Protocol for the Examination of Specimens from Patients with HPV-independent Cancers of the Oropharynx and Cancers of the Hypopharynx

Version: 1.0.0.0
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 HPV-independent cancers of the oropharynx (including the base of the tongue, tonsils, soft palate, and uvula) and cancers of the hypopharynx
Tumor Type	**Description**
Carcinoma	Includes HPV independent and unknown / indeterminate squamous cell carcinoma, and all neuroendocrine carcinoma (regardless of HPV status)

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
HPV-associated oropharyngeal squamous cell carcinoma (consider the HPV-associated Oropharynx 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.

CAP HN.HPV-Ind_Oropharynx_Hypopharynx.Res_1.0.0.0. REL_CAPCP Approved

Summary of Changes

v 1.0.0.0

- New protocol established to replace the retired Pharynx protocol, resulting from the separation of select Head and Neck protocols

Reporting Template

Protocol Posting Date: April 2026
Select a single response unless otherwise indicated.
CASE SUMMARY: (HPV-INDEPENDENT OROPHARYNX and HYPOPHARYNX)
Standard(s): AJCC 8

SPECIMEN

Procedure (select all that apply)
___ Excision: _____
___ Tonsillectomy: _____
___ Pharyngectomy: _____
___ 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)
___ Oropharynx: _____
+Tumor Subsite(s) (select all that apply)
___ Palatine tonsil
___ Tonsillar pillar
___ Tonsillar fossa
___ Lingual tonsil
___ Tonsil, NOS
___ Base of tongue
___ Soft palate
___ Uvula
___ Lateral wall of oropharynx
___ Posterior wall of oropharynx
___ Vallecula
___ Epiglottis, anterior surface (lingual aspect)
___ Other (specify): _____
___ Cannot be determined (explain): _____

___ Hypopharynx: _____
+Tumor Subsite(s) (select all that apply)
___ Pyriform sinus
___ Aryepiglottic fold, hypopharyngeal aspect
___ Postcricoid
___ Posterior wall of hypopharynx
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Not specified

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

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

Histologic Type# (Note B)
 # Please complete separate checklists if both an Oropharynx HPV-independent tumor and a Hypopharynx tumor are present and / or there are two separate primary sites
___ Oropharynx
Histologic Type (oropharynx)
Squamous Cell Carcinoma Subtypes of the Oropharynx
___ Squamous cell carcinoma, [conventional] keratinizing, HPV-independent
___ Squamous cell carcinoma, non-keratinizing, NOS, HPV-independent
___ Adenosquamous carcinoma, HPV-independent
___ Basaloid squamous cell carcinoma, HPV-independent
___ Papillary squamous cell carcinoma, HPV-independent
___ Spindle cell / sarcomatoid squamous carcinoma, HPV-independent
___ Verrucous carcinoma, HPV-independent
___ Carcinoma cuniculatum
___ Lymphoepithelial carcinoma (non-nasopharyngeal), HPV-independent
___ Hypopharynx
Histologic Type (hypopharynx)
Squamous Cell Carcinoma Subtypes of the Hypopharynx
___ Squamous cell carcinoma, conventional [keratinizing]
___ Squamous cell carcinoma, non-keratinizing, NOS
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Papillary squamous cell carcinoma
___ Spindle cell [sarcomatoid] squamous carcinoma
___ Verrucous carcinoma
___ Carcinoma cuniculatum

___ Lymphoepithelial carcinoma (non-nasopharyngeal)

___ Neuroendocrine

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

+Histologic Type Comment: _____

Histologic Grade (required only for non-neuroendocrine carcinomas) (Note C)

___ Not applicable
___ G1, well-differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ Other (specify): _____
___ GX, cannot be assessed: _____

Tumor Extent (specify other structures 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)

Main 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: _____

+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 (use orientation when provided)

___ Specify involved specimen margin(s): _____

___ Cannot be determined (explain): _____

___ Other (specify): _____

___ Cannot be determined (explain): _____

Main Specimen Margin Status for Non-invasive Tumor (High-grade Dysplasia) (required only if applicable)#

 # Applicable only to squamous cell carcinoma and its histologic subtypes and required only when closer than invasive carcinoma.

___ Not applicable

___ All specimen margins negative for high-grade dysplasia / in situ disease

+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

Specimen Margin(s) Involved by Non-invasive Tumor (use orientation when provided)

___ 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
___ 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

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: _____
+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)
___ 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
___ HPV-independent oropharynx
pT Category (HPV-independent oropharynx)
___ 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, 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)

___ Hypopharynx

pT Category (hypopharynx)

___ 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 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
 # Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat

___ 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#

 # 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 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

SPECIAL STUDIES

To use this protocol appropriately, the pathologist should 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. If needed, a consultation to another testing center prior to sign out is highly advised in order to use the correct TNM classification system. HPV testing should be performed according to the updated CAP guidelines for Head and Neck Carcinomas. For reporting other molecular and biomarker testing results, the CAP Head and Neck Biomarker Template should be used.

Ancillary Studies Performed (required only for oropharynx) (select all that apply)
___ Not applicable
___ p16 IHC
p16 IHC as a Surrogate for Transcriptionally Active High-Risk HPV
___ Negative (less than 50% moderate-to-strong nuclear and cytoplasmic staining)
___ Equivocal (less than 70% but greater than or equal to 50% moderate-to-strong nuclear and cytoplasmic staining)
___ Positive (greater than or equal to 70% moderate-to-strong nuclear and cytoplasmic staining)
___ 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 (if available): _____
___ Cannot be determined (explain): _____

___ HPV-DNA PCR
HPV-DNA PCR
___ Negative
___ Positive
Specify Subtypes (if available): _____
___ Cannot be determined (explain): _____

___ HPV E6 / E7 mRNA RT-PCR
HPV E6 / E7 mRNA RT-PCR
___ Negative

___ Positive
Specify Subtypes (if available): _____
___ Cannot be determined (explain): _____
___ Other studies (specify): _____
___ Pending studies (specify): _____
___ Not specified
___ Not performed

COMMENTS

Comment(s): _____

Explanatory Notes

A. Anatomical Sites and Subsites for Pharynx

The pharynx is divided into 3 parts including the nasopharynx, oropharynx, and hypopharynx (Figure 1). Only the oropharynx and hypopharynx are relevant to this protocol.

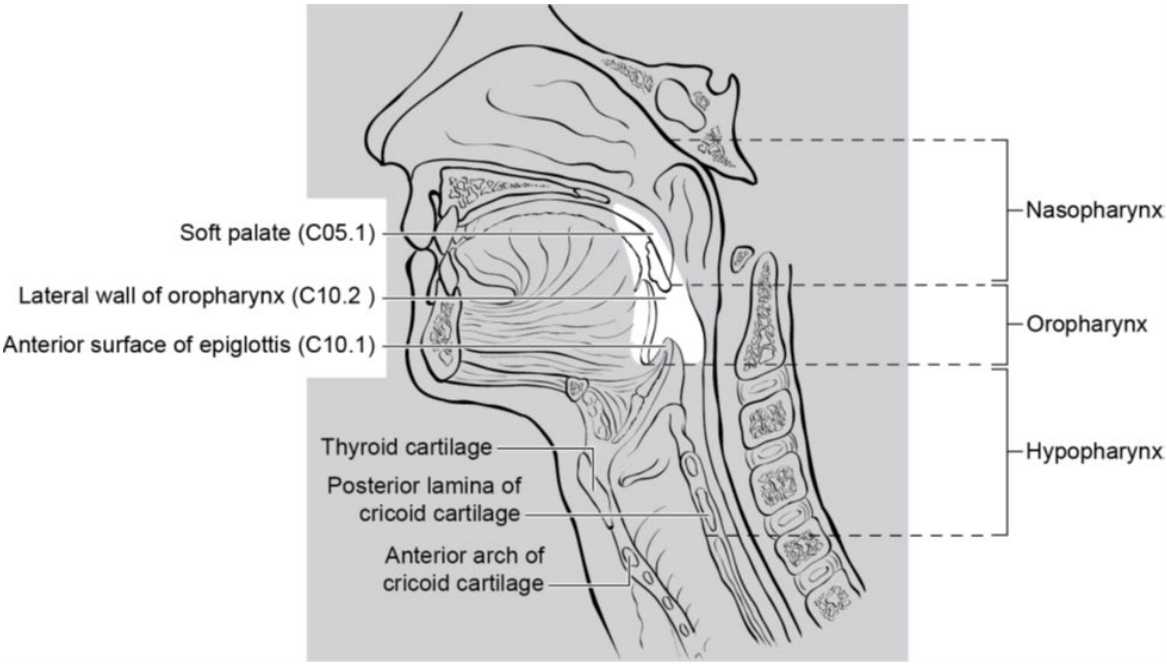

Figure 1. Anatomic subdivisions and "contents" of the pharynx. Evans M, Huang S, Ho A, et al., American Joint Committee on Cancer (AJCC). 2025. *AJCC Protocol for Cancer Staging: Oropharynx (HPV-Associated) (Version 9)*. Reproduced with permission.

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.[1,2] 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

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.[1] 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

References

1. Lydiatt WM, Ridge JA, Patel SG, et al. Oropharynx (p16 -) and hypopharynx. In: Amin MB, ed. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
2. Evans M, Huang S, Ho A, et al. American Joint Committee on Cancer (AJCC). 2025. *AJCC Protocol for Cancer Staging: Oropharynx (HPV-Associated)* (*Version 9*).

B. Histologic Type

A modification of the WHO classification of carcinomas of the oropharynx and the hypopharynx is shown below.[1] This list may not be complete. It is recognized that the AJCC 8th edition terminology[2] diverges slightly from the WHO 5th edition terminology[1] 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. However, cancers with discordant HPV and p16 status have a prognosis that is intermediate between HPV true positive and HPV true negative cancers.[3] HPV discordant cases are effectively considered indeterminate and grouped with HPV independent cancers for staging. This protocol applies only to carcinomas and does not apply to melanomas, lymphomas, or sarcomas.

Carcinomas of the Oropharynx and Hypopharynx

Squamous cell carcinoma

- HPV-independent squamous cell carcinoma (oropharynx and hypopharynx)
- Squamous cell carcinoma of the oropharynx, HPV-unknown or indeterminate

Subtypes of 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. The entities relevant to this protocol are listed below:

- Neuroendocrine tumor, grades 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, is HPV-associated. Despite this association, they are captured in this protocol, as the HPV-associated protocol is specifically for squamous cell carcinoma only.

References

1. WHO Classification of Tumours Editorial Board. *Head and neck tumours* [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2025, Nov 12]. (*WHO classification of tumours series, 5th ed.; vol. 9*). Available from: https://tumourclassification.iarc.who.int/chapters/52
2. Lydiatt WM, Ridge JA, Patel SG, et al. Oropharynx (p16 -) and hypopharynx. In: Amin MB, ed. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
3. Mehanna H, Taberna M, von Buchwald C, et al. Prognostic implications of p16 and HPV discordance in oropharyngeal cancer (HNCIG-EPIC-OPC): a multicentre, multinational, individual patient data analysis. *Lancet Oncol.* 2023 Mar;24(3):239-251.

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] 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.[1,2] 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.[2] 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.

References

1. WHO Classification of Tumours Editorial Board. *Head and neck tumours*. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2025, Nov 12]. (*WHO classification of tumours series, 5th ed.; vol. 9*). Available from: https://tumourclassification.iarc.who.int/chapters/52
2. Mete O, Gill A, and Nosé V. Neuroendocrine neoplasms and paraganglioma: Introduction. In: WHO Classification of Tumours Editorial Board. *Head and neck tumours.* Lyon (France): International Agency for Research on Cancer; 2022 [cited 2025 Nov 12]. (*WHO classification of tumours series, 5th ed.; vol. 9*). Available from: https://tumourclassification.iarc.who.int/chapters/52

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. 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] 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.

References

1. Smith BD, Haffty BG. Prognostic factors in patients with head and neck cancer. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and Neck Cancer: A Multidisciplinary Approach.* Philadelphia, PA: Lippincott Williams and Wilkins; 2009:51-75.
2. Fagan JJ, Collins B, Barnes L, D'Amico F, Myers EN, Johnson JT. Perineural invasion in squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg.* 1998;124(6):637-640.

3. Miller ME, Palla B, Chen Q, et al. A novel classification system for perineural invasion in noncutaneous head and neck squamous cell carcinoma: histologic subcategories and patient outcomes. *Am J Otolaryngol.* 2012;33(2):212-215.
4. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350(19):1937-1944.
5. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350(19):1945-1952.

E. Margins and Orientation

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).[1,2,3] Akin to other sites, there is no standard definition of a “close” margin, and definitions have ranged from 2 mm to 5 mm.[2] 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 are 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 Oral Cavity and Protocol for the Examination of Specimens from Patients with Carcinomas of the Larynx).

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.

References

1. Weinstein GS, O'Malley BW, Jr., Snyder W, Sherman E, Quon H. Transoral robotic surgery: radical tonsillectomy. *Arch Otolaryngol Head Neck Surg.* 2007;133(12):1220-1226.
2. Rubek N, Channir HI, Charabi BW, et al. Primary transoral robotic surgery with concurrent neck dissection for early stage oropharyngeal squamous cell carcinoma implemented at a Danish head and neck cancer center: a phase II trial on feasibility and tumour margin status. *Eur Arch Otorhinolaryngol.* 2017;274(5):2229-2237.
3. Weiss BG, Ihler F, Wolff HA, et al. Transoral laser microsurgery for treatment for hypopharyngeal cancer in 211 patients. *Head Neck.* 2017;39(8):1631-1638.

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

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 2), 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 2.

Figure 2. 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 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. 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),[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.

References

1. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350(19):1937-1944.
2. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350(19):1945-1952.
3. Gress DM, Edge SB, Greene FL et al. General Information on Cancer Staging and End-Results Reporting. In: Amin MB, ed. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
4. Singh A, Roy S, Tuljapurkar V, et al.Critical Review of the Current Evidence on Sentinel Node Biopsy in Oral Cancer. *Curr Oncol Rep.* 2022 Jun;24(6):783-791
5. Liokatis P, Liokati I, et al. Prognostic role of lymph node micrometastasis in oral and oropharyngeal cancer: A systematic review. *Oral Oncol.* 2024 Jul; 154:106808.
6. Broglie MA, Haerle SK, Huber GF, Haile SR, Stoeckli SJ. Occult metastases detected by sentinel node biopsy in patients with early oral and oropharyngeal squamous cell carcinomas: Impact on survival. *Head Neck.* 2013;35(5):660-666.
7. Ferlito A, Robbins KT, Shah JP, et al. Proposal for a rational classification of neck dissections. *Head Neck.* 2011;33(3):445-450.
8. Robbins KT, Shaha AR, Medina JE, et al. Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg.* 2008;134(5):536-538.
9. Seethala RR. Current state of neck dissection in the United States. *Head Neck Pathol.* 2009;3(3):238-245.
10. Suarez C, Rodrigo JP, Robbins KT, et al. Superselective neck dissection: rationale, indications, and results. *Eur Arch Otorhinolaryngol.* 2013; 270(11):2815-2821.

11. Ebrahimi A, Gil Z, Amit M. International Consortium for Outcome Research (ICOR) in Head and Neck Cancer. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. *JAMA Otolaryngol Head Neck Surg.* 2014;140(12):1138-1148.
12. Abou-Foul AK, Henson C, Chernock RD, et al. Standardised definitions and diagnostic criteria for extranodal extension detected on histopathological examination in head and neck cancer: Head and Neck Cancer International Group consensus recommendations. *The Lancet Oncology* 2024; 25(7): e286-e96.
13. Gupta R, Fielder T, Bal M, et al. International Consensus Recommendations of Diagnostic Criteria and Terminologies for Extranodal Extension in Head and Neck Squamous Cell Carcinoma: An HN CLEAR Initiative (Update 1). *Head and neck pathology* 2025; 19(1): 20.

G. pTNM Classification

The protocol recommends using the 8th edition of AJCC TNM classification for the HPV-independent oropharynx and hypopharynx.[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 clinical stage information supplemented/modified by operative findings and gross and microscopic evaluation of the resected specimens.[1] 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.

Pathological stage classification is usually performed after surgical resection of the primary tumor. Pathological staging depends on pathological 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 pathological classification and staging have been satisfied without total removal of the primary cancer.

TNM Descriptors[2]

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.

References

1. Lydiatt WM, Ridge JA, Patel SG, et al. Oropharynx (p16 -) and hypopharynx. In: Amin MB, ed. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
2. Gress DM, Edge SB, Greene FL et al. General Information on Cancer Staging and End-Results Reporting. In: Amin MB, ed. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.