# Protocol for the Examination of Specimens From Patients With Cancers of the Larynx

**Version:** 4.2.0.0
**Protocol Posting Date:** June 2023
**CAP Laboratory Accreditation Program Protocol Required Use Date:** March 2024
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

**For accreditation purposes, this protocol should be used for the following procedures AND tumor types:**

| Procedure | Description |
|---|---|
| Resection | Includes specimens designated larynx, supraglottis, glottis, and subglottis. |
| **Tumor Type** | **Description** |
| Carcinoma | Includes squamous cell carcinoma, neuroendocrine carcinoma, and minor salivary gland carcinoma |
| Mucosal Melanoma | |

**This protocol is NOT required for accreditation purposes for the following:**

| Procedure |
|---|
| Biopsy |
| Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy) |
| Cytologic specimens |
| Squamous cell carcinoma in situ (Tis) |

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

| Tumor Type |
|---|
| Hypopharyngeal squamous cell carcinoma (consider the Pharynx protocol) |
| Sarcoma (consider the Soft Tissue protocol) |
| Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols) |

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With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
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**Accreditation Requirements**

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

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

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

**Synoptic Reporting**

All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location

Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report ie, all required elements must be in the synoptic portion of the report in the format defined above.

**Summary of Changes**

**v 4.2.0.0**

- WHO 5th edition update to content and Explanatory Notes C, D, H, and J
- pTNM Classification update to content and Explanatory Note I
- LVI question update from “Lymphovascular Invasion” to “Lymphatic and/or Vascular Invasion”
- Explanatory Note B update to address transglottic carcinoma extension
- Cover page update: Squamous cell carcinoma in-situ (Tis) is not required for accreditation

**Reporting Template**

**Protocol Posting Date: June 2023**
**Select a single response unless otherwise indicated.**

**CASE SUMMARY: (LARYNX (SUPRAGLOTTIS, GLOTTIS, SUBGLOTTIS))**
**Standard(s)**: AJCC-UICC 8

**SPECIMEN (Note A)**

**Procedure (select all that apply)**
___ Excision
___ 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

**TUMOR**

**Tumor Focality**
___ Unifocal
___ Multifocal: _____
___ Cannot be determined: _____

**Multiple Primary Sites (e.g., anterior epiglottis and glottis)**
___ Not applicable (no additional primary site(s) present)
___ Present: _____
*Please complete a separate checklist for each primary site*

**Tumor Site (Note B) (select all that apply)**
___ Larynx, supraglottis: _____
**+Tumor Subsite (select all that apply)**
___ Epiglottis, lingual aspect
___ Epiglottis, laryngeal aspect
___ Aryepiglottic folds
___ Arytenoid(s)
___ False vocal cord
___ Ventricle
___ Larynx, glottis: _____
**+Tumor Subsite (select all that apply)**
___ True vocal cord

___ Anterior commissure
___ Posterior commissure
**+Subglottic Extension**
___ Not identified
___ Present
___ Larynx, subglottis: _____
___ Other (specify): _____
___ Not specified

**Transglottic Extension**
___ Not identified
___ Present

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

**Tumor Size**
___ Greatest dimension in Centimeters (cm): _____ cm
**+Additional Dimension in Centimeters (cm): ____ x ____ cm**
___ Cannot be determined (explain): _____

**Histologic Type (Note C)**
*Squamous cell carcinoma and subtypes*
___ Squamous cell carcinoma and subtypes
*Select all that apply*
___ Squamous cell carcinoma, conventional (keratinizing)
___ Squamous cell carcinoma, nonkeratinizing
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Papillary squamous cell carcinoma
___ Spindle cell squamous carcinoma
___ Verrucous carcinoma
___ Carcinoma cuniculatum
___ Lymphoepithelial carcinoma (non-nasopharyngeal)
*Carcinomas of minor salivary glands*
___ Carcinoma ex pleomorphic adenoma
**Architectural Type**
*Required in addition to carcinoma type*
___ Carcinoma ex pleomorphic adenoma, minimally invasive
___ Carcinoma ex pleomorphic adenoma, invasive
___ Carcinoma ex pleomorphic adenoma, intracapsular (noninvasive)
___ Carcinoma ex pleomorphic adenoma, extent cannot be determined
**Malignant Component Histologic Type(s) (select all that apply)**
___ Intraductal pattern

___ Salivary duct carcinoma
___ Epithelial-myoepithelial carcinoma
___ Myoepithelial carcinoma
___ Carcinosarcoma (sarcomatoid carcinoma)
___ Other (specify): _____
___ Mucoepidermoid carcinoma
___ Adenoid cystic carcinoma tubular / cribriform
*# If multiple patterns are present, select predominant pattern unless the solid pattern is greater than 30%, in which case the user should select a solid pattern.*
___ Adenoid cystic carcinoma, solid#
**+Percentage of Solid Component for Adenoid Cystic Carcinoma**
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined
___ Acinic cell carcinoma
___ Secretory carcinoma
___ Polymorphous adenocarcinoma, conventional
___ Polymorphous adenocarcinoma, cribriform subtype
**+Percentage of Papillary Component for Polymorphous Adenocarcinoma**
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined
**+Percentage of Cribriform Component for Polymorphous Adenocarcinoma**
___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined
___ Salivary duct carcinoma
___ Epithelial-myoepithelial carcinoma
___ Hyalinizing clear cell carcinoma
___ Microsecretory adenocarcinoma
___ Intraductal carcinoma (specify subtype): _____
___ Basal cell adenocarcinoma
___ Carcinosarcoma
___ Mucinous adenocarcinoma, not otherwise specified
___ Mucinous adenocarcinoma, intraductal papillary mucinous neoplasia subtype
___ Mucinous adenocarcinoma, colloid / signet ring subtype
___ Sclerosing microcystic adenocarcinoma
___ Lymphoepithelial carcinoma
___ Myoepithelial carcinoma
___ Sebaceous adenocarcinoma
___ Sialoblastoma
*Neuroendocrine*
___ Neuroendocrine tumor, grade 1
___ Neuroendocrine tumor, grade 2
___ Neuroendocrine tumor, grade 3
___ Neuroendocrine carcinoma, small cell type
___ Neuroendocrine carcinoma, large cell type

___ Combined (or composite) neuroendocrine carcinoma

**Type of Combined Histology# (select all that apply)**

*# Please note that the user must select at least one neuroendocrine type and at least one carcinoma type from the list below.*

___ Squamous cell carcinoma: _____

___ Adenocarcinoma: _____

___ Neuroendocrine carcinoma, small cell type

___ Neuroendocrine carcinoma, large cell type

___ Other (specify): _____

*Mucosal melanoma*

___ Mucosal melanoma

*Other*

___ Other histologic type not listed (specify): _____

___ Carcinoma, type cannot be determined: _____

**+Histologic Type Comment: _____**

**Histologic Grade# (Note D)**

*# Required for non-salivary, non-neuroendocrine carcinomas*

___ Not applicable

___ G1, well differentiated

___ G2, moderately differentiated

___ G3, poorly differentiated

___ Other (specify): _____

___ GX, cannot be assessed: _____

**Grade / Intrinsic Biologic Potential#**

*# Required for salivary carcinomas*

___ Not applicable

___ Low

___ Intermediate

___ High / High-grade transformation

___ Cannot be assessed: _____

**+Tumor Extent (specify other structures / spaces involved): _____**

**Lymphatic and / or Vascular Invasion**

___ Not identified

___ Present

___ Cannot be determined: _____

**Perineural Invasion (Note E)**

___ Not identified

___ Present

**+Extent / Type of Perineural Invasion**

___ Intratumoral

___ Extratumoral

___ Intraneural

**+Specify Diameter of Involved Nerve in Millimeters (mm): _____ mm**

___ Cannot be determined: _____

**+Tumor Comment: _____**

**MARGINS (Notes F,G)**

**Margin Status for Invasive Tumor**
___ All margins negative for invasive tumor
**Distance from Invasive Tumor to Closest Margin**
*Specify in Millimeters (mm)*
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
**Closest Margin(s) to Invasive Tumor (use orientation when provided)**
___ Specify location(s) of closest margin(s): _____
___ Cannot be determined
**+Other Close Margin(s) to Invasive Tumor**
___ Specify location(s) and distance(s) of other close margin(s): _____
___ Cannot be determined
___ Invasive tumor present at margin
**Margin(s) Involved by Invasive Tumor (per orientation)**
___ Specify involved margin(s): _____
___ Cannot be determined: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

**Margin Status for Noninvasive Tumor (High-grade Dysplasia)**
*Margin status for noninvasive tumor is required only for squamous cell carcinoma when closer than invasive tumor.*
___ Not applicable
___ All margins negative for noninvasive tumor
**+Distance from Noninvasive Tumor to Closest Margin**
*Specify in Millimeters (mm)*
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
**+Closest Margin(s) to Noninvasive Tumor (use orientation when provided)**
___ Specify location(s) of closest margin(s): _____
___ Cannot be determined
___ High-grade dysplasia / in situ disease present at margin
**Margin(s) Involved by Noninvasive Tumor (per orientation)**
___ Specify involved margin(s): _____
___ Cannot be determined: _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

**+Margin Comment: _____**

**REGIONAL LYMPH NODES (Note H)**

**Regional Lymph Node Status**
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)

**Number of Lymph Nodes with Tumor**
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined

**Laterality of Lymph Node(s) with Tumor (not applicable for mucosal melanoma)**
___ Not applicable
___ Ipsilateral (including midline): _____
___ Contralateral: _____
___ Bilateral: _____
___ Cannot be determined: _____

**+Nodal Site(s) with Tumor (select all that apply)**
___ Intra / periparotid
___ Level I
___ Level II
___ Level III
___ Level IV
___ Level V
___ Other (specify): _____
___ Cannot be determined: _____

**Size of Largest Nodal Metastatic Deposit (not applicable for mucosal melanoma)**
*Specify in Centimeters (cm)*
___ Not applicable
___ Exact size: _____ cm
___ At least: _____ cm
___ Greater than: _____ cm
___ Less than: _____ cm
___ Other (specify): _____
___ Cannot be determined

**Extranodal Extension (ENE) (not applicable for mucosal melanoma) (Note H)**
___ Not applicable
___ Not identified
___ Present

**+Distance of ENE from Lymph Node Capsule**

*Specify in Millimeters (mm)*
___ Exact distance: _____ mm
___ Greater than 2 mm (macroscopic ENE)
___ Less than or equal to 2 mm (microscopic ENE)
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
___ Cannot be determined: _____
___ Other (specify): _____
___ Cannot be determined: _____

**Number of Lymph Nodes Examined**
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined: _____

**+Regional Lymph Node Comment: _____**

**DISTANT METASTASIS**

**Distant Site(s) Involved, if applicable (select all that apply)**
___ Not applicable
___ Lung: _____
___ Bone: _____
___ Brain: _____
___ Liver: _____
___ Other (specify): _____
___ Cannot be determined: _____

**pTNM CLASSIFICATION (AJCC 8th Edition) (Note I)**
*Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.*
*The phrases in *asterisks* 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.*

**Modified Classification (required only if applicable) (select all that apply)**
___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

**pTNM Classification**
___ For all carcinomas

**pT Category**
___ Primary tumor cannot be assessed
___ Carcinoma *in situ*

*For the 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 (e.g., 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

*pT4: Moderately advanced or very advanced*

___ pT4a: Moderately advanced local disease. Tumor invades through the thyroid cartilage and / or invades tissues beyond the larynx (e.g., 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

___ pT4 (subgroup cannot be determined)

*For the Glottis*

*pT1: Tumor limited to the vocal cords (may involve anterior or posterior commissure) *with normal mobility**

___ pT1a: Tumor limited to one vocal cord

___ pT1b: Tumor involves both vocal cords

___ pT1 (subgroup cannot be determined)

___ 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 invasion of paraglottic space and / or inner cortex of the thyroid cartilage

*pT4: Moderately advanced or very advanced*

___ pT4a: Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and / or invades tissues beyond the larynx (e.g., trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

___ pT4b: Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

___ pT4 (subgroup cannot be determined)

*For the 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* and / or invasion of paraglottic space and / or inner cortex of the thyroid cartilage

*pT4: Moderately advanced or very advanced*

___ pT4a: Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and / or invades tissues beyond the larynx (e.g., 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

___ pT4 (subgroup cannot be determined)

**T Suffix (required only if applicable)**

___ Not applicable

___ (m) multiple primary synchronous tumors in a single organ

**pN Category# (Note H)**

*# Midline nodes are considered ipsilateral nodes.*

*Pathological ENE should be recorded as ENE(−) or ENE(+).*

*Measurement of the metastatic focus in the lymph nodes is based on the largest metastatic deposit size, which may include matted or fused lymph nodes.*

___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)

*pN2: Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); or larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); or in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)*

___ pN2a: Metastasis in a single ipsilateral node, 3 cm or smaller in greatest dimension and ENE(+); or in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
___ pN2b: Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
___ pN2c: Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)
___ pN2 (subgroup cannot be determined)

*pN3: Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(-); or metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral lymph nodes any with ENE(+); or a single contralateral node of any size and ENE(+)*

___ pN3a: Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(-)
___ pN3b: Metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral lymph nodes any with ENE(+); or a single contralateral node of any size and ENE(+)
___ pN3 (subgroup cannot be determined)

**pM Category (required only if confirmed pathologically)**

___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Distant metastasis

___ For mucosal melanoma

**pT Category**

___ pT3: Tumors limited to the mucosa and immediately underlying soft tissue, regardless of thickness or greatest dimension; for example, polypoid nasal disease, pigmented or nonpigmented lesions of the oral cavity, pharynx, or larynx

*pT4: Moderately advanced or very advanced 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
___ pT4 (subgroup cannot be determined)

**T Suffix (required only if applicable)**

___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

**pN Category**

___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ pN0: No regional lymph node metastasis

___ pN1: Regional lymph node metastases present

**pM Category (required only if confirmed pathologically)**

___ Not applicable - pM cannot be determined from the submitted specimen(s)

___ pM1: Distant metastasis

**ADDITIONAL FINDINGS (Note J)**

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

___ None identified

___ Dysplasia, low grade

*Select all that apply*

___ Hyperplasia

___ Mild dysplasia

___ Keratosis / keratinizing

___ Other (specify): _____

___ Dysplasia, high grade

*Select all that apply*

___ Moderate dysplasia

___ Severe dysplasia

___ Carcinoma in situ

___ Keratosis / keratinizing

___ Other (specify): _____

___ Squamous papilloma, solitary

___ Squamous papillomatosis

___ Inflammation (specify type): _____

___ Squamous metaplasia

___ Colonization, fungal

___ Colonization, bacterial

___ Other (specify): _____

**SPECIAL STUDIES**

*For reporting molecular testing and other cancer biomarker testing results, the CAP Head and Neck Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.*

*Specify test(s) (repeat as needed)*

**+Specify Test and Results: _____**

**COMMENTS**

**Comment(s): _____**

## Explanatory Notes

### A. Scope of Guidelines

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

References

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

### B. Anatomic Sites and Subsites for the Larynx

**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 cm 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. Like the paraglottic space, the pre-epiglottic 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).[1] The paraglottic and preglottic spaces contain lymphatics and blood vessels but no lymph nodes.[1]

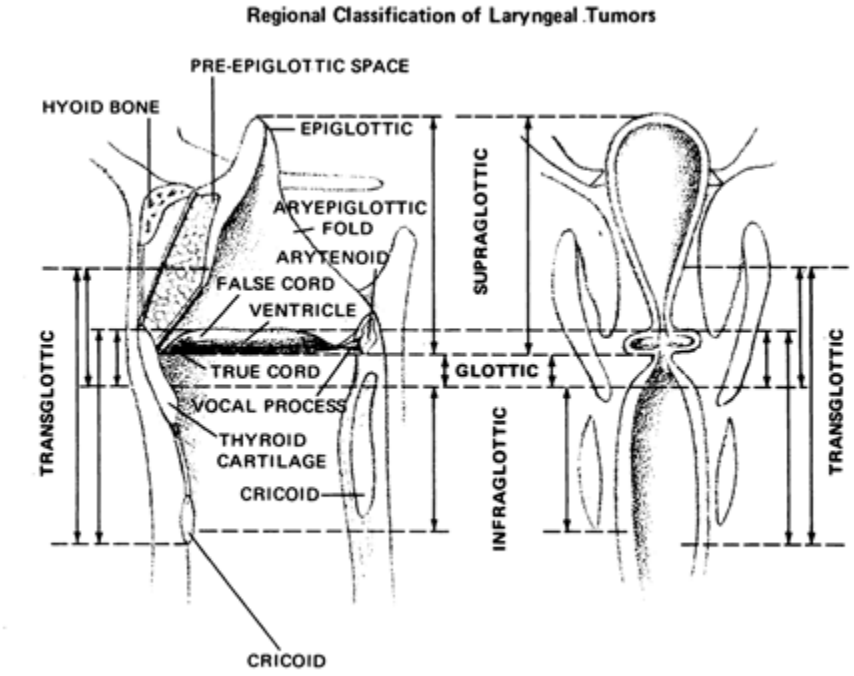


**Figure 1.** Anatomic compartments of the larynx. From Cocke EW Jr, Wang CC. Part I - Cancer of the larynx: selecting optimum treatment. *CA Cancer J Clin.* 1976;26:194-200. Figure by J.H. Ogura, MD. Reproduced with permission.

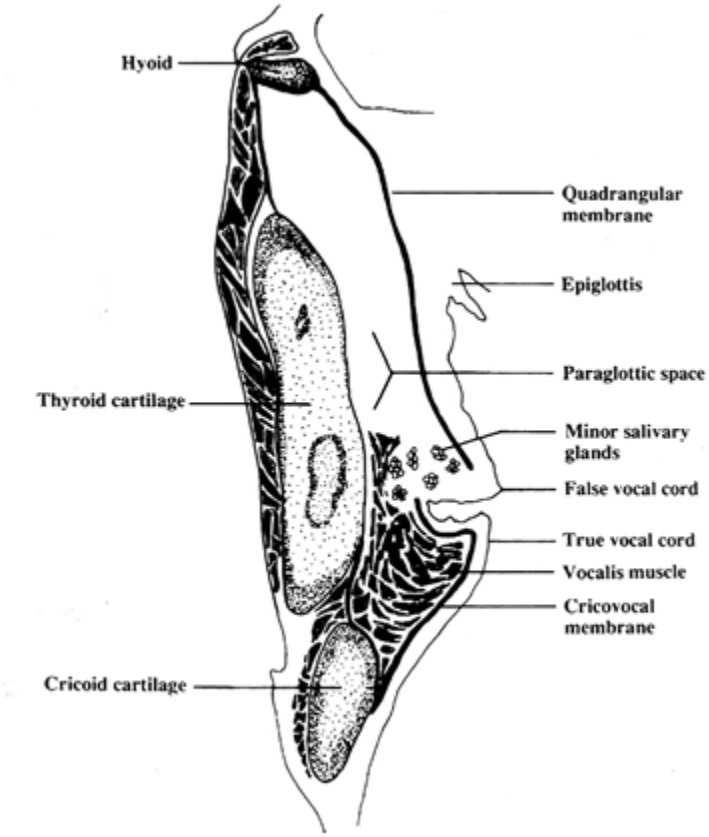


**Figure 2.** The paraglottic space. From *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours.* Lyon, France: IARC Press; 2005. Reproduced with permission.

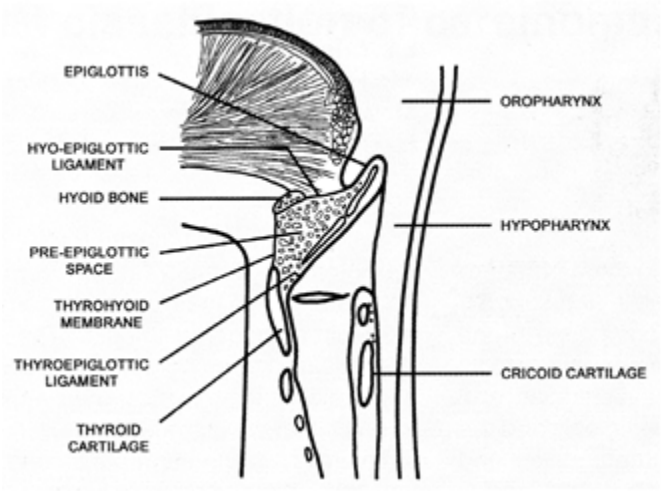


**Figure 3.** The pre-epiglottic space. From *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours.* Lyon, France: IARC Press; 2005. Reproduced with permission.

**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 aggressive carcinomas that cross the ventricles in a vertical direction arising in either the glottic or supraglottic larynx. Tumors usually cross the ventricle submucosally via paraglottic space invasion. This is not a specific site, as such, sites of involvement (i.e., supraglottic and glottic) should be recorded.

References

1. Patel SG, Lydiatt WM, Glastonbury CM, et al. Larynx. In: Amin MB, ed. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.

**C. Histologic Type**

A modification of the WHO classification of carcinomas of the larynx is shown below.[1] 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**

- Squamous cell carcinoma, conventional (keratinizing)
- Squamous cell carcinoma, nonkeratinizing
- Adenosquamous carcinoma
- Basaloid squamous cell carcinoma
- Papillary squamous cell carcinoma
- Spindle cell squamous carcinoma
- Verrucous carcinoma
- Carcinoma cuniculatum
- Lymphoepithelial carcinoma (non-nasopharyngeal)

**Carcinomas of Minor Salivary Glands**

The histologic classification recommended is the WHO classification of salivary gland tumors.[1]

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Acinic cell carcinoma
- Secretory carcinoma
- Polymorphous adenocarcinoma, conventional (classic) and cribriform subtypes
- Salivary duct carcinoma
- Epithelial-myoepithelial carcinoma
- Hyalinizing clear cell carcinoma

- Microsecretory adenocarcinoma
- Intraductal carcinoma (with subtypes)
- Basal cell adenocarcinoma
- Carcinosarcoma
- Mucinous adenocarcinoma (with subtypes)
- Sclerosing microcystic adenocarcinoma
- Lymphoepithelial carcinoma
- Myoepithelial carcinoma (malignant myoepithelioma)
- Sebaceous adenocarcinoma
- Squamous cell carcinoma
- Sialoblastoma
- Carcinoma, not otherwise specified

**Neuroendocrine Carcinoma**

The recommended histologic classification for neuroendocrine neoplasms has been standardized across all head and neck sites.[1] The entities relevant to this protocol are listed below:

Neuroendocrine tumor, grade 1-3
Neuroendocrine carcinoma, small cell type
Neuroendocrine carcinoma, large cell type

Additionally, composite tumors with non-neuroendocrine CA components exist throughout the upper aerodigestive tract. The carcinoma component can then be captured in this protocol accordingly.

**Mucosal Melanoma**

Given the rarity of mucosal melanoma, grading, and subtyping are not required.

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**D. Histologic Grade**

For histologic types of carcinomas that are amenable to grading, 3 histologic grades are suggested, as shown below. For conventional squamous cell carcinoma, histologic grading as a whole does not perform well as a prognosticator.[1,2] Nonetheless, it should be recorded when applicable, as it is a basic tumor characteristic. Selecting either the most prevalent grade or the highest grade for this synoptic protocol is acceptable. Subtypes of squamous cell carcinoma (i.e., verrucous, basaloid, etc.) have an intrinsic biologic potential.

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

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. Further, there is often a positive correlation between histologic grade and clinical stage.[3,4,5,6] However, most salivary gland carcinoma types have an intrinsic biologic behavior, and attempted application of a universal grading scheme is suboptimal given tumor specific nuances.[5] Thus, a generic grading scheme is no longer recommended for salivary gland carcinomas.[7]

However, within a given tumor type, grade remains an important prognostic parameter. Carcinoma types for which grading systems exist and are relevant are incorporated into histologic type. The classic categories that are still graded using three tier schemes include mucoepidermoid carcinoma, and carcinoma, not otherwise specified. While adenoid cystic carcinoma was historically stratified into three tiers, current classification no longer advocates for this.[4,5,8] Additionally, several tumor types can at least be stratified into low and high grade. High grade transformation (historically designated as dedifferentiation) refers to the phenomenon of progression from a conventional, usually indolent phenotype, to a pleomorphic aggressive morphology.

As such carcinomas can alternatively be stratified by their risk for structural recurrence by a combination of category, subtype, and category specific grade[9] as in Table 1.

**Table 1: Risk Stratification of Salivary Gland Carcinomas**

| **Low Aggression** | ***High Aggression*** |
|---|---|
| Mucoepidermoid carcinoma – Low grade | Mucoepidermoid carcinoma – High grade |
| Mucoepidermoid carcinoma – Intermediate grade* | |
| Acinic cell carcinoma – Conventional | Acinic cell carcinoma – High grade/HGT |
| Secretory carcinoma - Conventional | Secretory carcinoma – High grade/HGT |
| Microsecretory adenocarcinoma – Usual | Microsecretory adenocarcinoma – High grade/HGT |
| Polymorphous adenocarcinoma – Low grade, conventional | Polymorphous adenocarcinoma – High grade/HGT |
| Polymorphous adenocarcinoma – Low & intermediate grade, cribriform** | |
| Hyalinizing clear cell carcinoma – Conventional | Hyalinizing clear cell carcinoma – High grade/HGT |
| Basal cell adenocarcinoma – Conventional | Basal cell adenocarcinoma – High grade/HGT |
| Myoepithelial carcinoma – Low grade | Myoepithelial carcinoma – High grade |
| Epithelial-myoepithelial carcinoma – Conventional and subtypes | Epithelial-myoepithelial carcinoma – High grade/HGT |
| Sebaceous adenocarcinoma – Low grade | Sebaceous adenocarcinoma – High grade |
| | Adenoid cystic carcinoma – Solid/HGT |
| Adenoid cystic carcinoma – Tubular/cribriform^ | |
| | Carcinosarcoma (sarcomatoid carcinoma) |
| | (Metastatic) Squamous cell carcinoma (usually cutaneous) |
| Intraductal carcinoma, oncocytic and intercalated duct | |
| Intraductal carcinoma, apocrine | Salivary duct carcinoma |
| Mucinous adenocarcinoma “intraductal papillary mucinous neoplasm” type | Mucinous adenocarcinoma (not otherwise specified, and with colloid/signet ring features |
| | Lymphoepithelial carcinoma |

| | |
|---|---|
| Sclerosing microcystic adenocarcinoma | |
| Sialoblastoma | |
| Carcinoma ex pleomorphic adenoma# | |
| Salivary carcinoma, NOS@ | |

Abbreviations: HGT-high grade transformation. NOS-not otherwise specified
*Behavior varies with grading system or criteria
**The cribriform subtype of polymorphous adenocarcinoma has a high propensity for regional recurrence
^Adenoid cystic carcinoma though highly aggressive locally with capacity for distant spread, has somewhat lower risk for regional recurrence
#Carcinoma ex pleomorphic adenoma behavior is determined by carcinoma type and extent
@Salivary carcinoma, NOS behavior is determined by grade

Adenoid cystic carcinomas were historically stratified into three tiers based on tubular, cribriform, and solid (>30%) patterns respectively.[8] However currently, while solid pattern remains an integral prognosticator, no standard grading scheme is endorsed. The histologic grading of mucoepidermoid carcinoma includes a combination of growth pattern characteristics (e.g., cystic, solid, neurotropism) and cytomorphologic findings (e.g., anaplasia, mitoses, necrosis).[10,11,12] Carcinomas, not otherwise specified, do not have a formalized grading scheme and are graded intuitively based on cytomorphologic features.[6] Polymorphous adenocarcinomas and intraductal carcinomas are to be graded as per current WHO recommendations. Polymorphous adenocarcinomas should be subtyped into conventional and cribriform types (i.e., cribriform adenocarcinoma of minor salivary gland). The latter is more frequently extrapalatal and locoregionally aggressive. Along these lines, papillary components (>10%) and cribriform components (>30%) regardless of subtype have been shown to be prognostically relevant and these can be recorded optionally.[13] Intraductal carcinomas can be subtyped and graded, as both influence biologic behavior.[14] Additionally, two-tier grading schema have shown prognostic relevance for other tumor types such as myoepithelial carcinoma,[15] and acinic cell carcinoma.[16] Low grade and high grade are generally separated by mitotic counts and/or necrosis.

The current protocol is thus structured to allow for provision of grade or biologic potential for almost every epithelial tumor type in at least a two-tier fashion as per Table 1. For instance, epithelial-myoepithelial carcinoma, basal cell adenocarcinoma, and hyalinizing clear cell carcinoma can be assigned a default low grade/biologic potential category. Conversely, salivary duct carcinoma and lymphoepithelial carcinoma can be considered high grade/biologic potential category as a default. One key point is that adenoid cystic carcinoma should NEVER be assigned a low grade/biologic potential category. As this is one entity that does not fit into a standard risk of structural recurrence (i.e., discordant prevalence of local and regional aggression), this can be assigned N/A if non-solid and high grade if solid (>30%) or high grade transformed.

Carcinoma ex pleomorphic adenoma is subclassifed by histologic type and/or grade and extent of invasion, the latter including minimally invasive, invasive, and intracapsular (noninvasive) cancers. Previously the cut-off for minimal invasion was designated as 1.5 mm; however, more recent studies have shown a favorable prognosis even with cut-offs of 4 mm to 6 mm.[17] Thus, there is no agreement on an optimal cut-off. However, from a practical standpoint, the terms *intracapsular* and *minimally invasive* should only be applied to uninodular tumors (as opposed to carcinomas arising in multinodular recurrent pleomorphic adenomas) with a well-delineated interface for which the entire lesional border has been microscopically evaluated. Prognosis has been linked to degree of invasion with noninvasive and minimally invasive cancers apparently having a better prognosis than invasive cancers.[5,17,18] Carcinosarcoma is a rare subtype

morphology that while currently separated, appears to almost invariably arise in the setting of a precursor pleomorphic adenoma and should likely be regarded as a sarcomatoid carcinoma subtype ex pleomorphic adenoma.[19]

Aside from pleomorphic adenoma, other precursor lesions, most notably intercalated duct lesion/adenoma,[1,20] exist. Though biologically and diagnostically relevant, documentation of these precursors is currently optional (non-core) as there is limited literature[20] on these.

The WHO 5th edition has standardized the terminology for head and neck neuroendocrine neoplasms across all subsites.[21] Tumors previously designated as carcinoid and well-differentiated neuroendocrine carcinoma would now be considered grade 1 neuroendocrine tumors while atypical carcinoids/moderately-differentiated neuroendocrine carcinomas are now considered grade 2 neuroendocrine tumors. Grade 3 neuroendocrine tumor is a provisional category with no historical analogue. *It must be emphasized that this category in head and neck sites is provisional with no current evidence to support its use in head and neck sites.* Practically speaking, tumors that exceed the mitotic rate for grade 2 neuroendocrine tumors are usually more in keeping with neuroendocrine carcinomas (see below). Grading of neuroendocrine tumors is summarized in Table 2. Ki-67 proliferation indices are recommended for neuroendocrine tumors of head and neck, but are not required elements, and delineation of grade 1 and 2 at this site by proliferation index is not yet established.

**Table 2: WHO Classification of Head and Neck Neuroendocrine Tumors**

| Neuroendocrine Tumor Grade | Mitoses per two $mm^2$ | Necrosis |
|---|---|---|
| 1 | Less than 2 | Absent |
| 2 | 2-10 | Present |
| 3 | *Undefined* | |

Neuroendocrine carcinoma, small cell types and large cell types on the other hand, have not changed much in terms of their designation and reflect poorly differentiated neuroendocrine malignancies that were previously labeled small cell and large cell neuroendocrine carcinomas respectively. These characteristically show necrosis and have mitotic counts that exceed 10 per two $mm^2$. While neuroendocrine tumors and carcinomas are defined by neuroendocrine marker expression (synaptophysin, chromogranin, and/or INSM-1), other tumor types at each head and neck subsite may express these. Morphologic, other immunophenotypic and molecular features would then supersede this neuroendocrine marker expression for classification.

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**E. Perineural Invasion**

Traditionally, the presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.[1] 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.[1] Further, perineural invasion is associated with decrease in disease-specific survival and overall survival.[1] 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, while other studies showing no correlation with distant metastasis.[1] The relationship between perineural invasion and prognosis is independent of nerve diameter.[2] Additionally, emerging evidence suggests that extratumoral perineural invasion may be more prognostically relevant.[3] 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 (i.e., 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).[4,5] Given the significance relative to prognosis and treatment, perineural invasion is a required data element in the reporting of head and neck cancers.

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**F. Surgical Margins**

The definition of a positive margin is somewhat controversial given the varied results from prior studies.[1,2] However, overall, several studies support the definition of a positive margin to be invasive carcinoma or carcinoma in situ/high-grade dysplasia present at margins (microscopic cut-through of tumor).[3] Furthermore, reporting of surgical margins should also include information regarding the distance of invasive carcinoma, carcinoma in situ, or high-grade dysplasia (moderate to severe) from the surgical margin. Tumors with "close" margins also carry an increased risk for local recurrence.[2,3] The definition of a "close" margin is not standardized as the effective cut-off varies between studies and between anatomic subsites. Commonly used cut points to define close margins are 5 mm in general and 2 mm with respect to glottic larynx.[2] However, values ranging from 3 mm to 7 mm have been used with success,[2,4] and for glottic tumors as low as 1 mm.[5] Thus, distance of tumor from the nearest margin should be recorded.
Reporting of surgical margins for carcinomas of the minor salivary glands should follow those used for squamous cell carcinoma of larynx.

**Dysplasia**

The types of intraepithelial dysplasia of the upper aerodigestive tract (UADT) include nonkeratinizing ("classic") dysplasia and keratinizing dysplasia. Of the 2 types of dysplasias, the keratinizing dysplasias are significantly more common than the nonkeratinizing dysplasias. The current WHO advocates a 2-tiered approach with low-grade and high-grade dysplasia categories (see below under Note J).[6] High-grade dysplasia at a margin is regarded and reported as a positive margin, while low-grade dysplasia is not.

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**G. Orientation of Specimen**

Complex specimens should be examined and oriented with the assistance of the operating surgeon(s). 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 or photograph 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.

## H. Lymph Nodes

### Direct Extension of Tumor to Lymph Node

While data are essentially nonexistent for defining N status for lymph nodes involved by tumor via direct extension for head and neck cancers, the general convention based on other organ sites is to consider these positive for N categorization and counting purposes. It is recommended however to denote in the report the number of lymph nodes involved in this manner as it may influence more nuanced management decisions.

### Measurement of Tumor Metastasis

The cross-sectional diameter of the largest lymph node metastasis (not the lymph node itself) 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.[1,2]

### Special Procedures for Lymph Nodes

The risk of regional (cervical neck) nodal spread from cancers varies based on anatomic subsite. 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.

### 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. While the generic recommendation is that for lymph nodes with ITCs found by either histologic examination, immunohistochemistry, or nonmorphologic techniques (e.g., flow cytometry, DNA analysis, PCR amplification of a specific tumor marker), they should be classified as N0 or M0, respectively.[3,4] Evidence for the validity of this practice in head and neck squamous cell carcinoma and other histologic subtypes is lacking. In fact, rare studies relevant to head and neck sites indicate that isolated tumor cells may actually be a poor prognosticator in terms of local control.[5]

### Lymph Node Number

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

### 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 (Figure 4), defined by dissection of less than the 5 traditional levels of a radical and modified radical neck dissection. The following dissections are now under this category:[6,7,8]
    a. Supraomohyoid neck dissection
    b. Posterolateral neck dissection
    c. Lateral neck dissection
    d. Central compartment neck dissection
4. Superselective neck dissection (SSND), a relatively new term defined by dissection of the fibrofatty elements of 2 or less levels[9]
5. Extended radical neck dissection, as specified by the surgeon

For purposes of pathologic evaluation, lymph nodes are organized by levels as shown in Figure 4.


**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, e.g., scalene, suboccipital, and retropharyngeal, should be identified and reported from all levels separately. Midline nodes are considered ipsilateral nodes.

**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, particularly if there is gross extranodal extension. However generous sampling of the lymph node periphery is recommended if there is no gross extranodal extension to adequately assess microscopic extranodal extension. Reporting of lymph nodes containing metastasis should include whether there is presence or absence of extranodal extension (ENE),[10] which is now part of N staging. 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. A distance of extension from the native lymph node capsule is now suggested (but not yet required) with the proposed stratification of ENE into $ENE_{ma}$ (>2 mm) and $ENE_{mi}$ (≤2 mm).[11,12,13,14] However, pitfalls in the measurement (i.e., in larger, matted lymph nodes, in nodes post fine-needle aspiration, and in nodes with near total replacement of lymph node architecture), and the disposition of soft tissue deposits is still not resolved. In general, absence of ENE in a large (>3 cm) lymph node, especially with traversing fibrous bands, should be viewed with skepticism. Soft tissue deposits for lymph node metastases based on limited studies appear to be the equivalent of a positive lymph node with ENE and should be recorded as such.[15]

**Other Elements**
Anatomic compartment location of positive lymph nodes is now a non-core element.

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**I. TNM and Stage Groupings**

The protocol recommends the TNM staging system of the American Joint Committee on Cancer.[1] There are no significant alterations in the 8th edition to T stage of larynx. However, extranodal extension (ENE) is included in N stage. In essence, pathologic ENE(+) will increase the nodal category by 1.

The 8th edition of the AJCC staging of head and neck cancers includes mucosal melanomas; this does not show significant changes from the 7th edition. Approximately two-thirds of mucosal 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. Even small cancers behave aggressively with high rates of recurrence and death. 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 melanomas does not provide for the histologic definition of a T3 lesion; as the majority of mucosal 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.[2]

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 (e.g., 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.

**TNM Descriptors**

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y”, “r”, and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

The "m" suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The "y" prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy).

The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval and is identified by the "r" prefix: rTNM.

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

**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.

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**J. 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 (i.e., carcinoma in situ), the majority of the UADT mucosal lesions fall under the designation of keratinizing dysplasias, for which the aforementioned criteria are not as easily applied.
The current approach indicated by the WHO for laryngeal precursor lesions is to use a 2-tiered classification of low-grade and high-grade dysplasia. Hyperplasias and keratoses without atypia as well as those with mild dysplasia are categorized as "low-grade", while lesions with moderate and severe dysplasia, as well as carcinoma in situ, are considered "high-grade".[1] Separation of carcinoma in situ as a distinct category (i.e., 3 tiers) is an acceptable option, but data are limited to support this.[2]

Morphologic criteria for the classification of laryngeal precursor lesions are summarized below.[1]

| | |
|---|---|
| **Low-grade dysplasia (including previous category of mild dysplasia)** | |
| **Architectural criteria** | • Augmented basal/parabasal cells up to the lower half of the epithelium<br>• Perpendicular orientation to the basement membrane<br>• Stratification and maturation is preserved<br>• Spinous cell layer is retained in the upper half of epithelium |
| **Cytologic criteria** | • Minimal cellular atypia<br>• Basal/parabasal cells: increased cytoplasm, hyperchromatic nuclei, uniformly distributed chromatin<br>• Regular mitoses in lower half of epithelium<br>• Few dyskeratotic cells may be present |
| **High-grade dysplasia (including previous category of moderate and severe dysplasia, and carcinoma in situ)** | |
| **Architectural criteria** | • Abnormal maturation<br>• Keratinizing or non-keratinizing<br>• Variable degrees of disordered stratification and polarity up to the entire thickness of epithelium<br>• Two subtypes: basaloid, with no maturation, and large (spinous) cell, with maturation<br>• Variable degree of irregular shaped rete (bulbous, downwardly extending) |
| **Cytologic criteria** | • Cellular and nuclear atypia including marked variation in size and shape<br>• Marked nuclear hyperchromasia<br>• Nucleoli increased in number and size<br>• Increased nuclear/cytoplasmic ratio<br>• Increased mitoses up to the entire thickness of epithelium<br>• Atypical mitoses may be present<br>• Dyskeratotic and apoptotic cells may be present within the entire thickness of epithelium |
| **Carcinoma in situ – can be optionally delineated as follows:** | |
| **Architectural criteria** | • Complete loss of stratification and polarity<br>• Preserved basement membrane |
| **Cytologic criteria** | • Severe cellular and nuclear atypia (both qualitatively and quantitatively)<br>• Atypical mitoses |

The risk of malignant progression in low-grade dysplasia is ~1.6%, while that of high-grade dysplasia is ~12.5%. Limited data suggest that the specific designation of carcinoma in situ carries a risk of 40%.[1]

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