Protocol for the Examination of Specimens From Patients With Carcinomas of the Larynx

Protocol applies to all invasive carcinomas of the larynx, including supraglottis, glottis, and subglottis. Mucosal malignant melanoma is included. Lymphomas and sarcomas are not included.

Based on AJCC/UICC TNM, 7th edition
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Procedures
- Biopsy
- Resection

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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.

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CAP Larynx Protocol Revision History

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

Version: Larynx 3.2.0.0

Summary of Changes
The following changes have been made since the November 2011 release.

Incisional Biopsy, Excisional Biopsy, Resection

Procedure
"Stripping (glottis)" was changed to "Endolaryngeal excision."

Laryngectomy
"Required only if applicable" was added to this reporting element.

Tumor Laterality/Tumor Site
"Transglottic: Yes/No" was moved from Tumor Laterality to Tumor Site, as follows.

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

Tumor Site (select all that apply) (Note A)
___ Larynx, supraglottis
    ___ Epiglottis
        ___ Lingual aspect
        ___ Laryngeal aspect
    ___ Aryepiglottic folds
    ___ Arytenoid(s)
    ___ False vocal cord
    ___ Ventricle
___ Larynx, glottis
    ___ True vocal cord
    ___ Anterior commissure
    ___ Posterior commissure
___ Larynx, subglottis
___ Other (specify): _____
___ Not specified

Transglottic:
___ Yes
___ No

Explanatory Notes
Scope of Guidelines
The word "checklist(s)" was changed to "case summary(ies)" or "protocol" as appropriate.

Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

LARYNX (SUPRAGLOTTIS, GLOTTIS, SUBGLOTTIS): Incisional Biopsy, Excisional Biopsy, Resection

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)
___ Larynx, supraglottis
___ Larynx, glottis
___ Larynx, subglottis
___ Other (specify): _____
___ Not specified

Received:
___ Fresh
___ In formalin
___ Other (specify): _____

Procedure (select all that apply)
___ Incisional biopsy
___ Excisional biopsy
___ Resection
- ___ Endolaryngeal excision
- ___ Transoral laser excision (glottis)
- ___ Supraglottic laryngectomy
- ___ Supracricoid laryngectomy
- ___ Vertical hemilaryngectomy (specify side): _____
- ___ Partial laryngectomy (specify type): _____
- ___ Total laryngectomy

___ Neck (lymph node) dissection (specify): _____
___ Other (specify): _____
___ Not specified

+ Specimen Integrity
+ ___Intact
+ ___Fragmented

Laryngectomy (required only if applicable)
___ Open
___ Unopened

Specimen Size
Greatest dimensions: ___ x ___ x ___ cm
+ Additional dimensions (if more than one part): ___ x ___ x ___ cm

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

Tumor Site (select all that apply) (Note A)
___ Larynx, supraglottis
    ___ Epiglottis
        ___ Lingual aspect
        ___ Laryngeal aspect
    ___ Aryepiglottic folds
    ___ Arytenoid(s)
    ___ False vocal cord
    ___ Ventricle
___ Larynx, glottis
    ___ True vocal cord
    ___ Anterior commissure
    ___ Posterior commissure
___ Larynx, subglottis
___ Other (specify): _____
___ Not specified

Transglottic:
___ Yes
___ No

Tumor Focality
___ Single focus
___ Bilateral
___ Multifocal (specify): _____

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

+ Tumor Description (select all that apply)
+ Gross subtype:
+ ___ Polypoid
+ ___ Exophytic
+ ___ Endophytic
+ ___ Ulcerated
+ ___ Sessile
+ ___ Other (specify): _____

+ **Macroscopic Extent of Tumor**
+ Specify: _____

+ 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.

Histologic Type (select all that apply) (Note B)
___ Squamous cell carcinoma, conventional

Variants of Squamous Cell Carcinoma
___ Acantholytic squamous cell carcinoma
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Papillary squamous cell carcinoma
___ Spindle cell squamous cell carcinoma
___ Verrucous carcinoma

___ Giant cell carcinoma
___ Lymphoepithelial carcinoma (non-nasopharyngeal)

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

Carcinomas of Minor Salivary Glands
___ Adenoid cystic carcinoma
___ Mucoepidermoid carcinoma
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Other (specify): _____

___ Other carcinoma (specify): _____
___ Carcinoma, type cannot be determined

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

+ Microscopic Tumor Extension
+ Specify: _____

Margins (select all that apply) (Notes D and E)
___ 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 D)
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 D)
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 F)
___ Not identified
___ Present
___ Indeterminate

Lymph Nodes, Extranodal Extension (Note G)
___ Not identified
___ Present
___ Indeterminate

Pathologic Staging (pTNM) (Note H)

Note: The phrases in italics include clinical findings required for AJCC staging. This clinical information may not be available to the pathologist. However, if known, these findings should be incorporated into the pathologic staging.

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

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ

For All Carcinomas Excluding Mucosal Malignant Melanoma

Primary Tumor (pT): Supraglottis
___ pT1: Tumor limited to one subsite of supraglottis *with normal vocal cord mobility*
___ pT2: Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) *without fixation of the larynx*
___ pT3: Tumor limited to larynx *with vocal cord fixation* and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
___ pT4a: Moderately advanced local disease. Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of tongue, strap muscles, thyroid, or esophagus)
___ pT4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Primary Tumor (pT): Glottis
___ pT1: Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) *with normal mobility*
___ pT1a: Tumor limited to one vocal cord
___ pT1b: Tumor involves both vocal cords
___ pT2: Tumor extends to supraglottis and/or subglottis *and/or with impaired vocal cord mobility*
___ pT3: Tumor limited to the larynx *with vocal cord fixation* and/or invades paraglottic space and/or minor thyroid cartilage erosion (eg, inner cortex) (Note H)
___ pT4a: Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus) (Note H)
___ pT4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Primary Tumor (pT): Subglottis
___ pT1: Tumor limited to subglottis
___ pT2: Tumor extends to vocal cord(s) *with normal or impaired mobility*
___ pT3: Tumor limited to larynx *with vocal cord fixation*
___ pT4a: Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
___pT4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Regional Lymph Nodes (pN)[#] (Notes I through L)
___ 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
___ 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

___ No nodes submitted or found

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

Number of Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): _____
+ Size (greatest dimension) of the largest positive lymph node: ____ (Note K)

[#] 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): _____

For Mucosal Malignant Melanoma

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 M)
+ ___ Mild
+ ___ Moderate
+ ___ Severe (carcinoma in situ)
+ ___ Non-keratinizing dysplasia (Note M)
+ ___ Mild
+ ___ Moderate
+ ___ Severe (carcinoma in situ)
+ ___ Inflammation (specify type): _____
+ ___ Squamous metaplasia
+ ___ Epithelial hyperplasia
+ ___ Colonization
+ ___ Fungal
+ ___ Bacterial
+ ___ Other (specify): _____

+ Ancillary Studies (Note N)
+ Specify type(s): _____
+ Specify result(s): _____

+ **Clinical History (select all that apply)**
+ ___ Neoadjuvant therapy
+ ___ Yes (specify type): _____
+ ___ No
+ ___ Indeterminate
+ ___ Other (specify): _____

+ Comment(s)

Explanatory Notes

Scope of Guidelines
The reporting of oral cancer including the lip is facilitated by the provision of a case summary illustrating the features required for comprehensive patient care. However, there are many cases in which the individual practicalities of applying such a case summary may not be straightforward. Common examples include finding the prescribed number of lymph nodes, trying to determine the levels of the radical neck dissection, and determining if isolated tumor cells in a lymph node represent metastatic disease. Case summaries have evolved to include clinical, radiographic, morphologic, immunohistochemical, and molecular results in an effort to guide clinical management. Adjuvant and neoadjuvant therapy can significantly alter histologic findings, making accurate classification an increasingly complex and demanding task. This case summary 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 protocol is to be used as a guide and resource, an adjunct to diagnosing and managing cancers of the oral cavity in a standardized manner. It should not be used as a substitute for dissection or grossing techniques and does not give histologic parameters to reach the diagnosis. Subjectivity is always a factor, and elements listed are not meant to be arbitrary but are meant to provide uniformity of reporting across all the disciplines that use the information. It is a foundation of practical information that will help to meet the requirements of daily practice to benefit both clinicians and patients alike.

A. Anatomical Sites and Subsites for the Larynx (Figure 1)

Supraglottis
- Epilarynx, including marginal zone
  - Suprahyoid epiglottis, including tip, lingual (anterior) and laryngeal surfaces
  - Aryepiglottic fold, laryngeal aspect
  - Arytenoid
- Supraglottis, excluding epilarynx
  - Infrahyoid epiglottis
  - Ventricular bands (false cords)
  - Ventricle

Glottis
- Vocal cords
- Anterior commissure
- Posterior commissure

Subglottis

The protocol applies to all carcinomas arising at these sites.[1] The piriform sinus represents part of the hypopharynx which expands bilaterally and forward around the sides of the larynx and lies between the larynx and the thyroid cartilage. Cancers of the piriform sinus are included in the protocol on pharynx cancers.

Anatomic Compartments (Figure 1)
The anatomic compartments of the larynx include:

1. Supraglottic larynx extending from the tip of the epiglottis to a horizontal line passing through the apex of the ventricle; structures included in this compartment are the epiglottis (lingual and laryngeal aspects), aryepiglottic folds, arytenoids, false vocal cords and the ventricle.

2. Glottic region, which extends from the ventricle to approximately 0.5 to 1.0 cm below the free level of the true vocal cord and includes the anterior and posterior commissures and the true vocal cord.

3. Subglottic larynx, which extends approximately 1.0 cm below the level of the true vocal cord to the inferior rim of the cricoid cartilage.

4. The paraglottic space is a potential space deep to the ventricles and saccules filled with adipose tissue and connective tissue (Figure 2). It is bounded by the conus elasticus inferiorly, the thyroid cartilage laterally, the quadrangular membrane medially, and the piriform sinus posteriorly.[2] Like the paraglottic space, the preepiglottic space is filled with adipose tissue and connective tissue (Figure 3); it is triangular in shape and is bounded by the thyroid cartilage and thyrohyoid membrane anteriorly, the epiglottis and thyroepiglottic ligament posteriorly, and the hyoepiglottic ligament at its base (Figures 1 and 2).[2] The paraglottic and preglottic spaces contain lymphatics and blood vessels but no lymph nodes.[2]

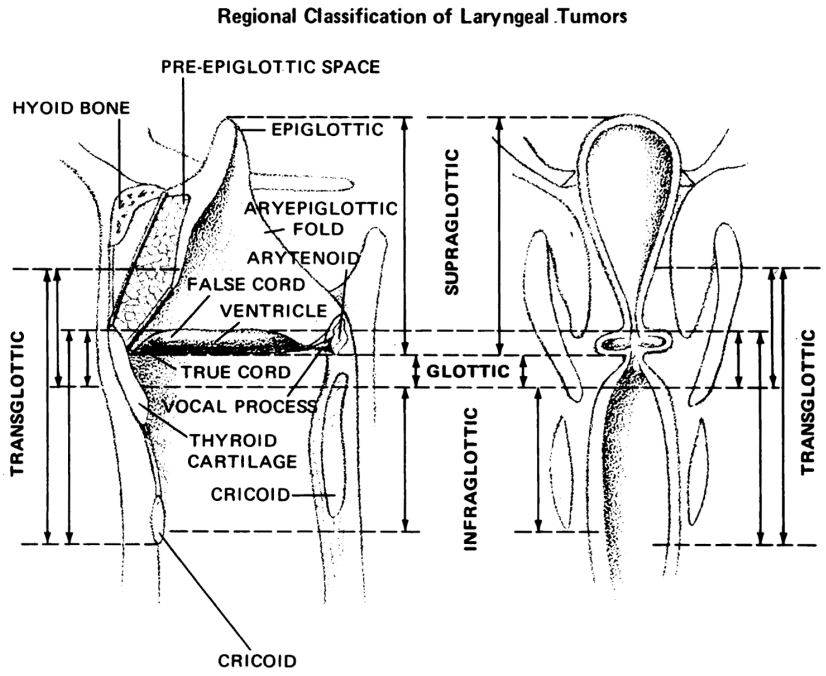

Figure 1. Anatomic compartments of the larynx. From Cocke EW Jr, Wang CC. Part I - Cancer of the larynx: selecting optimum treatment. *CA Cancer J Clin.* 1976;26:194-200. Figure by J.H. Ogura, MD.

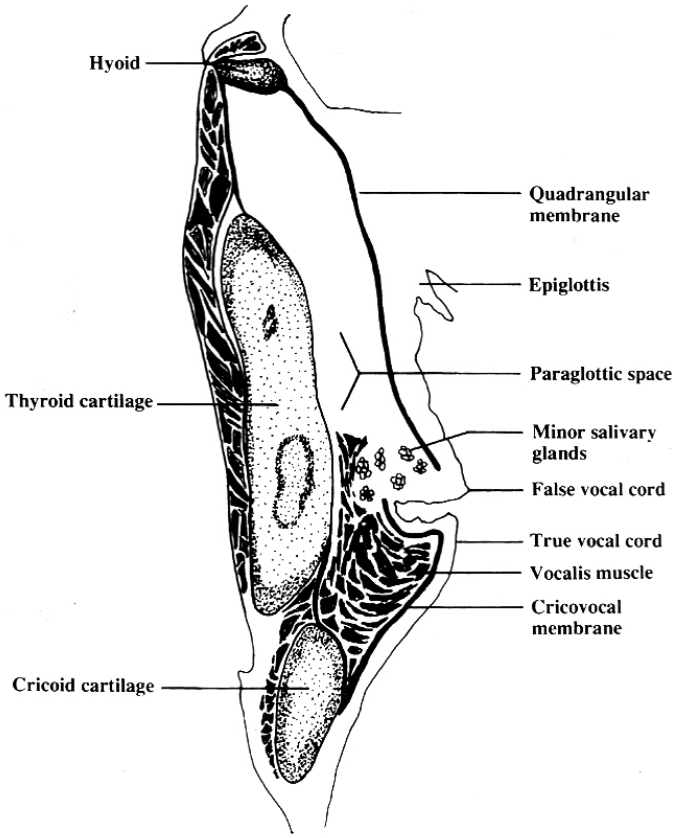

Figure 2. The paraglottic space. From *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours.* Lyon, France: IARC Press; 2005. Reproduced with permission.

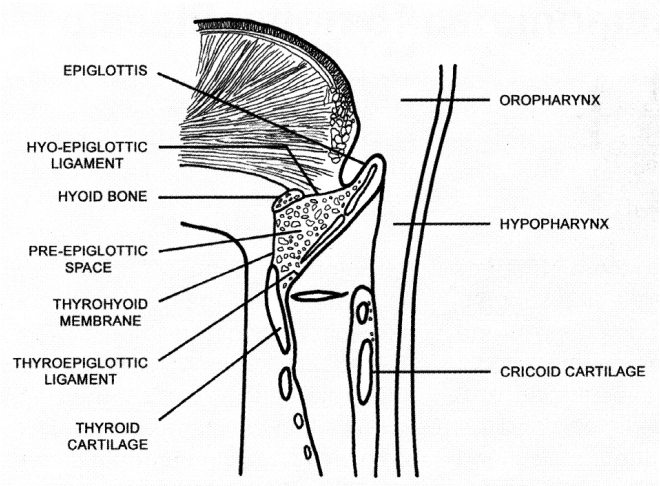

Figure 3. The pre-epiglottic space. From *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours.* Lyon, France: IARC Press; 2005. Reproduced with permission.

Site-Specific Carcinomas

1. Supraglottic squamous cell carcinoma represents a squamous cell carcinoma that involves the structures of the supraglottic larynx, including the epiglottis (laryngeal and lingual surfaces), aryepiglottic folds, arytenoids, false vocal cords and ventricles.

2. Glottic squamous cell carcinoma represents a squamous cell carcinoma that involves the structures of the glottis, including the true vocal cords, and the anterior and posterior commissures.

3. Subglottic squamous cell carcinoma represents a squamous cell carcinoma that involves the subglottis which begins 1 cm below the apex of the ventricle to its inferior border represented by the rim of the cricoid cartilage.

4. Transglottic carcinomas represent a carcinoma that crosses the ventricles in a vertical direction arising in either the glottic or supraglottic larynx

B. Histological Type
A modification of the World Health Organization (WHO) classification of carcinomas of the larynx is shown below.[3] This list may not be complete. This protocol applies to carcinomas and melanomas and does not apply to lymphomas or sarcomas.

Carcinomas of Larynx
Squamous cell carcinoma (conventional)
Squamous cell carcinoma, variant (in alphabetical order)
- Acantholytic squamous cell carcinoma
- Adenosquamous carcinoma
- Basaloid squamous cell carcinoma
- Papillary squamous cell carcinoma
- Spindle cell squamous carcinoma
- Verrucous carcinoma

Giant cell carcinoma
Lymphoepithelial carcinoma

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[#]

[#] Represents a carcinoma showing combined features of small cell neuroendocrine carcinoma associated with a squamous or adenocarcinomatous component.[4]

Mucosal malignant melanoma

Carcinomas of Minor Salivary Glands
Adenoid cystic carcinoma
Mucoepidermoid carcinoma
Other (specify type)

C. 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 one grade of differentiation, the surgical report must designate both the highest and the most prevalent tumor grades.[5,6]

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.[7-11] Further, there is often a positive correlation between histologic grade and clinical stage. With some exceptions, histologic grading is predicated on cytomorphologic 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.[7] Those adenoid cystic carcinomas showing 30% or greater of solid growth pattern are considered to be histologically high-grade carcinomas.[7,9,12] The histologic grading of mucoepidermoid carcinoma includes a combination of growth pattern characteristics (eg, cystic, solid, neurotropism) and cytomorphologic findings (eg, anaplasia, mitoses, necrosis).[13-15]

D. 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.[16-18] The ability to control surgical margins by transoral laser excision is, at best, uncertain. By the nature of the excised tissues precluding orientation and margin designation/identification, there is no need for the pathology report to include the margin status in laser excised specimens. Reporting of surgical margins for carcinomas of the minor salivary glands should follow those used for squamous cell carcinoma of oral cavity.

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 invasive carcinoma.[19] Due to the fact that invasive carcinoma develops 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,[19] 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.[20] 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.

E. 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.

F. Perineural Invasion
The presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.[21] 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.[21] Further, perineural invasion is associated with decrease in disease-specific survival and overall survival.[21] 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.[21] The relationship between perineural invasion and prognosis is independent of nerve diameter.[22] 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).[23,24] Given the significance relative to prognosis and treatment, perineural invasion is a required data element in the reporting of head and neck cancers.

G. 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.[25-28]

H. 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 larynx cancer.[1,29] Of note in the 7th edition of the AJCC staging of head and neck cancers[1] 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). Relative to supraglottic and glottic cancers, the

determination between a T3 cancer with "minor thyroid cartilage erosion" versus a T4a cancer with "invasion through thyroid cartilage" can be problematic as there is no specific definition whether "invasion through thyroid cartilage" means complete infiltration through and through the cartilage or whether tumors invading short of completely through the thyroid cartilage (eg, half way through, other) qualify as a pT4a cancer. When confronted with this issue, review of the operative report and imaging studies, as well as direct communication with the surgeon may provide insight or consensus of opinion. Generally, if the tumor invades at least into the center of the cartilage but not "through," most authorities would stage such a lesion as a T4a cancer.

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]

For All Carcinomas Excluding Mucosal Malignant Melanoma

Primary Tumor: Supraglottis

TX Cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor limited to one subsite of supraglottis *with normal vocal cord mobility*
T2 Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (eg, mucosa of base of tongue, vallecula, medial wall of pyriform sinus) *without fixation of the larynx*
T3 Tumor limited to larynx *with vocal cord fixation* and/or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space, and/or minor thyroid cartilage erosion (eg, inner cortex)
T4a Moderately advanced local disease. Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of tongue, strap muscles, thyroid, or esophagus)
T4b Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Primary Tumor: Glottis

TX Cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) *with normal mobility*
T1a Tumor limited to one vocal cord
T1b Tumor involves both vocal cords
T2 Tumor extends to supraglottis and/or subglottis *and/or with impaired vocal cord mobility*
T3 Tumor limited to the larynx *with vocal cord fixation* and/or invasion of paraglottic space, and/or inner cortex of thyroid cartilage

T4a Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Primary Tumor: Subglottis
TX Cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor limited to subglottis
T2 Tumor extends to vocal cord(s) *with normal or impaired mobility*
T3 Tumor limited to larynx *with vocal cord fixation*
T4a Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (eg, trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

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
N2 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
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 Melanoma

Primary 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 present

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
Supraglottis. Normal vocal cord mobility (T1), fixation of the larynx (T2), and vocal cord fixation (T3) may only be determined clinically.

Glottis. Normal vocal cord mobility (T1), impaired vocal cord mobility (T2), and vocal cord fixation (T3) may only be determined clinically.

Subglottis. Normal or impaired vocal cord mobility (T2) and vocal cord fixation (T3) may only be determined clinically.

Stage Groupings: Supraglottis, Glottis, and Subglottis - 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	N1	M0
	T2	N1	M0
	T3	N0,N1	M0
Stage IVA	T1,T2,T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	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 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.

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).

I. 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 4)[30-32]
5. Extended radical neck dissection, as specified by the surgeon

J. 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.[29,33,34]

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 4.[35]

Figure 4. 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 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 stylohyoid 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.

K. 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.[21] 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.[21]

L. Special Procedures for Lymph Nodes

The risk of regional (cervical neck) nodal spread from cancers of the pharynx is high.[1] At the current time, no additional special techniques are required other than routine histology for the assessment of nodal metastases. Immunohistochemistry and PCR to detect isolated tumor cells are considered investigational techniques at this time.

M. Dysplasia of the Upper Aerodigestive Tract (UADT)

In contrast to the uterine cervix in which the nonkeratinizing ("classic") form of epithelial dysplasia is most common resulting 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.[36] 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 cannot be CIS because keratosis shows maturation of the squamous epithelium. 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 develops from dysplasia limited in extent including only to the lower third (basal zone region) of the surface epithelium in the absence of full thickness dysplasia (ie, "classic" carcinoma in situ).
- 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. Keratotic epithelium without dysplasia carries a very low risk of developing subsequent carcinoma with reported incidences of 4% to 5%.[19] In contrast, keratotic epithelium with dysplasia is associated with an increased risk for the subsequent progression or development of premalignant or overtly carcinomatous changes varying from 16% to 19% of cases.[19] This risk of malignant transformation represents an increase of from 3 to 5 times as compared to carcinoma arising in keratotic lesions without atypia.[19] The risk for progression to invasive carcinoma in lesions diagnosed as keratosis with dysplasia varies depending on the degree of atypia/dysplasia[19]:
- for mild dysplasia – approximately 6%
- for moderate dysplasia – approximately 20%
- for severe dysplasia – approximately 24%

Given the absence of statistical significance in progression to invasive carcinoma between keratinizing moderate dysplasia and severe dysplasia, there may be merits in employing the 2-grade system currently in use for uterine cervical dysplasias (Bethesda classification) for keratinizing dysplasias of the UADT to include:
- Low-grade squamous intraepithelial lesion/neoplasia for mild dysplasia
- High-grade squamous intraepithelial lesion/neoplasia for moderate and severe dysplasias

Such a grading scheme for upper aerodigestive tract keratinizing dysplasias is not currently established or universally accepted.

N. Ancillary Testing

There is increasing evidence that human papillomavirus (HPV) plays an pathogenic role in a subset of head and neck cancers, termed HPV-associated head and neck squamous cell carcinoma (HPV-HNSCC).[37] HPV, in particular the high risk type 16 (HPV-16), is present in most oropharyngeal carcinomas.[38] These carcinomas arise predominantly from the palatine tonsil and lingual tonsils of the oropharynx (ie, tonsil or base of tongue) and are nonkeratinizing carcinomas characterized by a basaloid cell type.[39] The International Agency for Research of Cancer (IARC) recently concluded that there is sufficient evidence that HPV-16 is causal for a subset of oropharyngeal cancers.[40] A similar association has been suggested but not confirmed for oral cavity carcinoma.[40] To date, there are no data linking HPV with laryngeal carcinoma, and the utility of testing for the presence of HPV in laryngeal carcinomas is unproven.

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