Upper
 - ☐ Lower
- ☐ Alveolar process
 - ☐ Upper
 - ☐ Lower
- ☐ Mandible
- ☐ Maxilla
- ☐ Other (specify): _____
- ☐ Not specified

Received:

- ☐ Fresh
- ☐ In formalin
- ☐ Other (specify): _____

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Procedure (select all that apply)

- ☐ Incisional biopsy
- ☐ Excisional biopsy
- ☐ Resection
 - ☐ Glossectomy (specify): _____
 - ☐ Mandibulectomy (specify): _____
 - ☐ Maxillectomy (specify): _____
 - ☐ Palatectomy
- ☐ Neck (lymph node) dissection (specify): _____
- ☐ Other (specify): _____
- ☐ Not specified

***Specimen Integrity**

- * ☐ Intact
- * ☐ Fragmented

Specimen Size

Greatest dimensions: _____ x _____ x _____ cm

* Additional dimensions (if more than one part): _____ x _____ x _____ cm

Specimen Laterality

- ☐ Right
- ☐ Left
- ☐ Bilateral
- ☐ Midline
- ☐ Not specified

Tumor Site (select all that apply) (Note A)

- ☐ Vermilion border upper lip
- ☐ Vermilion border lower lip
- ☐ Mucosa of upper lip
- ☐ Mucosa of lower lip
- ☐ Commissure of lip
- ☐ Lateral border of tongue
- ☐ Ventral surface of tongue, NOS
- ☐ Dorsal surface of tongue, NOS
- ☐ Anterior two-thirds of tongue, NOS
- ☐ Upper gingiva (gum)
- ☐ Lower gingiva (gum)
- ☐ Anterior floor of mouth
- ☐ Floor of mouth, NOS
- ☐ Hard palate
- ☐ Buccal mucosa (inner cheek)
- ☐ Vestibule of mouth
 - ☐ Upper
 - ☐ Lower
- ☐ Alveolar process
 - ☐ Upper
 - ☐ Lower
- ☐ Mandible
- ☐ Maxilla

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

___ Other (specify): _____
___ Not specified

Tumor Focality

___ Single focus
___ Multifocal (specify): _____

Tumor Size

Greatest dimension: ___ cm
*Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

***Tumor Thickness (pT1 and pT2 tumors) (Note B)**

*Tumor thickness: ___ mm
*Intact surface mucosa: ____; or ulcerated surface: ____

***Tumor Description (select all that apply)**

*Gross subtype:
* ___ Polypoid
* ___ Exophytic
* ___ Endophytic
* ___ Ulcerated
* ___ Sessile
* ___ Other (specify): _____

***Macroscopic Extent of Tumor**

*Specify: _____

Histologic Type (select all that apply) (Note C)

___ Squamous cell carcinoma, conventional

Variants of Squamous Cell Carcinoma

___ Acantholytic squamous cell carcinoma
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Carcinoma cuniculatum
___ Papillary squamous cell carcinoma
___ Spindle cell squamous carcinoma
___ Verrucous carcinoma

___ Lymphoepithelial carcinoma (non-nasopharyngeal)

Carcinomas of Minor Salivary Glands

___ Acinic cell carcinoma
___ Adenoid cystic carcinoma
___ Adenocarcinoma, not otherwise specified (NOS)
 ___ Low grade
 ___ Intermediate grade
 ___ High grade
___ Basal cell adenocarcinoma

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

___ Carcinoma ex pleomorphic adenoma (malignant mixed tumor)

___ Low-grade

___ High-grade

___ Invasive

___ Minimally invasive (**Note C**)

___ Invasive (**Note C**)

___ Intracapsular (noninvasive)

___ Carcinoma, type cannot be determined

___ Carcinosarcoma

___ Clear cell adenocarcinoma

___ Cystadenocarcinoma

___ Epithelial-myoepithelial carcinoma

___ Mucoepidermoid carcinoma

___ Low grade

___ Intermediate grade

___ High grade

___ Mucinous adenocarcinoma (colloid carcinoma)

___ Myoepithelial carcinoma (malignant myoepithelioma)

___ Oncocytic carcinoma

___ Polymorphous low-grade adenocarcinoma

___ Salivary duct carcinoma

___ Other (specify): _____

Adenocarcinoma, Non-Salivary Gland Type

___ Adenocarcinoma, not otherwise specified (NOS)

___ Low grade

___ Intermediate grade

___ High grade

___ Other (specify): _____

Neuroendocrine Carcinoma

___ Typical carcinoid tumor (well differentiated neuroendocrine carcinoma)

___ Atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma)

___ Small cell carcinoma (poorly differentiated neuroendocrine carcinoma)

___ Combined (or composite) small cell carcinoma, neuroendocrine type

___ Other (specify): _____

___ Carcinoma, type cannot be determined

___ Mucosal malignant melanoma

Histologic Grade (Note D)

___ Not applicable

___ GX: Cannot be assessed

___ G1: Well differentiated

___ G2: Moderately differentiated

___ G3: Poorly differentiated

___ Other (specify): _____

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

***Microscopic Tumor Extension**

*Specify: _____

Margins (select all that apply) (Notes E and F)☐ Cannot be assessed☐ Margins uninvolved by invasive carcinoma

Distance from closest margin: ____ mm or ____ cm

Specify margin(s), per orientation, if possible: _____

☐ Margins involved by invasive carcinoma

Specify margin(s), per orientation, if possible: _____

☐ Margins uninvolved by carcinoma in situ (includes moderate and severe dysplasia[#])**(Note E)**

Distance from closest margin: ____ mm or ____ cm;

Specify margin(s), per orientation, if possible: _____

☐ Margins involved by carcinoma in situ (includes moderate and severe dysplasia[#])**(Note E)**

Specify margin(s), per orientation, if possible: _____

☐ Not applicable[#] *Applicable only to squamous cell carcinoma and histologic variants.****Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)*** ☐ Not identified* ☐ Present (specify): _____* ☐ Indeterminate**Lymph-Vascular Invasion**☐ Not identified☐ Present☐ Indeterminate**Perineural Invasion (Note G)**☐ Not identified☐ Present☐ Indeterminate**Lymph Nodes, Extranodal Extension (Note H)**☐ Not identified☐ Present☐ Indeterminate**Pathologic Staging (pTNM) (Note I)***Note: The phrases in italics include clinical findings required for AJCC staging. This clinical information may be unknown to the pathologist. It is included here only for the sake of completeness.*TNM Descriptors (required only if applicable) (select all that apply)☐ m (multiple primary tumors)☐ r (recurrent)☐ y (post-treatment)

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

For All Carcinomas Excluding Mucosal Malignant Melanoma*Primary Tumor (pT)*

- ☐ pTX: Cannot be assessed
☐ pT0: No evidence of primary tumor
☐ pTis: Carcinoma in situ
☐ pT1: Tumor 2 cm or less in greatest dimension
☐ pT2: Tumor more than 2 cm but not more than 4 cm in greatest dimension
☐ pT3: Tumor more than 4 cm in greatest dimension
☐ pT4a: Moderately advanced local disease.
 Lip: Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, ie, chin or nose
 Oral cavity: Tumor invades adjacent structures only (eg, through cortical bone [mandible, maxilla], into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
☐ pT4b: Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base, and/or encases internal carotid artery

Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.

Regional Lymph Nodes (pN)[#] (Notes J through M)

- ☐ pNX: Cannot be assessed
☐ pN0: No regional lymph node metastasis
☐ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or less 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

Specify: Number examined: ____
 Number involved: ____
 *Size (greatest dimension) of the largest positive lymph node: ____

(Note L)

[#] Superior mediastinal lymph nodes are considered regional lymph nodes (level VII).
 Midline nodes are considered ipsilateral nodes.

Distant Metastasis (pM)

- ☐ Not Applicable
☐ pM1: Distant metastasis
 *Specify site(s), if known: _____
 * Source of pathologic metastatic specimen (specify): _____

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

For Mucosal Malignant Melanoma (Note I)*Primary Tumor (pT)*

- ___ pT3: Mucosal disease
- ___ pT4a: Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone, or overlying skin
- ___ pT4b: Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

Regional Lymph Nodes (pN)

- ___ pNX: Regional lymph nodes cannot be assessed
- ___ pN0: No regional lymph node metastases
- ___ pN1: Regional lymph node metastases present

Distant Metastasis (pM)

- ___ Not applicable
- ___ pM1: Distant metastasis present
- *Specify site(s), if known: _____
- * Source of pathologic metastatic specimen (specify): _____

***Additional Pathologic Findings (select all that apply)**

- * ___ None identified
- * ___ Keratinizing dysplasia (**Note N**)
- * ___ Mild
- * ___ Moderate
- * ___ Severe (carcinoma in situ)
- * ___ Non-keratinizing dysplasia (**Note N**)
- * ___ Mild
- * ___ Moderate
- * ___ Severe (carcinoma in situ)
- * ___ Inflammation (specify type): _____
- * ___ Epithelial hyperplasia
- * ___ Colonization
- * ___ Fungal
- * ___ Bacterial
- * ___ Other (specify): _____

***Ancillary Studies (Note O)**

- *Specify type(s): _____
- *Specify result(s): _____

***Clinical History (select all that apply)**

- * ___ Neoadjuvant therapy
- * ___ Yes (specify type): _____
- * ___ No
- * ___ Indeterminate
- * ___ Other (specify): _____

***Comment(s)**

* Data elements with asterisks are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

Explanatory Notes

Scope of Guidelines

The reporting of oral cancer including the lip is facilitated by the provision of a checklist illustrating the features required for comprehensive patient care. However, there are many cases in which the individual practicalities of applying such a checklist 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. Checklists 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 checklist 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 classification of tumours, the TNM classification, the American College of Surgeons Commission on Cancer, and the International Union on Cancer (UICC). This checklist 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.

A. Anatomic Sites and Subsites for Lip and Oral Cavity (Figure 1)

Lip

- External upper lip (vermillion border)
- External lower lip (vermillion border)
- Commissures

Oral Cavity

- Buccal mucosa
 - Mucosa of upper and lower lips
 - Cheek mucosa
 - Retromolar areas
 - Bucco-alveolar sulci, upper and lower (vestibule of mouth)
- Upper alveolus and gingiva (upper gum)
- Lower alveolus and gingiva (lower gum)
- Hard palate
- Tongue
 - Dorsal surface and lateral borders anterior to circumvallate papillae (anterior two-thirds)
 - Inferior (ventral) surface
- Floor of mouth

The protocol applies to all carcinomas arising at these sites.¹

Mucosal Lip. The lip begins at the junction of the vermillion border with the skin and includes only the vermillion surface or that portion of the lip that comes in contact with the

opposing lip. It is well defined into an upper and lower lip joined at the commissures of the mouth.

Buccal Mucosa (Inner Cheek). This includes all the membrane lining of the inner surface of the cheeks and lips from the line of contact of the opposing lips to the line of attachment of mucosa of the alveolar ridge (upper and lower) and pterygomandibular raphe.

Lower Alveolar Ridge. This refers to the mucosa overlying the alveolar process of the mandible, which extends from the line of attachment of mucosa in the buccal gutter to the line of free mucosa of the floor of the mouth. Posteriorly it extends to the ascending ramus of the mandible.

Upper Alveolar Ridge. This refers to the mucosa overlying the alveolar process of the maxilla, which extends from the line of attachment of mucosa in the upper gingival buccal gutter to the junction of the hard palate. Its posterior margin is the upper end of the pterygopalatine arch.

Retromolar Gingiva (Retromolar Trigone). This is the attached mucosa overlying the ascending ramus of the mandible from the level of the posterior surface of the last molar tooth and the apex superiorly, adjacent to the tuberosity of the maxilla.

Floor of the Mouth. This is a semilunar space over the myelohyoid and hypoglossus muscles, extending from the inner surface of the lower alveolar ridge to the undersurface of the tongue. Its posterior boundary is the base of the anterior pillar of the tonsil. It is divided into two sides of the submaxillary and sublingual salivary glands.

Hard Palate. This is the semilunar area between the upper alveolar ridge and the mucous membrane covering the palatine process of the maxillary palatine bones. It extends from the inner surface of the superior alveolar ridge to the posterior edge of the palatine bone.

Anterior Two-Thirds of the Tongue (Oral Tongue). This is the freely mobile portion of the tongue that extends anteriorly from the line of circumvallate papillae to the undersurface of the tongue at the junction of the floor of the mouth. It is composed of four areas: the tip, the lateral borders, the dorsum, and the undersurface (nonvillous ventral surface of the tongue). The undersurface of the tongue is considered a separate category by the World Health Organization (WHO).

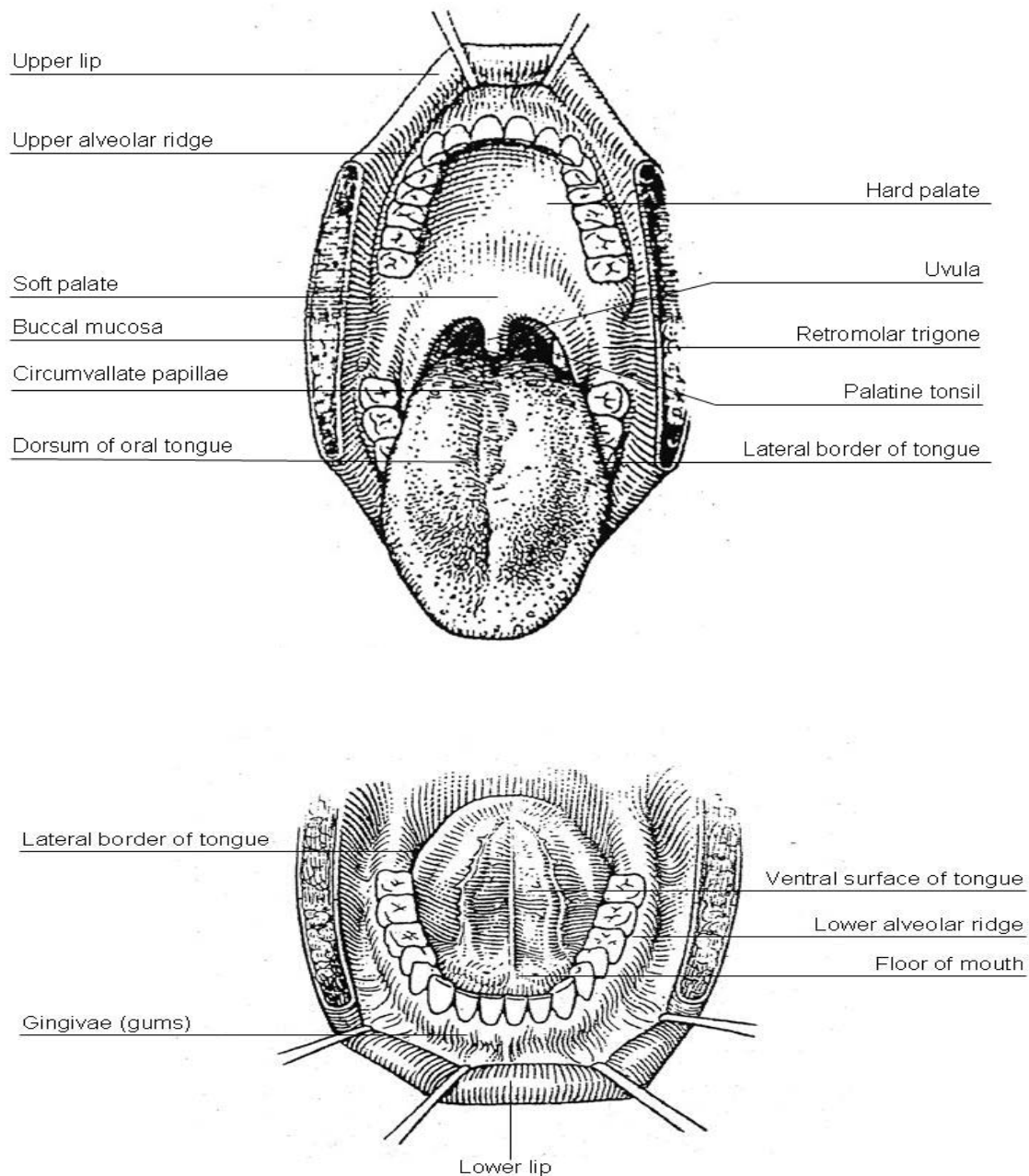
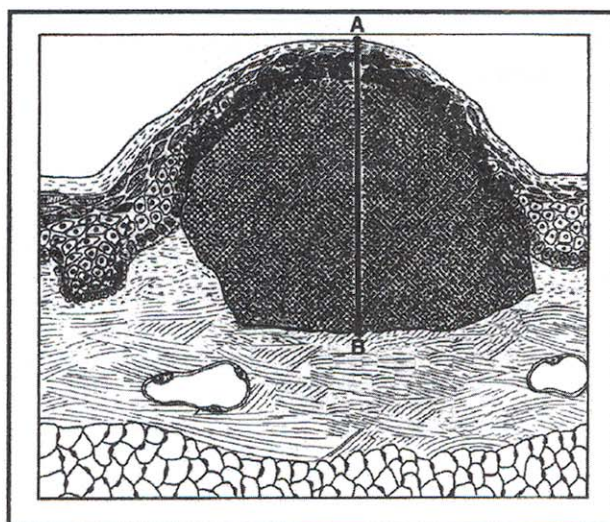


Figure 1. Diagrams illustrating the oral cavity anatomic subsites. Figure courtesy of Beth Israel Medical Center, St. Luke's and Roosevelt Hospitals, New York.

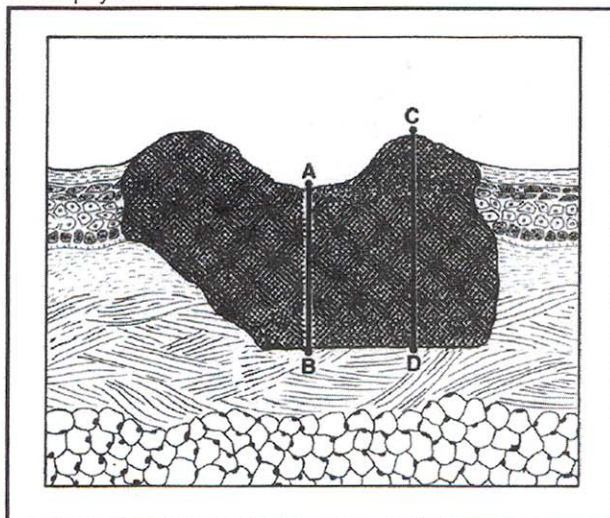
B. Tumor Thickness/Depth of Invasion

For small (T1, T2) oral squamous cell carcinomas, the microscopic measurement of tumor thickness is considered a valuable parameter for predicting regional nodal involvement and survival in oral cavity squamous cell carcinoma. Measurement of tumor thickness has been controversial in the literature and there is no standard method for measuring. Submission of 3- to 4-mm consecutive sections through the lesion will facilitate locating the deepest point of invasion and maximum tumor dimension. Tumor thickness is usually measured from the mucosal surface of the tumor to the deepest

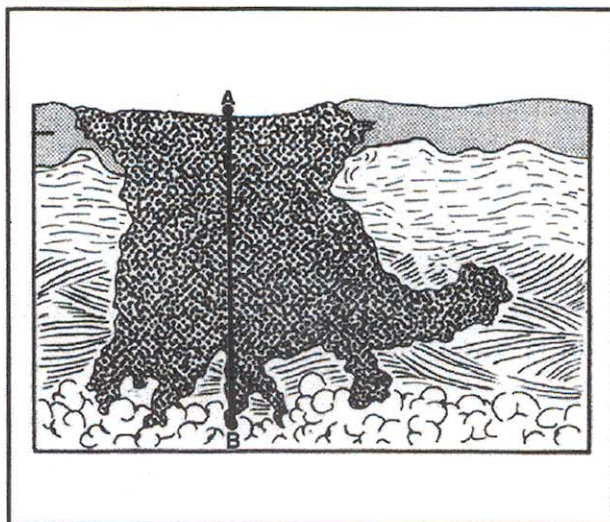
point of tissue invasion in a perpendicular fashion with an optical micrometer. The dimension should be recorded in millimeters. In heavily keratinized lesions, measurement occurs from the surface of the tumor exclusive of the keratin layer; alternatively, measurement might more appropriately occur from the epithelial basement membrane. If the lesion is ulcerated, then measurement should be from the surface of the ulcer²⁻⁵ to the deepest point of invasion (Figure 2). Gross examination of consecutive sections through the lesion and measuring tumor thickness from a histologic section with the least amount of tangential artifact should aid in accurately measuring tumor thickness.



A. Exophytic



B. Ulcerated



C Endophytic

Figure 2. Tumor thickness can be measured from an exophytic or heavily keratinized surface (A), ulcerated surface (B) or endophytic surface (C). Measurement occurs from the surface of the tumor exclusive of the keratin layer to the deepest point of invasion. From *AJCC Cancer Staging Manual*. 6th ed. New York: Springer; 2002. © American Joint Committee on Cancer. Reproduced with permission.

C. Histological Type

A modification of the World Health Organization (WHO) classification of carcinomas of the oral cavity including the lip is shown below.⁶ This list may not be complete. This protocol applies only to carcinomas and melanomas but does not apply to lymphomas or sarcomas.

Carcinomas of the Oral Cavity

Squamous cell carcinoma, conventional

Squamous cell carcinoma, variant

 Acantholytic squamous cell carcinoma

 Adenosquamous carcinoma

 Basaloid squamous cell carcinoma

 Carcinoma cuniculatum

 Papillary squamous cell carcinoma

 Spindle cell squamous carcinoma

 Verrucous carcinoma

Lymphoepithelial carcinoma (non-nasopharyngeal)

Carcinomas of Minor Salivary Glands

 Acinic cell carcinoma

 Adenoid cystic carcinoma

 Adenocarcinoma, not otherwise specified (NOS)

 Basal cell adenocarcinoma

 Carcinoma ex pleomorphic adenoma (malignant mixed tumor)

 Carcinoma, type cannot be determined

 Carcinosarcoma

 Clear cell carcinoma, NOS

 Cystadenocarcinoma

 Epithelial-myoepithelial carcinoma

 Mucoepidermoid carcinoma,

 Mucinous adenocarcinoma (colloid carcinoma)

 Myoepithelial carcinoma (malignant myoepithelioma)

 Oncocytic carcinoma

 Polymorphous low-grade adenocarcinoma

 Salivary duct carcinoma

Adenocarcinoma, Non-salivary Gland Type

 Papillary adenocarcinoma

 Intestinal-type adenocarcinoma

 Adenocarcinoma not otherwise specified (NOS), low grade

 Adenocarcinoma, NOS, intermediate grade

 Adenocarcinoma, NOS, high grade

Neuroendocrine Carcinoma[#]

 Typical carcinoid tumor (well differentiated neuroendocrine carcinoma)

 Atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma)

 Small cell carcinoma, neuroendocrine type (poorly differentiated neuroendocrine carcinoma)

 Combined (or composite) small cell carcinoma, neuroendocrine type^{##}

Mucosal Malignant Melanoma

Not included in WHO Classification.

Represents a carcinoma showing combined features of small cell neuroendocrine carcinoma associated with a squamous or adenocarcinomatous component.⁶

D. Histologic Grade

For histologic types of carcinomas that are amenable to grading, 3 histologic grades are suggested, as shown below. When a tumor manifests more than 1 grade of differentiation, the surgical report must designate both the highest and the most prevalent tumor grades.^{7,8}

Grade X	Cannot be assessed
Grade 1	Well differentiated
Grade 2	Moderately differentiated
Grade 3	Poorly differentiated

This grading system does not apply to all salivary gland tumors. The histologic (microscopic) grading of salivary gland carcinomas has been shown to be an independent predictor of behavior and plays a role in optimizing therapy.⁹⁻¹³ Further, there is often a positive correlation between histologic grade and clinical stage. With some exceptions, histologic grading is predicated on cytomorphic features. In this histologic grading scheme, 3 histologic grades are suggested, as follows:

Grade 1	Well differentiated = Low-grade
Grade 2	Moderately differentiated = Intermediate-grade
Grade 3	Poorly differentiated = High-grade
Grade X	Cannot be assessed

When a tumor manifests more than 1 grade of differentiation, the surgical report must designate both the highest and the most prevalent tumor grades. In some carcinomas, histologic grading may be based on growth pattern, such as in adenoid cystic carcinoma, for which a histologic high-grade variant has been recognized based on the percentage of solid growth.⁹ Those adenoid cystic carcinomas showing 30% or greater of solid growth pattern are considered to be histologically high-grade carcinomas.^{9,11,14} The histologic grading of mucoepidermoid carcinoma includes a combination of growth pattern characteristics (eg, cystic, solid, neurotropism) and cytomorphic findings (eg, anaplasia, mitoses, necrosis).¹⁵⁻¹⁷

Carcinoma ex pleomorphic adenoma is subclassified by histologic grade (low grade and high grade) and extent of invasion, the latter including minimally invasive, invasive and noninvasive cancers. Minimally invasive cancers measure less than or equal to 1.5 mm with penetration of the malignant component into extracapsular tissue; invasive carcinomas measure more than 1.5 mm of invasion; noninvasive cancers are completely confined to within the capsule without evidence of penetration into extracapsular tissue. Prior to diagnosing a noninvasive carcinoma ex pleomorphic adenoma, sectioning of the entire lesion for histologic evaluation is recommended in order to exclude the presence of invasive growth. Prognosis has been linked to degree of invasion with noninvasive

and minimally invasive cancers apparently having a better prognosis than invasive cancers.¹⁸

E. Surgical Margins

Reporting of surgical margins should include information regarding the distance of invasive carcinoma, carcinoma in situ, or high grade dysplasia (moderate to severe) from the surgical margin. Closeness of the above, microscopically less than 5 mm, from the surgical border should be noted in the report. Presence of the above lesions found within 5 mm of the surgical border carry a significant risk for subsequent local recurrence.¹⁹⁻²¹ Reporting of surgical margins for carcinomas of the minor salivary glands should follow those used for squamous cell carcinoma of oral cavity. There is no category of carcinoma in situ relative to carcinomas of salivary glands (major, minor).

Keratinizing Dysplasia

The types of intraepithelial dysplasia of the upper aerodigestive tract (UADT) include nonkeratinizing ("classic") dysplasia and keratinizing dysplasia. Of the two types of dysplasias, the keratinizing dysplasias are significantly more common than the nonkeratinizing dysplasias. For both types of UADT intraepithelial dysplasias, grading includes mild, moderate, and severe forms, with the latter category being synonymous with carcinoma in situ. It must be noted that in the setting of keratinizing dysplasia, full thickness dysplasia of the surface epithelium, representing the histologic definition for carcinoma in situ, is an uncommon occurrence. Nevertheless, there are keratinizing dysplasias that lack full thickness dysplasia and yet carry a significant risk to develop invasive carcinoma.²² Due to the fact that invasive carcinoma can develop from keratinizing dysplasia in which there is an absence of full thickness dysplasia, the grading of UADT dysplasias is problematic and lacks reproducibility among pathologists (see below under Note M). Since there is no significant statistical difference in the risk to invasive carcinoma between the category of keratinizing moderate dysplasia and keratinizing severe dysplasia,²² the suggestion has been entertained of adopting a Bethesda-like classification to keratinizing dysplasias of the UADT, including a low-grade category limited to keratinizing mild dysplasia and a high-grade category to include keratinizing moderate and severe dysplasias.²³ As such, it must be recognized that keratinizing severe dysplasia, even if not "full thickness," should for all intents and purposes be dealt with in a similar manner as classically defined carcinoma in situ so that in evaluating surgical margins for the presence or absence of dysplasia/carcinoma in situ, keratinizing moderate and severe dysplasias should be viewed as a single category relative to risk of progression to invasive carcinoma. Such a risk does not include keratinizing mild dysplasia. In summary, the presence of keratinizing mild dysplasia at (or near) a surgical margin should not be viewed/reported as a positive margin, whereas the presence of keratinizing moderate or severe dysplasia at (or near) a surgical margin should be viewed/reported as a positive margin.

F. Orientation of Specimen

Complex specimens should be examined and oriented with the assistance of attending surgeons. Direct communication between the surgeon and pathologist is a critical component in specimen orientation and proper sectioning. Whenever possible, the tissue examination request form should include a drawing of the resected specimen showing the extent of the tumor and its relation to the anatomic structures of the region. The lines and extent of the resection can be depicted on preprinted adhesive labels and attached to the surgical pathology request forms.

G. Perineural Invasion

The presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.²⁴ The presence of perineural invasion (neurotropism) in the primary cancer is associated with poor local disease control and regional control, as well as being associated with metastasis to regional lymph nodes.²⁴ Further, perineural invasion is associated with decrease in disease-specific survival and overall survival.²⁴ There is conflicting data relative to an association between the presence of perineural invasion and the development of distant metastasis, with some studies showing an increased association with distant metastasis, but other studies not showing any correlation with distant metastasis.²⁴ The relationship between perineural invasion and prognosis is independent of nerve diameter.²⁵ Although perineural invasion of small unnamed nerves may not produce clinical symptoms, the reporting of perineural invasion includes nerves of all sizes including small peripheral nerves (ie, less than 1 mm in diameter). Aside from the impact on prognosis, the presence of perineural invasion also guides therapy. Concurrent adjuvant chemoradiation therapy has been shown to improve outcomes in patients with perineural invasion (as well as in patients with extranodal extension and bone invasion).^{26,27} Given the significance relative to prognosis and treatment, perineural invasion is a required data element in the reporting of head and neck cancers.

H. Extranodal Extension

The status of cervical lymph nodes is the single most important prognostic factor in aerodigestive cancer. All macroscopically negative or equivocal lymph nodes should be submitted in toto. Grossly positive nodes may be partially submitted for microscopic documentation of metastasis. Reporting of lymph nodes containing metastasis should include whether there is presence or absence of extra-nodal extension (EE). This finding consists of extension of metastatic tumor, present within the confines of the lymph node, through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction. If macroscopic examination suggests EE, this tissue should be submitted for microscopic confirmation. EE is a predictor of regional relapse and a criterion for postoperative radiotherapy.²⁸⁻³¹

I. TNM and Stage Groupings

The protocol recommends the TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) for lip and oral cavity cancer.^{1,32} Of note in the 7th edition of the AJCC staging of head and neck cancers¹ is the division of T4 lesions into T4a (moderately advanced local disease) and T4b (very advanced local disease), leading to the stratification of stage IV into stage IVA (moderately advanced local/regional disease), stage IVB (very advanced local/regional disease), and stage IVC (distant metastatic disease).

The 7th edition of the AJCC staging of head and neck cancers includes mucosal malignant melanomas.¹ Approximately two-thirds of mucosal malignant melanomas arise in the sinonasal tract, one quarter are found in the oral cavity and the remainder occur only sporadically in other mucosal sites of the head and neck.¹ Even small cancers behave aggressively with high rates of recurrence and death.¹ To reflect this aggressive behavior, primary cancers limited to the mucosa are considered T3 lesions. Advanced mucosal melanomas are classified as T4a and T4b. The anatomic extent criteria to define *moderately advanced* (T4a) and *very advanced* (T4b) disease are given below. The AJCC staging for mucosal malignant melanomas does not provide for the histologic definition of a T3 lesion; as the majority of mucosal malignant melanomas are invasive at

presentation, mucosal based melanomas (T3 lesions) include those lesions that involve either the epithelium and/or lamina propria of the involved site. Rare examples of *in situ* mucosal melanomas occur, but *In situ* mucosal melanomas are excluded from staging, as they are extremely rare.¹

Carcinomas of minor salivary glands of the upper aerodigestive tract site, including the oral cavity, are staged according to schemes corresponding to the anatomic site of occurrence. A proposed staging system for rare salivary gland cancers that occur within gnathic bone (eg, mandible) is based on the status of the overlying bone³³ including:

Stage I – intact overlying cortex with no evidence of bony expansion;
 Stage II - intact overlying cortex with some degree of bony expansion;
 Stage III – perforation of the cortex or metastatic spread.

For All Carcinomas Excluding Mucosal Malignant Melanoma

Primary Tumor

TX	Cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Moderately advanced local disease. Lip: Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, ie, chin or nose Oral cavity: Tumor invades adjacent structures (eg, through cortical bone [mandible, maxilla], into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)
T4b	Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base, and/or encases internal carotid artery

Regional Lymph Nodes[#]

NX	Cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

[#]Superior mediastinal lymph nodes are considered regional lymph nodes (level VII).
 Midline nodes are considered ipsilateral nodes.

Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

For Mucosal Malignant MelanomaPrimary Tumor

T3	Mucosal disease
T4a	Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone, or overlying skin.
T4b	Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures.

Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases present

Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

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. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) 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

Superficial erosion alone of bone/tooth socket by primary gingival tumor is not sufficient to classify a tumor as T4.

Stage Groupings – For All Cancers Except Mucosal Malignant Melanoma

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1,T2	N1	M0
	T3	N0,N1	M0
Stage IVA	T1,T2,T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0

Stage IVC	Any T	Any N	M1
-----------	-------	-------	----

Stage Groupings – For Mucosal Malignant Melanoma

Stage III	T3	N0	M0
Stage IVA	T4a	N0	M0
	T3-T4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y” and “r” 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.

Additional DescriptorsResidual 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.

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).

J. Classification of Neck Dissection

1. Radical neck dissection
2. Modified radical neck dissection, internal jugular vein and/or sternocleidomastoid muscle spared
3. Selective neck dissection (SND), as specified by the surgeon
 - a. Supraomohyoid neck dissection

- b. Posterolateral neck dissection
- c. Lateral neck dissection
- d. Central compartment neck dissection
- 4. Selective neck dissection (SND), as specified by the surgeon -“SND” with levels and sublevels designated (**Figure 3**).³⁴⁻³⁶
- 5. Extended radical neck dissection, as specified by the surgeon

K. Regional Lymph Nodes (pN0): Isolated Tumor Cells

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. Lymph nodes or distant sites with ITCs found by either histologic examination, immunohistochemistry, or non-morphologic techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be classified as N0 or M0, respectively. Specific denotation of the assigned N category is suggested as follows for cases in which ITCs are the only evidence of possible metastatic disease.^{32,37,38}

pN0	No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)
pN0(i-)	No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(i+)	No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(mol-)	No regional lymph node metastasis histologically, negative non-morphologic (molecular) findings for ITCs
pN0(mol+)	No regional lymph node metastasis histologically, positive non-morphologic (molecular) findings for ITCs

For purposes of pathologic evaluation, lymph nodes are organized by levels as shown in **Figure 3**.³⁹



Figure 3. The six sublevels of the neck for describing the location of lymph nodes within levels I, II, and V. Level IA, submental group; level IB, submandibular group; level IIA, upper jugular nodes

along the carotid sheath, including the subdigastric group; level IIB, upper jugular nodes in the submuscular recess; level VA, spinal accessory nodes; and level VB, the supraclavicular and transverse cervical nodes. From: Flint PW, et al, eds. *Cummings Otolaryngology: Head and Neck Surgery*. 5th ed. Philadelphia, PA; Saunders: 2010. Reproduced with permission © Elsevier.

In order for pathologists to properly identify these nodes, they must be familiar with the terminology of the regional lymph node groups and with the relationships of those groups to the regional anatomy. Which lymph node groups surgeons submit for histopathologic evaluation depends on the type of neck dissection they perform. Therefore, surgeons must supply information on the types of neck dissections that they perform and on the details of the local anatomy in the specimens they submit for examination or, in other manners, orient those specimens for pathologists.

If it is not possible to assess the levels of lymph nodes (for instance, when the anatomic landmarks in the excised specimens are not specified), then the lymph node levels may be estimated as follows: level II, upper third of internal jugular (IJ) vein or neck specimen; level III, middle third of IJ vein or neck specimen; level IV, lower third of IJ vein or neck specimen, all anterior to the sternocleidomastoid muscle.

Level I. Submental Group (Sublevel IA)

Lymph nodes within the triangular boundary of the anterior belly of the digastric muscles and the hyoid bone.

Level I. Submandibular Group (Sublevel IB)

Lymph nodes within the boundaries of the anterior and posterior bellies of the digastric muscle and the body of the mandible. The submandibular gland is included in the specimen when the lymph nodes within this triangle are removed.

Level II. Upper Jugular Group (Sublevels IIA and IIB)

Lymph nodes located around the upper third of the internal jugular vein and adjacent spinal accessory nerve extending from the level of the carotid bifurcation (surgical landmark) or hyoid bone (clinical landmark) to the skull base. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the sternohyoid muscle.

Level III. Middle Jugular Group

Lymph nodes located around the middle third of the internal jugular vein extending from the carotid bifurcation superiorly to the omohyoid muscle (surgical landmark), or cricothyroid notch (clinical landmark) inferiorly. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the sternohyoid muscle.

Level IV. Lower Jugular Group

Lymph nodes located around the lower third of the internal jugular vein extending from the omohyoid muscle superiorly to the clavicle inferiorly. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the sternohyoid muscle.

Level V. Posterior Triangle Group (Sublevels VA and VB)

This group comprises predominantly the lymph nodes located along the lower half of the spinal accessory nerve and the transverse cervical artery. The supraclavicular nodes are

also included in this group. The posterior boundary of the posterior triangle is the anterior border of the trapezius muscle, the anterior boundary of the posterior triangle is the posterior border of the sternocleidomastoid muscle, and the inferior boundary of the posterior triangle is the clavicle.

Level VI. Anterior (Central) Compartment

Lymph nodes in this compartment include the pre- and paratracheal nodes, precricoid (Delphian) node, and the perithyroidal nodes, including the lymph nodes along the recurrent laryngeal nerve. The superior boundary is the hyoid bone, the inferior boundary is the suprasternal notch, the lateral boundaries are the common carotid arteries, and the posterior boundary by the prevertebral fascia.

Level VII. Superior Mediastinal Lymph Nodes

Metastases at level VII are considered regional lymph node metastases; all other mediastinal lymph node metastases are considered distant metastases.

Lymph node groups removed from areas not included in the above levels, eg, scalene, suboccipital, and retropharyngeal, should be identified and reported from all levels separately. Midline nodes are considered ipsilateral nodes.

L. Lymph Nodes**Lymph Node Number**

Histological examination of a selective neck dissection specimen will ordinarily include 6 or more lymph nodes. Histological examination of a radical or modified radical neck dissection specimen will ordinarily include 10 or more lymph nodes in the untreated neck.

Measurement of Tumor Metastasis

The cross-sectional diameter of the largest metastasis in a lymph node containing metastatic tumor is measured in the gross specimen at the time of macroscopic examination or if necessary, on the histologic slide at the time of microscopic examination. There is conflicting data in the literature on the significance of the size of the largest metastatic lymph node on the risk of regional recurrence and a predictor of poor overall survival.²⁴ While the diameter of the largest positive lymph node may potentially serve as a predictor of outcome, it may not represent an independent predictor of outcome when other pathologic factors are considered.²⁴

M. Special Procedures for Lymph Nodes

At the current time, no additional special techniques are required other than routine histology for the assessment of nodal metastases. Immunohistochemistry and polymerase chain reaction (PCR) to detect isolated tumor cells are considered investigational techniques at this time.

N. Dysplasia of the Upper Aerodigestive Tract (UADT)

In contrast to the uterine cervix in which the nonkeratinizing ("classic") form of epithelial dysplasia most commonly results in a reproducible and clinically useful grading scheme of mild, moderate, and severe dysplasia (ie, carcinoma in situ), the majority of the UADT mucosal lesions fall under the designation of keratinizing dysplasias. The criteria for evaluating keratinizing dysplasias are less well defined, and the diagnosis of severe keratinizing (intraepithelial) dysplasia remains controversial. In particular, the definition of

severe dysplasia in the setting of keratosis is broader than the highly reproducible pattern seen in the uterine cervix and includes a microscopically heterogeneous group of lesions. In the setting of keratinizing dysplasia where surface maturation is retained with only partial replacement of the epithelium by atypical cells, severe dysplasia includes those lesions in which the epithelial alterations are so severe that there would be a high probability for the progression to an invasive carcinoma if left untreated. The evaluation of keratinizing dysplasia includes cellular abnormalities (ie, cytomorphology) and maturation abnormalities (ie, architectural alterations). At present, the preferred grading for keratinizing dysplasias of the UADT include mild, moderate, and severe dysplasia depending on the degree and extent of cellular and maturation alterations that are present.⁴⁰ Using the definition of carcinoma in situ (CIS) as applied to the uterine cervix requires loss of maturation of squamous epithelium; therefore, by this definition most keratotic lesion would not be classified as CIS because keratinization would represent a type of maturation. Therefore, the use of the specific term CIS in keratinizing dysplasias of the UADT has been questioned and is likely inappropriate in this setting; a more appropriate designation is keratinizing severe dysplasia.

Several points should be stressed relative to keratinizing dysplasia of the UADT:

- Invasive carcinoma can develop from keratinizing dysplasia that is limited in extent and in the absence of full thickness dysplasia (ie, “classic” carcinoma in situ) progression can occur even in the setting of lesions with atypia limited to the lower third (basal zone region) of the surface epithelium.
- Keratinizing severe dysplasia is often multifocal and frequently occurs adjacent to or near synchronous foci of invasive carcinoma.
- Keratinizing severe dysplasia has a rate of progression to invasive carcinoma that is greater than that of “classic” carcinoma in situ.
- A diagnosis of severe dysplasia requires therapeutic intervention, as well as clinical evaluation of the entire upper aerodigestive tract to exclude the possible presence of additional foci of dysplasia or carcinoma that may exist from field effect.

The end point for the grading of dysplasia is to convey to the clinician what is the potential biologic behavior of a given epithelial lesion. Relative to the oral cavity, clinical lesions include leukoplakia (white mucosal) lesions and erythroplakia (red mucosal) lesions. Leukoplakic lesions can be divided into homogenous (thick white lesion with smooth appearance) and nonhomogenous (thickened leukoplakia with irregular appearing surface). The clinical diagnosis of leukoplakia is not necessarily an indicator and does not necessarily correlate with histopathologic confirmation of an underlying dysplasia. The precancerous potential of leukoplakia is predicated on the fact that keratosis is associated with an increase risk of malignant transformation as compared to non-keratotic oral lesions, and that keratosis is present in a significant percentage (greater than one-third of cases) of oral carcinomas.²³ There is a correlation between the site of leukoplakia and the incidence of an associated dysplasia; the greatest frequency of epithelial dysplasia is found in leukoplakic lesions of the floor of mouth, tongue (lateral and ventral), and vermilion border of the lip. The incidence of malignant transformation for homogeneous leukoplakia is 3% and for non-homogeneous leukoplakia is 15%.⁴¹

In contrast to leukoplakia, the presence of erythroplakia is thought to correlate with a higher incidence of significant dysplasia (ie, moderate to severe dysplasia) and of carcinomas. Despite this association, not all erythroplakic lesions herald dysplasia/carcinoma; a subset will be attributed to inflammatory etiologies. Oral

erythroplakia occurs most commonly on the floor of the mouth, tongue (lateral and ventral), soft palate, tonsillar region, and retromolar region. Given the clinical appearance of erythroplakia, the surface epithelium is usually devoid of keratinization, and therefore these epithelial dysplasias are usually of the non-keratinizing ("classical") type.²³ In erythroplakic lesions, invasive carcinoma is present in 50% of cases, carcinoma in-situ in 40%, and mild to moderate dysplasia in 10%.⁴¹

O. Ancillary Testing

There is increasing evidence that human papillomavirus (HPV) plays a pathogenic role in a subset of head and neck cancers, termed HPV-associated head and neck squamous cell carcinoma (HPV-HNSCC).⁴² HPV, in particular the high-risk type 16 (HPV-16), is present in most oropharyngeal carcinomas, and for those oropharyngeal cancers positive for high risk HPV, HPV16 was detected in 93% of cases.⁴³ These carcinomas arise predominantly from the palatine tonsil and lingual tonsils of the oropharynx (i.e., tonsil or base of tongue) and are nonkeratinizing carcinomas characterized by a basaloid cell type.⁴⁴ Such oropharyngeal carcinomas may be small and clinically/radiographically difficult to detect, and may present as metastatic cancer to a cervical neck lymph node from an unknown primary site (See Note L in the Protocol for the Examination of Specimens from Patients with Carcinomas of the Pharynx). HPV-associated oropharyngeal carcinoma represents a unique subtype of HNSCC. HPV-positive oropharyngeal carcinomas frequently occur in patients with no known risk factors for HNSCC (ie, nonsmokers and nondrinkers), in younger aged patients, and is associated with a better outcome (better overall- and disease-specific survival). The International Agency for Research of Cancer (IARC) recently concluded that there is sufficient evidence that HPV16 is causal for a subset of oropharyngeal cancers.⁴⁵ A similar association has been suggested but not confirmed for oral cavity carcinoma.⁴⁵

References

1. Patel S, Shah JP. Part II: Head and neck sites. In: Edge SB, Byrd DR, Carducci MA, Compton CA, eds. *AJCC Cancer Staging Manual*. 7th ed. New York, NY: Springer; 2009.
2. Moore C, Kuhns JG, Greenberg RA. Thickness as prognostic aid in upper aerodigestive tract cancer. *Arch Surg*. 1986;121:1410-1414.
3. Pentenero M, Gandolfo S, Carrozzo M. Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. *Head Neck*. 2005;27:1080-1091.
4. Woolgar JA. Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. *Oral Oncol*. 2006;42:229-23
5. Gonzalez-Moles MA et al. Importance of tumour thickness measurement in prognosis of tongue cancer. *Oral Oncol*. 2002;38:394-297.
6. Barnes L, Eveson JW, Reichart P, et al, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon, France: IARC Press; 2005.
7. Crissman JD, Sakr WA. Squamous neoplasia of the upper aerodigestive tract. Intraepithelial and invasive squamous cell carcinoma. In: Pilch BZ, ed. *Head and Neck Surgical Pathology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
8. Mills SE, Gaffey MJ, Frierson HF, Jr. Tumors of the upper aerodigestive tract and ear. In: *Atlas of Tumor Pathology*. 3rd Series. Fascicle 26. Washington, DC: Armed Forces Institute of Pathology; 2000.

9. Ellis GL, Auclair PL. Salivary gland tumors: general considerations. In: Silverberg SG, ed. *Tumors of the Salivary Glands. Atlas of Tumor Pathology. Series 4. Fascicle 9.* Washington, DC: Armed Forces Institute of Pathology. Washington, DC. 2008.
10. Spiro RH, Huvos AG, Strong EW. Adenocarcinoma of salivary gland origin: clinicopathologic study of 204 patients. *Am J Surg.* 1982;144:423-431.
11. Szanto PA, Luna MA, Tortoledo ME, White RA. Histologic grading of adenoid cystic carcinoma of the salivary glands. *Cancer.* 1984;84:1062-1069.
12. Spiro RH, Thaler HT, Hicks WF, Kher UA, Huvos AG, Strong EW. The importance of clinical staging in minor salivary gland carcinoma. *Am J Surg.* 1991;162:330-336.
13. Kane WJ, McCaffrey TV, Olsen KD, Lewis JE. Primary parotid malignancies. A clinical and pathologic review. *Arch Otolaryngol Head Neck Surg* 1991;117:307-315.
14. Greiner TC, Robinson RA, Maves MD. Adenoid cystic carcinoma: a clinicopathologic study with flow cytometric analysis. *Am J Clin Pathol.* 1989;92:711-720.
15. Auclair PL, Goode RK, Ellis GL. Mucoepidermoid carcinoma of intraoral salivary glands. Evaluation and application of grading criteria in 143 cases. *Cancer.* 1992;69:2021-30.
16. Goode RK, Auclair PL, Ellis GL. Mucoepidermoid carcinoma of the major salivary glands: clinical and histopathologic analysis of 234 cases with evaluation of grading criteria. *Cancer.* 1998;82:1217-24.
17. Brandwein MS, Ivanov K, Wallace DI, et al. Mucoepidermoid carcinoma: a clinicopathologic study of 80 patients with special reference to histological grading. *Am J Surg Pathol.* 2001;25:835-45.
18. Brandwein M, Huvos AG, Dardick I, et al. Noninvasive and minimally invasive carcinoma ex mixed tumor. A clinicopathologic and ploidy study of 12 patients with major salivary tumors of low (or no?) malignant potential. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996;81:655-664.
19. Bradley PJ et al. Status of primary tumour surgical margins in squamous head and neck cancer: prognostic implications. *Curr Opin Otolaryngol Head Neck Surg.* 2007;15:74-81.
20. Laramore GE, Scott CB, al-Sarraf M, et al. Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034. *Int J Radiat Oncol Biol Phys.* 1992;23:705-713.
21. Zelefsky MJ, Harrison LB, Fass DE, Armstrong JG, Shah JP, Strong EW. Postoperative radiation therapy for squamous cell carcinomas of the oral cavity and oropharynx: impact of therapy on patients with positive surgical margins. *Int J Radiat Oncol Biol Phys.* 1993;25:17-21.
22. Barnes L. Diseases of the larynx, Hypopharynx, and trachea. In: Barnes E, ed. *Surgical pathology of the head and neck.* Third edition. New York: Informa; 2009.
23. Wenig BM. Epithelial precursor lesions. in: Wenig BM, ed. *Atlas of Head and Neck Pathology.* 2nd ed. Philadelphia, PA: W.B. Saunders- Elsevier; 2008.
24. Smith BD, Haffty BG. Prognostic factors in patients with head and neck cancer. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and neck cancer. A multidisciplinary approach.* Third edition. Philadelphia. Lippincott Williams & Wilkins. 2009:51-75.
25. Fagan JJ, Collins B, Barnes L, et al. Perineural invasion in squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 1998;124:637-640.

26. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;350:1937-1944.
27. Bernier J, Dumenige C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;350:1945-1952.
28. Woolgar J, Triantafyllou A. Neck dissections: a practical guide for the reporting histopathologist. *Curr Diag Pathol*. 2007;13:499-511.
29. Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Regional lymph node involvement and its significance in the development of distant metastases in head and neck carcinoma. *Cancer*. 1993;71:452-456.
30. Johnson JT, Barnes EL, Meyers EN, et al. The extracapsular spread of tumors in cervical node metastases. *Head Neck Surg*. 1981;107:725-729
31. Woolgar JA, Rogers SN, Lowe D, Brown JS, Vaughn ED. Cervical lymph node metastasis in oral cancer: the importance of even microscopic extracapsular spread. *Oral Oncol*. 2003;39:130-137.
32. Sobin LH, Gospodarowicz MK, Wittekind CH, eds *UICC TNM Classification of Malignant Tumors*. 7th ed. New York, NY: Wiley-Liss; in press.
33. Martinez-Madrigel F, Pineda-Daboin K, Casiraghi O, Luna MA. Salivary gland tumors of the mandible. *Ann Diagn Pathol*. 2000;4:347-353.
34. Robbins KT, et al. Neck dissection classification update. *Arch Otolaryngol Head Neck Surg*. 2002;128:751-758.
35. Robbins TK, et al. Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg*. 2008;134:536-538
36. Robbins T, Medina JE, Wolfe GT, Levine PA, Sessions RB, Pruet CW. Standardizing neck dissection terminology: official report of the academy's committee for head and neck surgery and oncology. *Arch Otolaryngol Head Neck Surg*. 1991;117:601-605.
37. Wittekind C, Greene FL, Henson DE, Hutter RVP, Sobin LH, eds. *TNM Supplement: A Commentary on Uniform Use*. 3rd ed. New York: Wiley-Liss; 2003.
38. Singletary SE, Greene FL, Sobin LH. Classification of isolated tumor cells: clarification of the 6th edition of the American Joint Committee on Cancer Staging Manual. *Cancer*. 2003;90(12):2740-2741.
39. Flint PW, et al, eds. *Cummings Otolaryngology: Head and Neck Surgery*. 4th ed. Philadelphia, PA: Saunders; 2010.
40. Gale N, Pilch BZ, Sidransky D, Westra WH, Califano J. Epithelial precursor lesions. In: Barnes L, Eveson JW, Reichart P et al, eds. *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours*. Lyon, France: IARC Press; 2005.
41. Slootweg PJ, Merks TMAW. Premalignant lesions of the oral cavity. In: Barnes L, ed. *Surgical Pathology of the Head and Neck*. 3rd ed. New York, NY: Informa Healthcare; 2009.
42. Gillison ML. Human Papillomavirus and Prevention and Therapy of Head and Neck Cancer. In: Harrison LB, Sessions RB, Waun KH, eds. *Head and Neck Cancer: A Multidisciplinary Approach*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009.
43. Kreimer AR, Clifford GM, Boyle P, et al. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. *Cancer Epidemiol Biomarkers Prev*. 2005;14:467-475.

44. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst.* 2000;92:709-720.
45. IACR Monographs on the Evaluation of Carcinogenic Risks to Humans. *Human Papillomavirus: IACR Monographs Volume 90*. Geneva, Switzerland: WHO Press; 2007: 1-636.