



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

**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 pharynx (oropharynx, nasopharynx, hypopharynx) including the base of the tongue, tonsils, soft palate, and uvula
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
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 B, C, and G
- pTNM classification update to content and Explanatory Note H
- LVI update from “Lymphovascular Invasion” to “Lymphatic and / or Vascular Invasion”
- Cover page update: Squamous cell carcinoma in-situ (Tis) is not required for accreditation

RETIRED

## Reporting Template

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**Protocol Posting Date: June 2023**

**Select a single response unless otherwise indicated.**

**CASE SUMMARY: (PHARYNX (OROPHARYNX, HYPOPHARYNX, NASOPHARYNX))**

**Standard(s): AJCC-UICC 8**

### SPECIMEN

#### Procedure (select all that apply)

- Excision
- Tonsillectomy
- Laryngopharyngectomy
- Neck (lymph node) dissection (specify): \_\_\_\_\_
- Other (specify): \_\_\_\_\_
- Not specified

### TUMOR

#### Tumor Focality

- Unifocal
- Multifocal: \_\_\_\_\_
- Cannot be determined: \_\_\_\_\_

#### Multiple Primary Sites (e.g., oropharynx and nasopharynx)

- Not applicable (no additional primary site(s) present)
- Present: \_\_\_\_\_

*Please complete a separate checklist for each primary site*

#### Tumor Site (Note [A](#))

- Oropharynx: \_\_\_\_\_
- +Tumor Subsite (select all that apply)**
  - Palatine tonsil
  - Tonsillar pillar or fossa
  - Base of tongue, including lingual tonsil
  - Soft palate
  - Uvula
  - Pharyngeal wall (posterior)
  - Vallecula
- Nasopharynx: \_\_\_\_\_
- +Tumor Subsite (select all that apply)**
  - Superior / Posterior
  - Lateral (including Rosenmuller fossa)
  - Nasopharyngeal tonsils (adenoids)
- Hypopharynx: \_\_\_\_\_

**+Tumor Subsite (select all that apply)**

- Piriform sinus
- Postcricoid
- Pharyngeal wall (posterior and / or lateral)
- Other (specify): \_\_\_\_\_
- Not specified

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

- Left
- Right
- 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 B)**

*Carcinomas of the oropharynx and hypopharynx*

- Oropharyngeal squamous cell carcinoma, HPV-associated (oropharynx only)
- Oropharyngeal squamous cell carcinoma, HPV-independent (oropharynx only)
- Oropharyngeal squamous cell carcinoma, HPV status unknown (see “ancillary studies” for additional notes)
- Hypopharyngeal squamous cell carcinoma

*Squamous cell carcinoma 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 the nasopharynx*

- Squamous cell carcinoma, keratinizing
- Squamous cell carcinoma, nonkeratinizing
- Basaloid squamous cell carcinoma
- Low-grade nasopharyngeal papillary adenocarcinoma

*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 pattern
- # If multiple patterns are present, select the predominant pattern unless the solid pattern is greater than 30%, in which case the user should select the 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, not otherwise specified
- Neuroendocrine carcinoma, small cell type, HPV associated (oropharynx)
- Neuroendocrine carcinoma, small cell type, HPV independent (oropharynx)
- 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 C)**

*# Required only for non-salivary (HPV-independent / negative) 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):** \_\_\_\_\_

**Lymphatic and / or Vascular Invasion**

- Not identified
- Present
- Cannot be determined: \_\_\_\_\_

**Perineural Invasion (Note D)**

- Not identified

Present

**+Extent / Type of Perineural Invasion#**

# Select the most aggressive type

Intratumoral

Extratumoral

Intraneural

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

Cannot be determined: \_\_\_\_\_

**+Tumor Comment:** \_\_\_\_\_

**MARGINS (Notes [E](#),[F](#))**

**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 (use orientation when provided)**

Specify involved margin(s): \_\_\_\_\_

Cannot be determined

Other (specify): \_\_\_\_\_

Cannot be determined: \_\_\_\_\_

**Margin Status for Noninvasive Tumor (High-grade Dysplasia)**

*Applicable only to nonoropharyngeal and HPV-independent oropharyngeal squamous cell carcinoma and histologic subtypes and required only when closer than invasive tumor.*

Not applicable

All margins negative for high grade dysplasia / in situ disease

**+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 (use orientation when provided)**

- Specify involved margin(s): \_\_\_\_\_
- Cannot be determined
- Other (specify): \_\_\_\_\_
- Cannot be determined (explain): \_\_\_\_\_

**+Margin Comment:** \_\_\_\_\_

**REGIONAL LYMPH NODES (Note [G](#))**

**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)**

*Required only for hypopharyngeal carcinomas and HPV-independent oropharyngeal squamous cell carcinomas.*

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 (explain): \_\_\_\_\_

**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 [H](#))**

*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)

**pTNM Classification (Note [H](#))**

\_\_\_ For all carcinomas

**pT Category and pN Category**

\_\_\_ For HPV-Associated Oropharynx

**pT Category**

\_\_\_ pT0: No primary identified

\_\_\_ pT1: Tumor 2 cm or smaller in greatest dimension

\_\_\_ pT2: Tumor larger than 2 cm but not larger than 4 cm in greatest dimension

\_\_\_ pT3: Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis

\_\_\_ pT4: Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond#

*Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.*

**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: Metastasis in 4 or fewer lymph nodes

\_\_\_ pN2: Metastasis in more than 4 lymph nodes

\_\_\_ For HPV-Independent Oropharynx

**pT Category**

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

\_\_\_ pTis: Carcinoma \*in situ\*

\_\_\_ pT1: Tumor 2 cm or smaller in greatest dimension

\_\_\_ pT2: Tumor larger than 2 cm but not larger than 4 cm in greatest dimension

\_\_\_ pT3: Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis

*pT4: Moderately advanced or very advanced local disease*

*# Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx*

\_\_\_ pT4a: Moderately advanced local disease. Tumor invades larynx, extrinsic muscle of tongue, medial pterygoid muscles, hard palate, or mandible#

\_\_\_ pT4b: Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery

\_\_\_ pT4 (subcategory 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)

*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.*

*# Midline nodes are considered ipsilateral nodes.*

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

\_\_\_ 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 single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); OR a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)

\_\_\_ pN2b: Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)

\_\_\_ pN2c: Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)

\_\_\_ pN2 (subcategory cannot be determined)

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

\_\_\_ pN3a: Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)

\_\_\_ pN3b: Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); OR multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); OR a single contralateral node of any size and ENE(+)

\_\_\_ pN3 (subcategory cannot be determined)

\_\_\_ For Nasopharynx

#### **pT Category**

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

\_\_\_ pT0: No evidence of primary tumor, but EBV-positive cervical node(s) involvement

\_\_\_ pT1: Tumor confined to nasopharynx, or extension to oropharynx and / or nasal cavity without parapharyngeal involvement#

\_\_\_ pT2: Tumor with extension to parapharyngeal space, and / or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)

\_\_\_ pT3: Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and / or paranasal sinuses

\_\_\_ pT4: Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and / or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle

#### **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: Unilateral metastasis in cervical lymph node(s) and / or unilateral or bilateral metastasis in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage

\_\_\_ pN2: Bilateral metastasis in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage

\_\_\_ pN3: Unilateral or bilateral metastasis in cervical lymph node(s), larger than 6 cm in greatest dimension, and / or extension below the caudal border of cricoid cartilage

\_\_\_ For Hypopharynx

**pT Category**

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

\_\_\_ pTis: Carcinoma \*in situ\*

\_\_\_ pT1: Tumor limited to one subsite of hypopharynx and / or 2 cm or smaller in greatest dimension

\_\_\_ pT2: Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures larger than 2 cm but not larger than 4 cm in greatest dimension without fixation of hemilarynx

\_\_\_ pT3: Tumor measures larger than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophageal mucosa

*pT4: Moderately advanced and very advanced local disease*

\_\_\_ pT4a: Moderately advanced local disease. Tumor invades thyroid / cricoid cartilage, hyoid bone, thyroid gland, esophageal muscle or central compartment soft tissue

\_\_\_ pT4b: Very advanced local disease. Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

\_\_\_ pT4 (subcategory 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)

*# 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.*

\_\_\_ 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 single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); OR a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)

\_\_\_ pN2b: Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)

\_\_\_ pN2c: Metastasis in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)

\_\_\_ pN2 (subcategory cannot be determined)

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

\_\_\_ pN3a: Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)

pN3b: Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); or a single contralateral node of any size and ENE(+)

pN3 (subcategory 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 (subcategory 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 !)**

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

*# Applicable only to nonoropharyngeal and HPV-independent oropharyngeal squamous cell carcinoma and histologic subtypes.*

None identified

Keratinizing dysplasia, mild#

Keratinizing dysplasia, moderate#

Keratinizing dysplasia, severe (carcinoma in situ)#

Nonkeratinizing dysplasia, mild#

Nonkeratinizing dysplasia, moderate#

Nonkeratinizing dysplasia, severe (carcinoma in situ)#

Inflammation (specify type): \_\_\_\_\_

Squamous metaplasia

Epithelial hyperplasia

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. Note that some form of high-risk HPV testing is required for staging of oropharyngeal squamous cell carcinoma.*

*It is highly recommended to perform p16 or other form of HPV testing prior to submitting the pT and pN sections of the synoptic checklist rather than listing the status as pending. Using the "Oropharyngeal squamous cell carcinoma, HPV status unknown" option simply because of a lack of access to these tests is highly discouraged. A consultation to another testing center prior to sign out is highly advised in order to use the correct staging system. In the event of an equivocal p16 or HPV test, or insufficient remaining tissue, the use of "Oropharyngeal squamous cell carcinoma, HPV status unknown" is appropriate. The recommendation in these instances is to test a separate sample, if available, and otherwise the staging system defaults to the HPV negative pT and pN criteria (although the tumor should NOT be labeled HPV negative).*

### Ancillary Studies Performed# (select all that apply)

# Please note that some method of HPV testing is required for oropharyngeal squamous cell carcinoma.

\_\_\_ Not applicable

\_\_\_ p16 IHC

#### p16 IHC as a Surrogate for Transcriptionally Active High-Risk HPV

\_\_\_ Negative (less than 50% diffuse and moderate-to-strong nuclear and cytoplasmic staining)

\_\_\_ Equivocal (less than 70% but greater than 50% diffuse and moderate-to-strong nuclear and cytoplasmic staining)

\_\_\_ Positive (greater than or equal to 70% diffuse and moderate-to-strong nuclear and cytoplasmic staining)

\_\_\_ Other results, including cytology specimen(s) (specify): \_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_

\_\_\_ HPV E6 / E7 mRNA ISH

#### HPV E6 / E7 mRNA ISH

\_\_\_ Negative (no signal)

\_\_\_ Positive (cytoplasmic and / or nuclear signals)

+Specify Subtypes: \_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_

\_\_\_ HPV-DNA ISH

#### HPV-DNA ISH

\_\_\_ Negative (no nuclear signal)

\_\_\_ Positive (punctate and / or diffuse nuclear staining)

+Specify Subtypes: \_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_

\_\_\_ HPV-DNA PCR

#### HPV-DNA PCR

\_\_\_ Negative (no signal)

\_\_\_ Positive (cytoplasmic and / or nuclear signals)

+Specify Subtypes: \_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_

\_\_\_ HPV E6 / E7 mRNA RT-PCR

#### HPV E6 / E7 mRNA RT-PCR

\_\_\_ Negative (no signal)

\_\_\_ Positive (cytoplasmic and / or nuclear signals)

**+Specify Subtypes:** \_\_\_\_\_

\_\_\_ Cannot be determined (explain): \_\_\_\_\_

\_\_\_ Epstein-Barr virus (EBV) testing

**EBV Early mRNA (EBER) ISH**

\_\_\_ Negative (no nuclear signal)

\_\_\_ Positive (nuclear signal)

\_\_\_ Cannot be determined (explain): \_\_\_\_\_

\_\_\_ Other studies (specify): \_\_\_\_\_

\_\_\_ Pending studies (specify): \_\_\_\_\_

\_\_\_ Not specified

\_\_\_ Not performed: \_\_\_\_\_

**COMMENTS**

**Comment(s):** \_\_\_\_\_

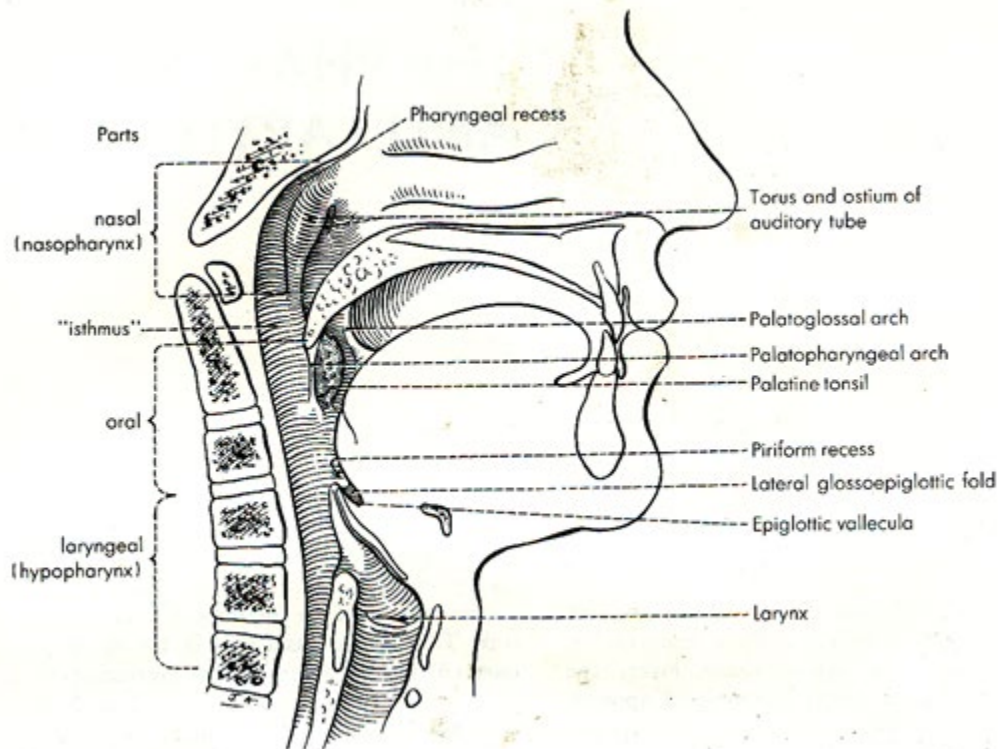
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## Explanatory Notes

### A. Anatomical Sites and Subsites for Pharynx

The pharynx is divided into 3 parts including the nasopharynx, oropharynx, and hypopharynx (Figure 1).



**Figure 1.** Anatomic subdivisions and “contents” of the pharynx. From Hollinshead WH. *Anatomy for Surgeons: The Head and Neck*. 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 1982. Reproduced with permission (<http://lww.com>).

#### Oropharynx (Figure 1)

The oropharynx is the portion of the continuity of the pharynx extending from the plane of the superior surface of the soft palate to the superior surface of the hyoid bone or floor of the vallecula.<sup>1,2</sup> The contents of the oropharynx include:

- soft palate
- palatine tonsils
- anterior and posterior tonsillar pillars
- tonsillar fossa and tonsillar (faucial) pillars
- uvula
- base of tongue, including the lingual tonsils
- vallecula
- posterior oropharyngeal wall

### Nasopharynx (Figure 1)

The nasopharynx is situated behind the nasal cavity and above the soft palate; it begins anteriorly at the posterior choana and extends along the plane of the airway to the level of the free border of the soft palate.<sup>3</sup> The contents of the nasopharynx include:

- nasopharyngeal tonsils (adenoids) lie along the posterior and lateral of the nasopharynx
- orifice of Eustachian tube lies along the lateral aspects of the nasopharyngeal wall
- fossa of Rosenmüller

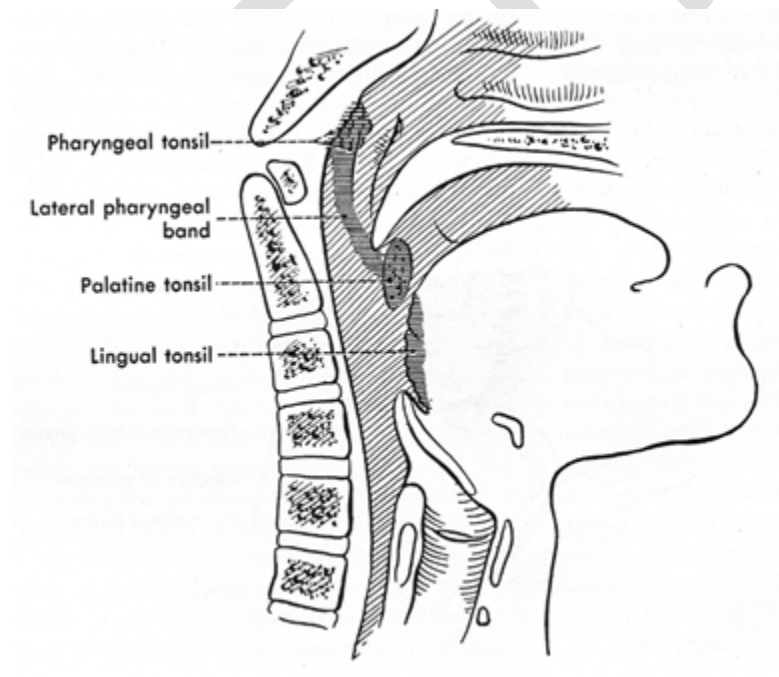
### Hypopharynx (Figure 1)

The hypopharynx is the portion of the pharynx extending from the plane of the superior border of the hyoid bone (or floor of the vallecula) to the plane corresponding to the lower border of the cricoid cartilage.<sup>1</sup> The contents of the hypopharynx include:

- piriform sinus (right and left) - 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
- lateral and posterior hypopharyngeal walls
- postcricoid region extending from the level of the arytenoid cartilage and connecting folds to the inferior border of the cricoid cartilage; it connects the 2 piriform sinuses, thereby forming the anterior wall of the hypopharynx

**Waldeyer ring** is formed by a ring or group of extranodal lymphoid tissues about the upper end of the pharynx (Figure 2) which consists of the:

- palatine tonsils
- pharyngeal tonsils (adenoids)
- base of tongue/lingual tonsils
- adjacent submucosal lymphatics



**Figure 2.** Waldeyer tonsillar tissues. From Hollinshead WH. *Anatomy for Surgeons: The Head and Neck*. 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 1982. Reproduced with permission (<http://lww.com>).

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#### **B. Histologic Type**

A modification of the WHO classification of carcinomas of the oropharynx, the nasopharynx, and the hypopharynx is shown below.<sup>1</sup> This list may not be complete. It is recognized that the AJCC 8th edition terminology<sup>2</sup> diverges slightly from the WHO 5th edition terminology<sup>1</sup> for oropharyngeal squamous cell carcinomas. In the oropharynx, p16 status is considered an acceptable surrogate for HPV status, assuming prototypical non-keratinizing morphology and a high HPV attributable fraction in the patient population, and p16 positive can be considered synonymous. This protocol applies only to carcinomas and melanomas and does not apply to lymphomas or sarcomas.

#### **Carcinomas of the Oropharynx and Hypopharynx**

##### **Squamous cell carcinoma**

- Human papillomavirus (HPV)-associated squamous cell carcinoma (oropharynx only)
- HPV-independent squamous cell carcinoma (oropharynx and hypopharynx)

##### **Subtypes of 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 the Nasopharynx**

- Keratinizing squamous cell carcinoma
- Nonkeratinizing squamous cell carcinoma
- Basaloid squamous cell carcinoma
- Low-grade nasopharyngeal papillary adenocarcinoma

#### **Carcinomas of the Minor Salivary Gland**

The histologic classification recommended is the WHO classification of salivary gland tumors.<sup>1</sup>

- 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. 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.

Furthermore, a subset of neuroendocrine carcinomas, small cell type are HPV associated and can be captured accordingly.

### **Mucosal Melanoma**

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

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### 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.<sup>1</sup> Nonetheless, it should be recorded when applicable, as it is a basic tumor characteristic. Specifically, it is only applicable for HPV-independent oropharyngeal carcinomas and hypopharyngeal carcinomas. HPV-associated squamous cell carcinoma is not graded, and nasopharyngeal carcinoma is typed as above but does not otherwise require grading.<sup>2,3</sup> 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.<sup>4,5,6,7</sup> 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.<sup>8</sup> Thus, a generic grading scheme is no longer recommended for salivary gland carcinomas.<sup>8</sup>

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.<sup>5,6,9</sup> 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<sup>10</sup> as in Table 1.

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

<i>Low Aggression</i>	<i>High Aggression</i>
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 <sup>^</sup>	
	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 <sup>#</sup>	
Salivary carcinoma, NOS <sup>@</sup>	

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

<sup>^</sup>Adenoid cystic carcinoma though highly aggressive locally with capacity for distant spread, has somewhat lower risk for regional recurrence

<sup>#</sup>Carcinoma ex pleomorphic adenoma behavior is determined by carcinoma type and extent

<sup>@</sup>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.<sup>9</sup> 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 cytomorphic findings (e.g., anaplasia, mitoses, necrosis).<sup>11,12,13</sup> Carcinomas, not otherwise specified, do not have a formalized grading scheme and are graded intuitively based on cytomorphic features.<sup>6</sup> 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.<sup>14</sup> Intraductal carcinomas can be subtyped and graded, as both influence biologic behavior.<sup>15</sup> Additionally, two-tier grading schema have shown prognostic relevance for other tumor types such as myoepithelial carcinoma,<sup>16</sup> and acinic cell carcinoma.<sup>17</sup> 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 subclassified 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.<sup>18</sup> 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.<sup>6,18,19</sup> 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.<sup>20</sup>

Aside from pleomorphic adenoma, other precursor lesions, most notably intercalated duct lesion/adenoma,<sup>1,21</sup> exist. Though biologically and diagnostically relevant, documentation of these precursors is currently optional (non-core) as there is limited literature<sup>21</sup> on these.

The WHO 5th edition has standardized the terminology for head and neck neuroendocrine neoplasms across all subsites.<sup>22</sup> 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 <sup>2</sup>	Necrosis
1	Less than 2	Absent
2	2-10	Present
3	<i>Undefined</i>	

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<sup>2</sup>. 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.<sup>1</sup> 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.<sup>1</sup> Further, perineural invasion is associated with decrease in disease-specific survival and overall survival.<sup>1</sup> 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.<sup>1</sup> The relationship between perineural invasion and prognosis is independent of nerve diameter.<sup>2</sup> Additionally, emerging evidence suggests that extratumoral perineural invasion may be more prognostically relevant.<sup>3</sup> 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).<sup>4,5</sup> While oropharyngeal, hypopharyngeal, and nasopharyngeal site specific data are limited, given the significance relative to prognosis and treatment for head and neck cancers in general, perineural invasion is a required data element in the reporting at these sites as well.

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#### E. Surgical Margins

Historically, documentation of margin status for many oropharyngeal and hypopharyngeal tumors was not possible, and they were not oncologically resected but rather treated with chemotherapy and radiation. With the advent of transoral robotic and laser surgery, however, intact resections have become increasingly common. Limited evidence suggests that at the very minimum, a positive margin is represented by invasive carcinoma present at margin (microscopic cut-through of tumor).<sup>1,2,3</sup> Akin to other sites, there is no standard definition of a “close” margin, and definitions have ranged from 2 mm to 5 mm.<sup>2</sup> Despite the paucity of data, in keeping with other sites, the distance from the nearest margin should be recorded.

For hypopharyngeal and HPV-negative oropharyngeal tumors, in situ disease and high-grade dysplasia is plausible, and if present at a margin, the margin is considered positive in line with other sites. When such lesions are identified in pharyngeal sites, it usually occurs in association with an invasive carcinoma. In this setting, the same criteria detailed in the oral cavity and laryngeal protocols apply (see Protocol for the Examination of Specimens from Patients with Carcinomas of the Lip and Oral Cavity and Protocol for the Examination of Specimens from Patients with Carcinomas of the Larynx).

For HPV-positive oropharyngeal carcinoma, in situ disease for practical purposes nonexistent, likely given their derivation from the specialized “lymphoepithelium” of tonsillar crypt.<sup>4</sup>

Nasopharyngeal tumors are still generally not resected and margin status is usually not able to be documented.

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## F. 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.

## G. 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.<sup>1,2</sup>

### Special Procedures for Lymph Nodes

The risk of regional (cervical neck) nodal spread from cancers of the pharynx is high. The majority of metastatic carcinomas to the cervical lymph nodes take origin from a head and neck primary carcinoma. The most common histologic type of carcinoma to metastasize to cervical neck lymph nodes is squamous cell carcinoma. Cervical nodal metastases may occur in the setting of an unknown primary carcinoma referred to as metastatic cervical carcinoma with an unknown primary (CUP).

As per AJCC 8<sup>th</sup> edition guidelines,<sup>3</sup> 3 separate approaches are employed to stage patients who present with an occult primary tumor. The primary T category is described as T0 and the N category is designated according to the respective anatomic site based on Epstein-Barr virus (EBV) and HPV status:

1. Patients with EBV-related cervical adenopathy are staged according to N staging in nasopharynx.
2. Patients with HPV-mediated (positive) cervical adenopathy are staged according to N staging in HPV-mediated/p16 positive oropharyngeal cancer.
3. All other patients with EBV-unrelated and HPV-unrelated cervical adenopathy are staged according to the generic N stage category used for the other head and neck sites, and for unknown primary.

This takes into account the site-specific differences in prognostic impact for metastatic nodal disease. Both HPV- and EBV-driven nodal metastases are typically nonkeratinizing, with the former often being cystic.

When encountering this morphology, HPV and EBV testing as suggested in the CAP Head and Neck Biomarker template is critical.

Aside from these, 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.<sup>4,5</sup> 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.<sup>6</sup>

### **Lymph Node Number**

For assessment of pN, a selective neck dissection will ordinarily include 10 or more lymph nodes, and a comprehensive neck dissection (radical or modified radical neck dissection) will ordinarily include 15 or more lymph nodes. 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 3), 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:<sup>7,8,9</sup>
  - 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<sup>10</sup>
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 3.



**Figure 3.** The six sublevels of the neck for describing the location of lymph nodes within levels I, II, and V. Level IA, submental group; level IB, submandibular group; level IIA, upper jugular nodes along the carotid sheath, including the subdigastric group; level IIB, upper jugular nodes in the submuscular recess; level VA, spinal accessory nodes; and level VB, the supraclavicular and transverse cervical nodes. From Flint PW et al, eds. *Cummings Otolaryngology: Head and Neck Surgery*. 5th ed. Philadelphia, PA; Saunders: 2010. Reproduced with permission © Elsevier.

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

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

#### **Level I. Submental Group (Sublevel IA)**

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

#### **Level I. Submandibular Group (Sublevel IB)**

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

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

Lymph nodes located around the upper third of the internal jugular vein and adjacent spinal accessory nerve extending from the level of the carotid bifurcation (surgical landmark) or hyoid bone (clinical landmark) to the skull base. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the 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. When staging lymph node involvement by metastases from nasopharyngeal carcinoma, the supraclavicular fossa refers to a triangular region, the base of which is the superior margin of the clavicle between its sternal and lateral ends, and the apex of which is the point where the neck meets the shoulder. This includes caudal portions of Levels IV and V (see above). All cancers metastatic to the posterior nodes in the supraclavicular fossa are designated as N3b. 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. For HPV-unrelated/p16-negative oropharyngeal cancers and hypopharyngeal cancers, reporting of lymph nodes containing metastasis should include whether there is presence or absence of extranodal extension (ENE),<sup>11</sup> which is now part of N staging for these tumor types. 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<sub>ma</sub> (greater than 2 mm) and ENE<sub>mi</sub> (less than or equal to 2 mm).<sup>12,13,14,15</sup> 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 are still not resolved. In general, absence of ENE in a large (greater than 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.<sup>16</sup>

However, ENE as of AJCC 8<sup>th</sup> edition, was not considered sufficiently prognostically relevant for HPV-mediated/p16-positive and nasopharyngeal cancers. While it may be recorded, it is currently not required under AJCC guidelines.<sup>17,18</sup>

### Other Elements

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

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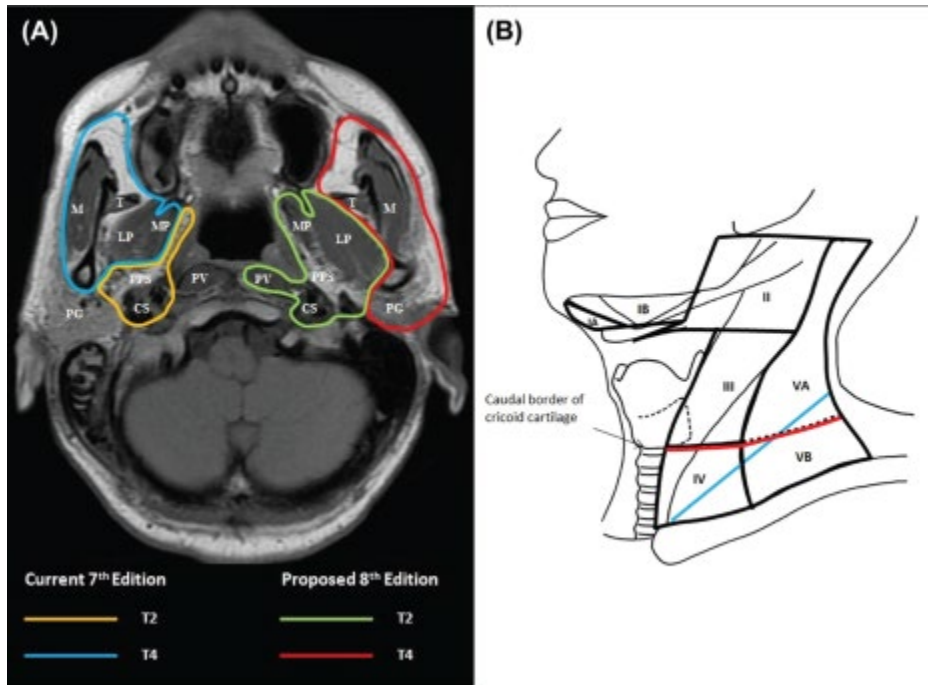
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#### H. TNM and Stage Groupings

The protocol recommends the TNM staging system of the American Joint Committee on Cancer and the International Union Against Cancer for the oropharynx, nasopharynx, and hypopharynx.<sup>1,2,3</sup> AJCC 8<sup>th</sup> edition staging has introduced several changes. Notably HPV-mediated (p16-positive) squamous cell carcinomas of the oropharynx have their own staging system, with respect to both T and N stage. ENE is not relevant to this category and is not incorporated into the N stage. However, ENE is still required for N staging of HPV-unrelated (p16-negative) squamous cell carcinoma and hypopharyngeal carcinomas. For nasopharyngeal carcinomas, T stage has been revised. The extent of structural involvement for T2 and T4 in particular have been redefined. T2 denotes tumors with extension to parapharyngeal space and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles). T4 indicates tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle. Additionally, N stage for nasopharyngeal squamous cell carcinoma has been simplified, removing N3a and N3b substratification. The anatomic border for defining N3 has been revised from supraclavicular fossa (Level VB) to caudal border of the cricoid cartilage (Level IV, and VB). T and N anatomic definitions are summarized in Figure 4.





**Figure 4.** Differences in defining criteria between the 7<sup>th</sup> edition and the 8<sup>th</sup> edition for staging of NPC: (A) changing the extent of soft tissue involvement as T2 and T4 criteria. Abbreviations: CS = carotid space, LP = lateral pterygoid muscle, M = masseter muscle, MP = medial pterygoid muscle, PG = parotid gland, PPS = parapharyngeal space, PV = prevertebral muscle, T = temporalis muscle; (B) replacing supraclavicular fossa (blue) by lower neck, i.e., below caudal border of cricoid cartilage (red) as N3 criteria.<sup>4</sup> From *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017. © American Joint Committee on Cancer. Reproduced with permission.

The 8<sup>th</sup> edition of the AJCC staging of head and neck cancers includes mucosal melanomas; this does not show significant changes from the 7<sup>th</sup> 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.<sup>5</sup>

Carcinomas of minor salivary glands of the upper aerodigestive tract site, including the oral cavity, are staged according to schemes corresponding to the anatomic site of occurrence. There is no currently accepted staging for central (primary intraosseous) salivary gland tumors.

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 clinical stage information supplemented/modified by operative findings and gross and microscopic evaluation of the resected specimens.<sup>1</sup> 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, 8<sup>th</sup> 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.

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### **I. Dysplasia of the Upper Aerodigestive Tract (UADT)**

The concept of epithelial precursor lesions, including dysplasia and carcinoma in situ of the oropharyngeal (base of tongue and tonsils) and nasopharyngeal mucosa, are not well defined. In biopsies of nasopharyngeal carcinoma, only a minority of cases (less than 10%) will have an in situ component.<sup>1</sup> Further, carcinoma in situ of the oropharynx and nasopharynx as confirmed by biopsy to rule out an invasive carcinoma component is very rare. Histologically, carcinoma in situ of the oropharynx and nasopharynx may be confined to the surface or crypt epithelium without invasive carcinoma and, when present, are most often of the nonkeratinizing type. Hypopharyngeal precursor lesions are rarely identified as hypopharyngeal cancers by virtue of their anatomic site and often remain clinically quiescent commonly presenting as invasive carcinomas.

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### **J. Scope of Guidelines**

The reporting of pharynx cancer including the lip is facilitated by the provision of a case summary illustrating the features required for comprehensive patient care. However, there are many cases in which the individual practicalities of applying such a case summary may not be straightforward. Common examples include finding the prescribed number of lymph nodes, trying to determine the levels of the radical neck dissection, and determining if isolated tumor cells in a lymph node represent metastatic disease. Case summaries have evolved to include clinical, radiographic, morphologic, immunohistochemical, and molecular results in an effort to guide clinical management. Adjuvant and neoadjuvant therapy can significantly alter histologic findings, making accurate classification an increasingly complex and demanding task. This 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, 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 pharynx 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.