COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens from Patients with HPV-associated Squamous Cell Carcinoma of the Oropharynx

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 oropharynx
Tumor Type	**Description**
Carcinoma	Includes HPV-associated carcinoma and its subtypes

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)

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

Tumor Type
HPV-independent or unknown/indeterminate oropharyngeal and hypopharyngeal squamous cell carcinoma (consider the HPV Independent Oropharynx and Hypopharynx protocol)
Neuroendocrine carcinoma (regardless of HPV status) (consider the HPV Independent Oropharynx and Hypopharynx protocol)
Sarcoma (consider the Soft Tissue protocol)
Hematologic malignancies (consider the Precursor and Mature Lymphoid Malignancies, Myeloid and Mixed / Ambiguous Lineage Neoplasms, and Plasma Cell Malignancies protocols)
Mucosal melanoma (consider the Head and Neck Mucosal Melanoma protocol)
Salivary glands (consider the Salivary Gland protocol)

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

Replaced by version 1.1.0.0 on June 17, 2026, Obsolete as of March 2027 (8 months after newest release date)

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

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

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).
Full accreditation requirements can be found on the CAP website under Accreditation Checklists.
A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.
**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

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

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

Summary of Changes

v 1.0.0.0

- New protocol established to replace the retired Pharynx protocol, resulting from the separation of select Head and Neck protocols
- Update to AJCC Version 9 pTNM Classification

Reporting Template

Protocol Posting Date: April 2026
Select a single response unless otherwise indicated.
CASE SUMMARY: (HPV-ASSOCIATED OROPHARYNX)
Standard(s): AJCC 9

SPECIMEN

Procedure (select all that apply)
___ Excision: _____
___ Tonsillectomy: _____
___ 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): _____

Oropharynx Tumor Subsite(s) (Note A) (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): _____

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)
___ Squamous cell carcinoma, non-keratinizing, HPV-associated
___ Squamous cell carcinoma, keratinizing, HPV-associated
___ Adenosquamous carcinoma, HPV-associated
___ Ciliated adenosquamous carcinoma, HPV-associated
___ Basaloid squamous cell carcinoma, HPV-associated
___ Papillary squamous cell carcinoma, HPV-associated
___ Spindle cell / sarcomatoid squamous carcinoma, HPV-associated
___ Lymphoepithelial carcinoma (non-nasopharyngeal), HPV-associated
___ Other HPV-associated histologic type not listed (specify): _____
___ HPV-associated carcinoma, type cannot be determined: _____

+Histologic Type Comment: _____

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

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

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

+Tumor Comment: _____

MARGINS (Note D)

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 (explain): _____

+Other Close Specimen Margin(s) to Invasive Tumor

___ Specify location(s) and distance(s) of other close specimen margin(s): _____

___ Cannot be determined: _____

___ Invasive tumor present at specimen margin(s)

Specimen Margin(s) Involved by Invasive Tumor (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): _____

___ Other (specify): _____

___ Cannot be determined: _____

___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES (Note E)

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: _____
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 Version 9) (Note F)

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

___ pT0: No evidence of primary tumor
___ pT1: Tumor is less than or equal to 2 cm in greatest dimension
___ pT2: Tumor greater than 2 cm but less than or equal to 4 cm in greatest dimension
___ pT3: Tumor is greater than 4 cm in greatest dimension or extension to lingual surface of epiglottis

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

___ pT4: Tumor invades any of the following: larynx; OR deep / extrinsic muscle of the tongue (genioglossus, hypoglossus, palatoglossus, and styloglossus); OR pterygoid muscles (medial and / or lateral); OR hard palate; OR mandible; OR pterygoid plates (medial and / or lateral); OR nasopharynx; OR skull base; OR encases carotid artery#

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)

 # A minimum of 6 lymph nodes is required to assign pN0 status based on AJCC Version 9 guidelines described in Explanatory Note E.

___ pN0: No tumor involvement of regional lymph node(s)#

pN1: Tumor involvement of 1-4 lymph nodes without definitive pathological extranodal extension

___ pN1a: Tumor involvement of 1 lymph node without definitive pathological extranodal extension

___ pN1b: Tumor involvement of 2-4 lymph nodes without definitive pathological extranodal extension

___ pN1 (subcategory cannot be determined)

___ pN2: Tumor involvement of 1-4 lymph nodes with definitive pathological extranodal extension OR Tumor involvement of greater than 4 lymph nodes without definitive pathological extranodal extension

___ pN3: Tumor involvement of greater than 4 lymph nodes with definitive pathological extranodal extension

pM Category (required only if confirmed pathologically)

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

___ pM1: Microscopic confirmation of 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# (select all that apply)

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

___ 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)

___ Other (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 (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 Subsites

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

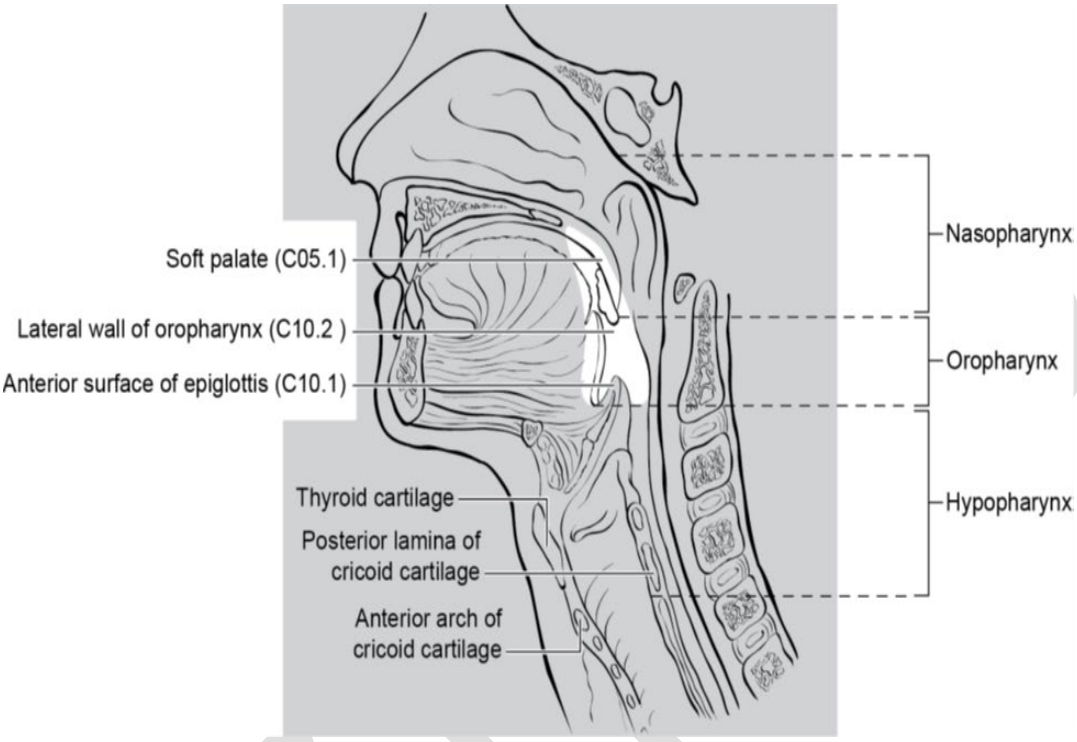

Figure 1. Anatomic subdivisions and "contents" of the pharynx. Evans M, Huang S, Ho A, et al. American Joint Committee on Cancer (AJCC). 2025. *AJCC Protocol for Cancer Staging: Oropharynx (HPV-Associated)* (Version 9).

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] The contents of the oropharynx include:

- Base of tongue, NOS
- Lingual tonsil
- Soft palate, NOS
- Uvula
- Tonsillar fossa
- Tonsillar pillar
- Tonsil, NOS
- Vallecula
- Lateral wall of oropharynx
- Posterior pharyngeal wall

References
1. 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 and Grade

The WHO classification of HPV-associated squamous cell carcinomas of the oropharynx is shown below.[1] There is no standard grading system for HPV-associated squamous cell carcinoma. Cancers with discordant HPV and p16 status have a prognosis that is intermediate between HPV true positive and HPV true negative cancers.[2] HPV discordant cases are effectively considered indeterminate and grouped with HPV independent cancers for staging and should not be entered into this protocol.

- Squamous cell carcinoma, non-keratinizing, HPV-associated
- Squamous cell carcinoma, keratinizing, HPV-associated
- Adenosquamous carcinoma, HPV-associated
- Ciliated adenosquamous carcinoma, HPV-associated
- Basaloid squamous cell carcinoma, HPV-associated
- Papillary squamous cell carcinoma, HPV-associated
- Spindle cell / sarcomatoid squamous carcinoma, HPV-associated
- Lymphoepithelial carcinoma (non-nasopharyngeal), HPV-associated

References
1. WHO Classification of Tumours Editorial Board. Head and neck tumours. Lyon (France): International Agency for Research on Cancer; 2022. (*WHO classification of tumours series, 5th ed.; vol. 9*). Available from: https://tumourclassification.iarc.who.int/chapters/52
2. 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. Lymphatic and/or Vascular Invasion and Perineural Invasion

Lymphatic/vascular and perineural invasion are considered intermediate risk factors for all head and neck squamous cell carcinomas including HPV-associated oropharyngeal squamous cell carcinoma, and help determine the need for postoperative radiation.[1,2,3] Perineural invasion correlates with extranodal extension.[4,5]

References
1. 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)*.
2. Haughey BH, Sinha P, Kallogjeri D, et al. Pathology-based staging for HPV-positive squamous carcinoma of the oropharynx. *Oral Oncol.* 2016 Nov; 62:11-19.
3. Albergotti WG, Schwarzbach HL, Abberbock S, et al. Defining the Prevalence and Prognostic Value of Perineural Invasion and Angiolymphatic Invasion in Human Papillomavirus-Positive Oropharyngeal Carcinoma. *JAMA Otolaryngol Head Neck Surg.* 2017 Dec 1;143(12):1236-1243.
4. Xu B, Saliba M, Alzumaili B, et al. Prognostic impact of extranodal extension (ENE) in surgically managed treatment-naive HPV-positive oropharyngeal squamous cell carcinoma with nodal metastasis. *Mod Pathol.* 2022 Nov;35(11):1578-1586.

5. Olson B, Bogan A, Abdel-Halim CN, et al. Identification of clinical and pathologic features associated with extranodal extension in patients with HPV-mediated oropharyngeal squamous cell carcinoma. *Oral Oncol.* 2025 Jul: 166:107308.

D. Margins and Orientation

With the advent of transoral robotic and laser surgery, 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. Despite the paucity of data, in keeping with other sites, the distance from the nearest margin should be recorded.

Complex specimens should be examined and oriented with the assistance of the operating surgeon(s). Direct communication between the surgeon and pathologist is a critical component in specimen orientation and proper sectioning. Whenever possible, the tissue examination request form should include a drawing or photograph of the resected specimen showing the extent of the tumor and its relation to the anatomic structures of the region. The lines and extent of the resection can be depicted on preprinted adhesive labels and attached to the surgical pathology request forms.

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: Aug;39(8):1631-1638.

E. 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.

Special Procedures for Lymph Nodes

Cervical nodal metastases may occur in the setting of an unknown primary carcinoma referred to as metastatic cervical carcinoma with an unknown primary (CUP).

Patients with HPV-associated cervical adenopathy without an identifiable primary are assigned a pT0 as per AJCC Version 9 TNM classification of HPV-associated oropharyngeal squamous cell carcinoma.[1] The

updated CAP guidelines for HPV testing in Head and Neck Carcinomas recommend HPV specific testing (i.e., RNA in situ hybridization, DNA or RNA PCR) in addition to p16.[2]

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. 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. AJCC Version 9 now introduces a minimum requirement of 6 lymph nodes to be examined in order to assign a pN0 status.[1]

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.

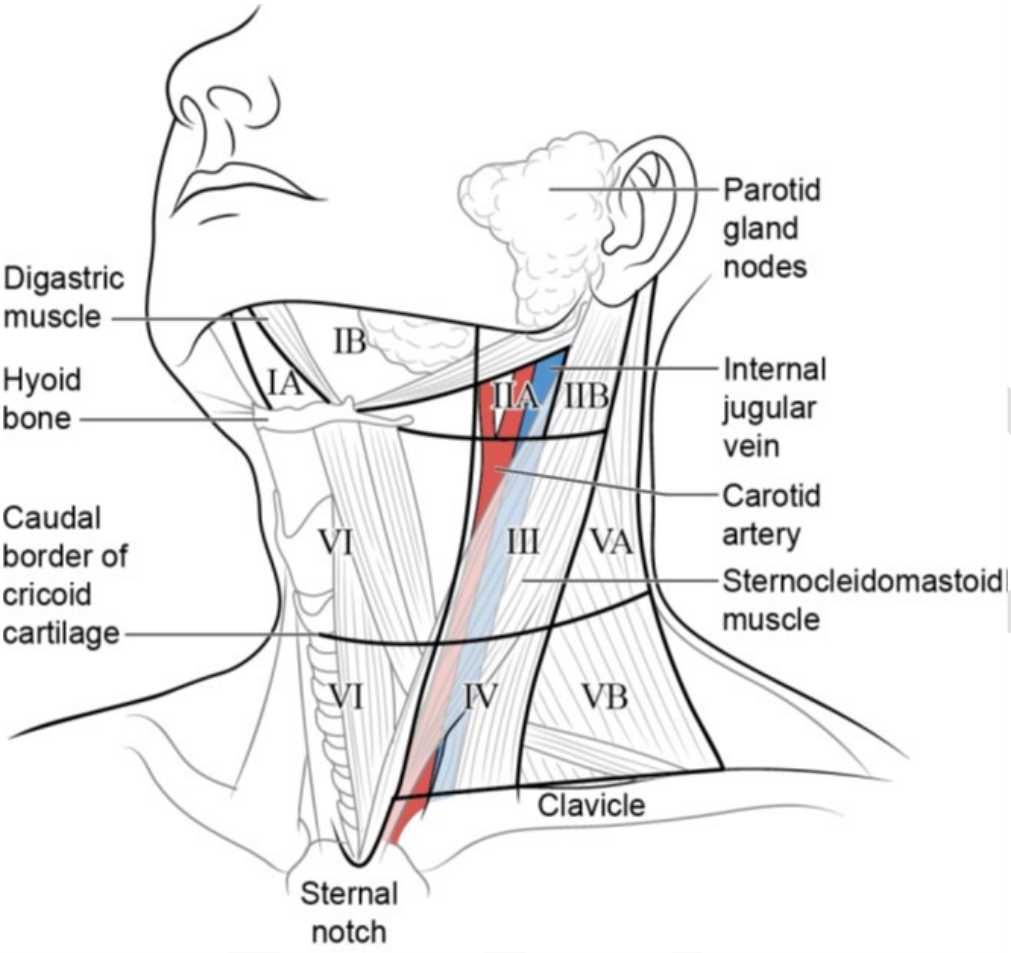

Figure 2. The six levels of the neck for describing the location of lymph nodes along with sublevels: Level IA, submental group; level IB, submandibular group; level IIA, upper jugular nodes along the carotid sheath, including the subdigastric group; level IIB, upper jugular nodes in the submuscular recess; level VA, spinal accessory nodes; and level VB, the supraclavicular and transverse cervical nodes. 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.

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. Midline nodes are considered ipsilateral nodes.

Extranodal Extension

Extranodal extension (ENE) is again a core element for AJCC Version 9 pathological TNM classification of HPV-associated oropharyngeal squamous cell carcinoma.[1,11] Analysis of 14,447 surgically treated oropharyngeal squamous cell carcinoma patients within the National Cancer Database demonstrated that inclusion of ENE in N-classification showed superior performance characteristics as compared to AJCC 8th edition N-classification without ENE.

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 the detection of 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 but 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

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F. pTNM Classification

The protocol recommends using the AJCC Version 9 pathological TNM classification of HPV-associated oropharyngeal squamous cell carcinoma for reporting. For the AJCC Version 9, no changes to the pT classification have been made. However, for pN classification, pENE classifies AJCC 8th Edition N1 and N2 one stratum higher (i.e., less than or equal to 4 positive lymph nodes and ENE is N2, while greater than 4 positive lymph nodes with ENE is N3). Additionally, pN1 without ENE is now subdivided into pN1a (1 single node without definitive pENE) and pN1b (2-4 nodes without definitive pENE).[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 pathological 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 pathological 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.

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