Protocol for the Examination of Specimens from Patients with Cancers of the Larynx

Version: 4.3.0.0
Protocol Posting Date: April 2026

CAP Laboratory Accreditation Program Protocol Required Use Date: January 2027
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 and neuroendocrine 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 HPV-Independent Oropharynx and Hypopharynx protocol)
Sarcoma (consider the Soft Tissue protocol)
Hematologic malignancies (consider the Precursor and Mature Lymphoid Malignancies, Myeloid and Mixed / Ambiguous Lineage Neoplasms, and Plasma Cell Malignancies protocols)
Mucosal melanoma (consider the Head and Neck Mucosal Melanoma protocol)
Salivary glands (consider the Salivary Gland Cancer protocol)

Version Contributors

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Glossary:

Author: Expert who is designated by the chair of the Cancer Committee.
Expert Panel Contributors: Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

Accreditation Requirements
Synoptic reporting with core and conditional data elements for designated specimen types* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with "+". Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under Accreditation Checklists.
A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.
**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

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 i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Summary of Changes

v 4.3.0.0

- Updates to cover page, content, and explanatory notes reflecting the separation of select Head and Neck protocols
- Procedure, Tumor Site and Histologic Type question updates
- Removal of Grade / Intrinsic Biologic Potential, Extent / Type of Perineural Invasion questions, and ADDITIONAL FINDINGS section
- Addition of Tumor Bed Margin Status section
- Laterality of Lymph Nodes(s) with Tumor, Size of Largest Nodal Metastatic Deposit, Extranodal Extension (ENE) questions changed from conditionally required to required (core)
- Separation of “Intraparotid” and “Periparotid” terms to Nodal Site(s) with Tumor question
- Modification to pTNM Classification pT, pN, and pM categories to remove mucosal melanoma staging and make minor typographical updates

Reporting Template

Protocol Posting Date: April 2026
Select a single response unless otherwise indicated.
CASE SUMMARY: (LARYNX (SUPRAGLOTTIS, GLOTTIS, SUBGLOTTIS))
Standard(s): AJCC 8

SPECIMEN

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

TUMOR

Multiple Primary Sites (required only if applicable)#
 # Please complete a separate checklist for each primary site
___ Not applicable (no additional primary site(s) present)
___ Present: _____

Tumor Focality
___ Unifocal
___ Multifocal: _____
___ Cannot be determined (explain): _____

Tumor Site (Note A) (select all that apply)
___ Supraglottic larynx: _____
+Tumor Subsite(s) (select all that apply)
___ Epiglottis, posterior surface (laryngeal aspect)
___ Aryepiglottic folds (laryngeal aspect)
___ False vocal cord
___ Ventricle
___ Glottic larynx: _____
+Tumor Subsite(s) (select all that apply)
___ True vocal cord
___ Anterior commissure
___ Posterior commissure
___ Subglottic larynx: _____

___ Not specified

Transglottic Extension
___ Not identified
___ Present
___ Cannot be determined (explain): _____

+Subglottic Extension
___ Not identified
___ Present

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

Tumor Size
___ Greatest dimension in Centimeters (cm): _____ cm
___ Cannot be determined (explain): _____

Histologic Type (Note B)

Squamous cell carcinoma and subtypes
___ Squamous cell carcinoma and subtypes
- ___ Squamous cell carcinoma, conventional [keratinizing]
- ___ Squamous cell carcinoma, nonkeratinizing
- ___ Adenosquamous carcinoma
- ___ Basaloid squamous cell carcinoma
- ___ Papillary squamous cell carcinoma
- ___ Spindle cell [sarcomatoid] squamous carcinoma
- ___ Verrucous carcinoma
- ___ Carcinoma cuniculatum
- ___ Lymphoepithelial carcinoma (non-nasopharyngeal)

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): _____

Other
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined: _____

+Histologic Type Comment: _____

Histologic Grade (required only if applicable)# (Note C)
 # Required for squamous cell carcinoma and subtypes
___ Not applicable
___ G1, well-differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ Other (specify): _____
___ GX, cannot be assessed: _____

Tumor Extent (specify other structures / spaces involved) (required only if pT defined elements are applicable): _____

Lymphatic and / or Vascular Invasion
___ Not identified
___ Present: _____
___ Cannot be determined (explain): _____

Perineural Invasion (Note D)
___ Not identified
___ Present
___ Cannot be determined (explain): _____

+Tumor Comment: _____

MARGINS (Note E)

Specimen Margin Status for Invasive Tumor
___ All specimen margins negative for invasive tumor
Distance from Invasive Tumor to Closest Specimen Margin
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined (explain): _____
Closest Specimen Margin(s) to Invasive Tumor (use orientation when provided)
___ Specify location(s) of closest specimen margin(s): _____
___ Cannot be determined (explain): _____

+Other Close Specimen Margin(s) to Invasive Tumor
___ Specify location(s) and distance(s) of other close specimen margin(s): _____
___ Cannot be determined: _____
___ Invasive tumor present at specimen margin(s)
Specimen Margin(s) Involved by Invasive Tumor (per orientation)
___ Specify involved specimen margin(s): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

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

+Tumor Bed Margin Status (separately submitted)
___ Tumor bed margins assessed

Tumor Bed Margin Orientation
___ Oriented to true margin surface
___ Unoriented to true margin surface
___ Cannot be determined (explain): _____

Tumor Bed Margin Status for Invasive Tumor
___ All tumor bed margins negative for invasive tumor
+Distance from Invasive Tumor to True Margin Surface (pertinent to oriented specimens which are sectioned perpendicularly)
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm

___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
___ Invasive tumor present at tumor bed margin(s)

Tumor Bed Margin(s) Involved by Invasive Tumor (per part labeling)
___ Specify involved tumor bed margin(s): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Tumor Bed Margin Status for Non-invasive Tumor (High-grade Dysplasia / Carcinoma In Situ)
___ All tumor bed margins negative for high-grade dysplasia / in situ disease
+Distance from Non-invasive Tumor to True Margin Surface (pertinent to oriented specimens which are sectioned perpendicularly)
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
___ High-grade dysplasia / in situ disease present at tumor bed margin(s)
Tumor Bed Margin(s) Involved by Non-invasive Tumor (per part labeling)
___ Specify involved tumor bed margin(s): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES (Note F)

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 (explain): _____
Laterality of Lymph Node(s) with Tumor
___ Ipsilateral (including midline): _____

___ Contralateral: _____
___ Bilateral: _____
___ Cannot be determined (explain): _____
+Nodal Site(s) with Tumor (select all that apply)
___ Intraparotid: _____
___ Periparotid: _____
___ Level I: _____
___ Level II: _____
___ Level III: _____
___ Level IV: _____
___ Level V: _____
___ Other (specify): _____
___ Cannot be determined: _____

Size of Largest Nodal Metastatic Deposit
Specify in Centimeters (cm)
___ Exact size: _____ cm
___ At least: _____ cm
___ Greater than: _____ cm
___ Less than: _____ cm
___ Other (specify): _____
___ Cannot be determined (explain): _____

Extranodal Extension (ENE) (Note F)
___ Not identified
___ Present
+Distance of ENE from Lymph Node Capsule
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than 2 mm (major ENE)
___ Less than or equal to 2 mm (minor ENE)
___ Less than 1 mm (minor ENE)
___ Other (specify): _____
___ Cannot be determined: _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

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

+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 (explain): _____

pTNM CLASSIFICATION (AJCC 8th Edition) (Note G)
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.

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

pT Category
___ Supraglottis
pT Category (supraglottis)
___ pT not assigned (cannot be determined based on available pathological information)
___ pTis: Carcinoma in situ
___ 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 outer cortex of 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)

___ Glottis
pT Category (glottis)
___ pT not assigned (cannot be determined based on available pathological information)
___ pTis: Carcinoma in situ
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
___ 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)

___ Subglottis

pT Category (subglottis)

___ pT not assigned (cannot be determined based on available pathological information)

___ pTis: Carcinoma in situ

___ 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 G)

 # 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 metastasis 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

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.

COMMENTS

Comment(s): _____

Explanatory Notes

A. Anatomic Sites and Subsites for the Larynx

Supraglottis

Epilarynx, including marginal zone

- Suprahyoid epiglottis, including tip, 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

Other

Cancers of the pyriform sinus are included in the protocol on hypopharynx cancers.[1]

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 pyriform 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]

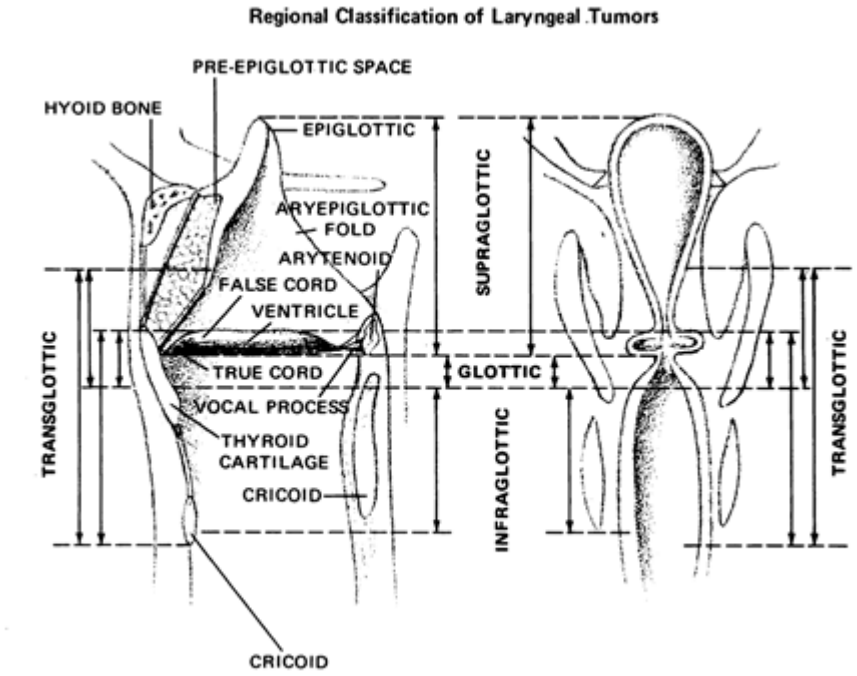

Figure 1. Anatomic compartments of the larynx. From Cocke EW Jr, Wang CC. Part I - Cancer of the larynx: selecting optimum treatment. *CA Cancer J Clin.* 1976; 26:194-200. Figure by J.H. Ogura, MD. Reproduced with permission.

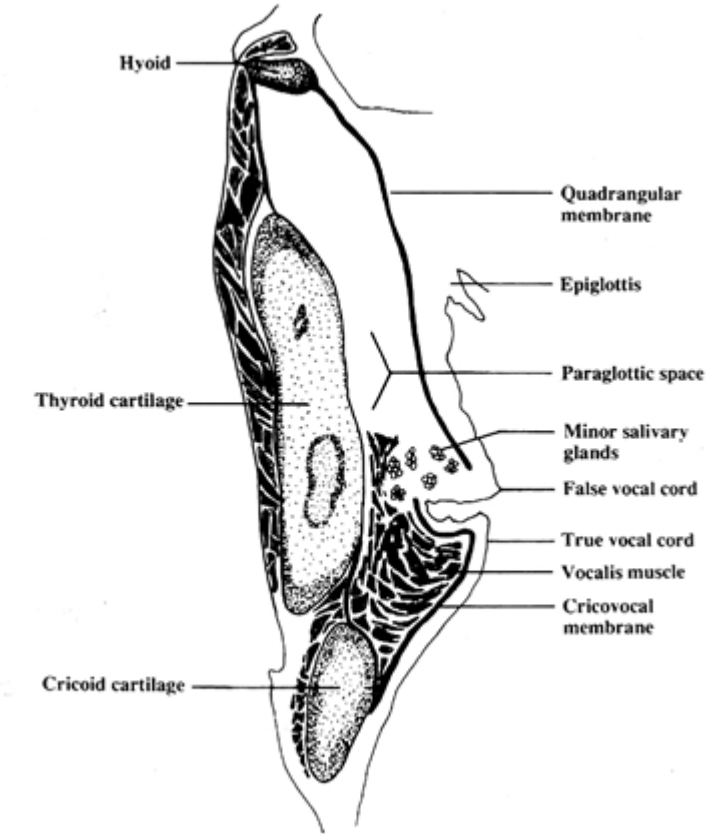

Figure 2. The paraglottic space. From *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours.* Lyon, France: IARC Press; 2005. Reproduced with permission.

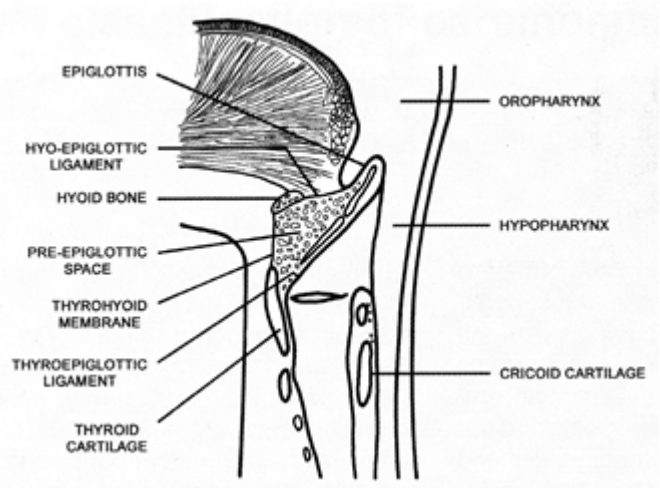

Figure 3. The pre-epiglottic space. From *World Health Organization Classification of Tumours: Pathology and Genetics of Head and Neck Tumours.* Lyon, France: IARC Press; 2005. Reproduced with permission.

Site-Specific Carcinomas

Tumors are categorized by site as below. For tumors with multisite contiguous involvement (i.e., transglottic and subglottic extension), determination of this site requires integration of clinical history, macroscopic findings (i.e., epicenter location), and microscopic features (i.e., site of transition from surface dysplasia). When multiple distinct tumors are noted (i.e., separate primaries), a protocol should be completed for each tumor.

1. Supraglottic squamous cell carcinoma represents a squamous cell carcinoma that involves the structures of the supraglottic larynx, including the laryngeal surface of epiglottis, 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, and as such, tumors are still classified by site of origin (i.e., supraglottic vs. glottic).
5. Subglottic extension from glottic and supraglottic tumors is actually more common than true subglottic tumors. While alone it not considered “transglottic”, subglottic extension increases the risk of central compartment lymph node involvement which is an adverse prognosticator.[2] This can be captured as an optional element.

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.
2. Deganello A, Ruaro A, Gualtieri T, et al. Central Compartment Neck Dissection in Laryngeal and Hypopharyngeal Squamous Cell Carcinoma: Clinical Considerations. *Cancers* (Basel). 2023 Jan 28;15(3):804.

B. 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 squamous cell carcinomas and neuroendocrine tumors and does not apply to salivary gland carcinomas, melanomas, lymphomas, or sarcomas.

Carcinomas of Larynx

Squamous cell carcinoma

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

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.

References

1. WHO Classification of Tumours Editorial Board. *Head and neck tumours*. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2025, Nov 6]. (WHO classification of tumours series, 5th ed.; vol. 9). Available from: https://tumourclassification.iarc.who.int/chapters/52

C. 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 WHO 5th edition has standardized the terminology for head and neck neuroendocrine neoplasms across all subsites.[3] 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 1. 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 1: 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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D. 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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E. Margins and Orientation

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 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.[5,6] Thus, distance of tumor from the nearest margin should be recorded.

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.

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F. Regional 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]

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. The generic recommendation is that lymph nodes with ITCs found by either histologic examination, immunohistochemistry, or non-morphologic techniques (e.g., flow cytometry, DNA analysis, PCR amplification of a specific tumor marker) should be classified as N0 or M0, respectively.[3] Evidence for the validity of this practice in head and neck squamous cell carcinoma and other histologic subtypes is however lacking even on systematic review.[4,5] 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.[6]

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. Examination of fewer tumor-free nodes still mandates a pN0 designation.

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:[7,8,9]
    1. Supraomohyoid neck dissection
    2. Posterolateral neck dissection
    3. Lateral neck dissection
    4. 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[10]
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 6 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. For laryngeal cancers, reporting of lymph nodes containing metastasis should include whether there is presence or absence of extranodal extension (ENE),[11] which is part of N classification for these tumor types.

Extranodal extension criteria and gross submission guidelines have been recently outlined by international consensus groups, HNCIG, and HN-CLEAR.[12,13] Sampling should optimize surface area/perimeter examined, and to optimize this, serial sectioning is recommended for all lymph nodes above 5 mm. Grossly negative lymph nodes should be submitted entirely while grossly positive lymph nodes can be representatively submitted. However, focus on sampling of the nodal periphery is recommended to enrich for extranodal extension.[13]

Only definitive ENE as per HNCIG, HN-CLEAR[12,13] criteria should be recorded as positive. New terminology for microscopic expression includes:[13]

- 'Matted' where tumor crosses from one lymph node to another adjacent lymph node. This is considered ENE positive
- 'Fused, adherent, confluent, and conglomerate' lymph nodes refer to lymph nodes that are adherent based on inflammation and stromal reaction and show no transgression of tumor across capsules. These are considered ENE negative

Additionally, soft tissue deposits are considered ENE positive, while extranodal lymphatic/vascular invasion and perineural invasion are considered ENE negative but count towards lymphatic/vascular invasion and perineural invasion even if the primary tumor does not show this locally.

Other Elements

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

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G. pTNM Classification

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 classification of larynx. However, extranodal extension (ENE) is included in N classification. In essence, pathologic ENE(+) will increase the nodal category by 1.

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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