

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

Protocol applies to carcinomas of the pharynx (oropharynx, nasopharynx, hypopharynx) including the base of tongue, tonsils, soft palate, and uvula. Mucosal melanoma is included. This protocol does not apply to lymphoma or sarcoma.

Based on:

- AJCC/UICC TNM, 8th edition
- CAP Cancer Protocol version: Pharynx 4.0.0.1
- CAP Protocol Web Posting Date: June 2017
- AAPA Macroscopic Examination Template Version 2.0
- AAPA Web Posting Date: September 2018

Revision History:

None

Summary of Changes:

This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual and the current version of the CAP Cancer Protocol Pharynx 4.0.0.1.

Procedures Covered in this Protocol:

- Excision
- Resection
- Neck (lymph node) dissection

Authors:

- Stefanie Stephan, PA(ASCP)^{CM*}
Department of Pathology, University of Colorado, Aurora, CO
- Courtney Hyland, PA(ASCP)^{CM}
Mayo Clinic, Rochester, MN
- Darryl Kinnear, PA(ASCP)^{CM}
Department of Pathology, Baylor College of Medicine, Houston, TX
- John Lehman, PA(ASCP)^{CM}
Mayo Clinic, Rochester, MN
- Stephanie Miller, PA(ASCP)^{CM}
Providence Health & Services, Portland, OR
- Chandra Pettry, PA(ASCP)^{CM}
Mayo Clinic, Rochester, MN
- Tina Rader, PA(ASCP)^{CM}
Drexel University College of Medicine, Philadelphia, PA
- Erica Reed, PA(ASCP)^{CM}
Mayo Clinic, Rochester, MN
- Chevanne Scordinsky, PA(ASCP)^{CM}
Department of Pathology, Atlantic Health System, Morris Plains, NJ
- Mike Sovocool, MHS, PA(ASCP)^{CM}
Pathology Associates of Syracuse, Syracuse, NY
- Dennis Strenk, PA(ASCP)^{CM}
Wisconsin Diagnostic Laboratories, Milwaukee, WI
- Connie Thorpe, PA(ASCP)^{CM}
Department of Pathology, Saint Louis University, St. Louis, MO
- Jon Wagner, PA(ASCP)^{CM}
Department of Pathology, Sutter Roseville Medical Center, Roseville, CA



**AAPA Macroscopic Examination Guidelines:
Utilization of the CAP Cancer Protocols at the Surgical Gross Bench**

*Denotes primary author. All other contributing authors are listed alphabetically.

Previous Lead Contributors:

None

Art Director | Illustrator Liaison:

Jesse McCoy, BFA, MHS, PA(ASCP)^{CM}

Hampton Roads Pathology, Chesapeake Regional Medical Center, Chesapeake, VA

Illustrator:

Matthew Brownstein

Copyright:

© 2018 American Association of Pathologists' Assistants. All rights reserved.

The American Association of Pathologists' Assistants (the "AAPA") hereby authorizes use of The AAPA Macroscopic Examination Guidelines: Utilization of the CAP Cancer Protocols at the Surgical Gross Bench Second Edition (the "Protocols") solely by pathologists' assistants, pathology residents, and/or pathologists (collectively "Laboratory Personnel") within the laboratories in which they work for the purposes of processing of cancer cases and the education of Laboratory Personnel related to the processing of cancer cases (collectively "Permitted Uses"). The modification or creation of derivative works of the Protocols is prohibited. Any reproduction of the Protocols must be of the complete, unmodified Protocols and solely for the Permitted Uses of the Laboratory Personnel within the laboratories in which they work. Reproduction or distribution of: (a) only a portion of the Protocols; (b) all or a portion of these Protocols outside of the laboratories in which the Laboratory Personnel work; or (c) for commercial use of the Protocols beyond the Permitted Uses, is strictly prohibited.

The purpose of the Protocols is to support Laboratory Personnel engaged in the macroscopic examination of cancer resection specimens. The Protocols are based on specified relevant source documents, drafted by pathologists' assistant experts, and supported by information provided by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC). These Protocols are intended to serve patients by ensuring that the macroscopic examination of cancer resection specimens is compliant with CAP Cancer Protocols, the AJCC Cancer Staging Manual, and provide optimization of the pre-analytic steps necessary to promote appropriate molecular studies.

The AAPA cautions that the use of the Protocols in practice may require the use of additional considerations that are beyond the scope of the Protocols. The AAPA does not offer medical advice or diagnoses, or engage in the practice of medicine. The information provided in the Protocols is not intended or implied to be a substitute for the Laboratory Personnel's own training, professional medical opinion, diagnosis, or treatment advice. All content, including text, graphics, images and information contained in the Protocols are for the above stated purposes only. Laboratory Personnel are encouraged to confirm any information provided in these Protocols with other sources. The inclusion of a product name, organization, or service in an AAPA publication, including without limitation the Protocols, should not be construed as an endorsement of such product, organization, or service, nor is failure to include the name of a product, organization or service to be construed as disapproval.

THE AAPA IS NOT RESPONSIBLE NOR LIABLE FOR ANY ADVICE, COURSE OF TREATMENT, DIAGNOSIS OR ANY OTHER INFORMATION, SERVICES OR PRODUCTS THAT LABORATORY PERSONNEL PROVIDE WHETHER OR NOT IN RELATION TO USING THE PROTOCOLS. THE AAPA DOES NOT WARRANT OR MAKE ANY REPRESENTATION REGARDING USE, OR THE RESULT OF USE, OF THE CONTENT OF THE PROTOCOLS IN TERMS OF ACCURACY, RELIABILITY, OR OTHERWISE. THE CONTENT OF THE PROTOCOLS MAY INCLUDE TECHNICAL INACCURACIES OR TYPOGRAPHICAL ERRORS, AND THE AAPA MAY MAKE CHANGES OR IMPROVEMENTS AT ANY TIME. YOUR USE OF THESE PROTOCOLS IS AT YOUR OWN RISK. THE CONTENT IS PROVIDED "AS IS" AND WITHOUT WARRANTIES OF ANY KIND, EITHER EXPRESSED OR IMPLIED. THE AAPA DISCLAIMS ALL WARRANTIES, INCLUDING ANY IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, TITLE, OR NON-INFRINGEMENT.

TO THE FULL EXTENT ALLOWED BY THE LAW, THE AAPA, ITS MEMBERS, AFFILIATES, LICENSORS, SERVICE PROVIDERS, CONTENT PROVIDERS, EMPLOYEES, AGENTS, OFFICERS, AND DIRECTORS (THE "AAPA PARTIES") WILL NOT BE LIABLE FOR ANY INCIDENTAL, DIRECT, INDIRECT, PUNITIVE, ACTUAL, CONSEQUENTIAL, SPECIAL, EXEMPLARY, OR OTHER DAMAGES, INCLUDING LOSS OF REVENUE OR INCOME, PAIN AND SUFFERING, EMOTIONAL DISTRESS, OR SIMILAR DAMAGES IN RELATION TO THE PROTOCOLS, EVEN IF THE AAPA PARTIES HAVE BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. IN NO EVENT WILL THE COLLECTIVE LIABILITY OF THE AAPA PARTIES TO ANYONE IN RELATION TO THE PROTOCOLS (REGARDLESS OF THE FORM OF ACTION, WHETHER IN CONTRACT, TORT, OR OTHERWISE) EXCEED THE MINIMUM AMOUNT ALLOWED BY LAW. SOME JURISDICTIONS DO NOT ALLOW THE LIMITATION OR EXCLUSION OF LIABILITY OR



**AAPA Macroscopic Examination Guidelines:
Utilization of the CAP Cancer Protocols at the Surgical Gross Bench**

WARRANTIES FOR CERTAIN TYPES OF DAMAGES. AS A RESULT, THE ABOVE LIMITATIONS OR EXCLUSIONS MAY NOT FULLY APPLY TO YOU.

Molecular Considerations:

Testing for high-risk type 16 human papillomavirus (HPV-16) by in situ hybridization and p16 immunohistochemical staining has been shown to reliably predict the presence of a head and neck squamous cell carcinoma (HNSCC) or, in particular, head and neck squamous cell carcinoma (HNSCC) correlated with an oropharyngeal orifice (i.e., tonsil and base of tongue).

Epstein-Barr virus (EBV) is associated with non-keratinizing types of nasopharyngeal carcinomas, including both differentiated and undifferentiated subtypes. The most reliable detection method for EBV is in situ hybridization for Epstein Barr virus encoded RNA (EBER), facilitating the diagnosis of nasopharyngeal carcinoma, even in a metastatic cervical carcinoma with an unknown primary, (MCCUP) suspected of having a nasopharyngeal origin.

A rarer type of tumor, NUT midline carcinoma, may occur in the head and neck region. The NUT gene translocation can be detected through FISH or RT-PCR.

Immunohistochemistry Considerations:

Immunohistochemical staining including S-100, HMB-45, Melanin-A, MITF, and PNL-2 will help confirm a mucosal melanoma diagnosis.

These tests can be performed on formalin fixed paraffin embedded tissue sections. The macroscopic description should provide the fixative used. 10% neutral buffered formalin is the preferred fixative. It is recommended that the duration of fixation be provided as well.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

■ Procedures Covered by this Protocol:

- Excision
- Tonsillectomy
- Laryngopharyngectomy
- Neck (lymph node) dissection (specify)
- Other (specify)

■ Specimen Size and Extent of Resection:

- Specify the type of specimen received: *
 - Oropharynx
 - Nasopharynx
 - Hypopharynx
- Provide three dimensions in cm.
- Include measurements of additional structures, if present.
- Specify laterality.
- Specify orientation. **

**Complex specimens should be examined and oriented with the assistance of the surgeon. Direct communication between the surgeon and pathologist is an essential component in specimen orientation and proper sectioning. A drawing or photograph of the resected specimen demonstrating the extent of the tumor and its relation to the regional anatomic structures can offer significant benefit.

***Anatomic Sites and Subsites of the Pharynx: (Figure 1)**

Nasopharynx

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. The contents of the nasopharynx include:

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

Oropharynx

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. 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

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. 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 forming the anterior wall of the hypopharynx

Waldeyer's ring is formed by an annular arrangement of extranodal lymphoid tissues at the upper end of the pharynx which consists of the:

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

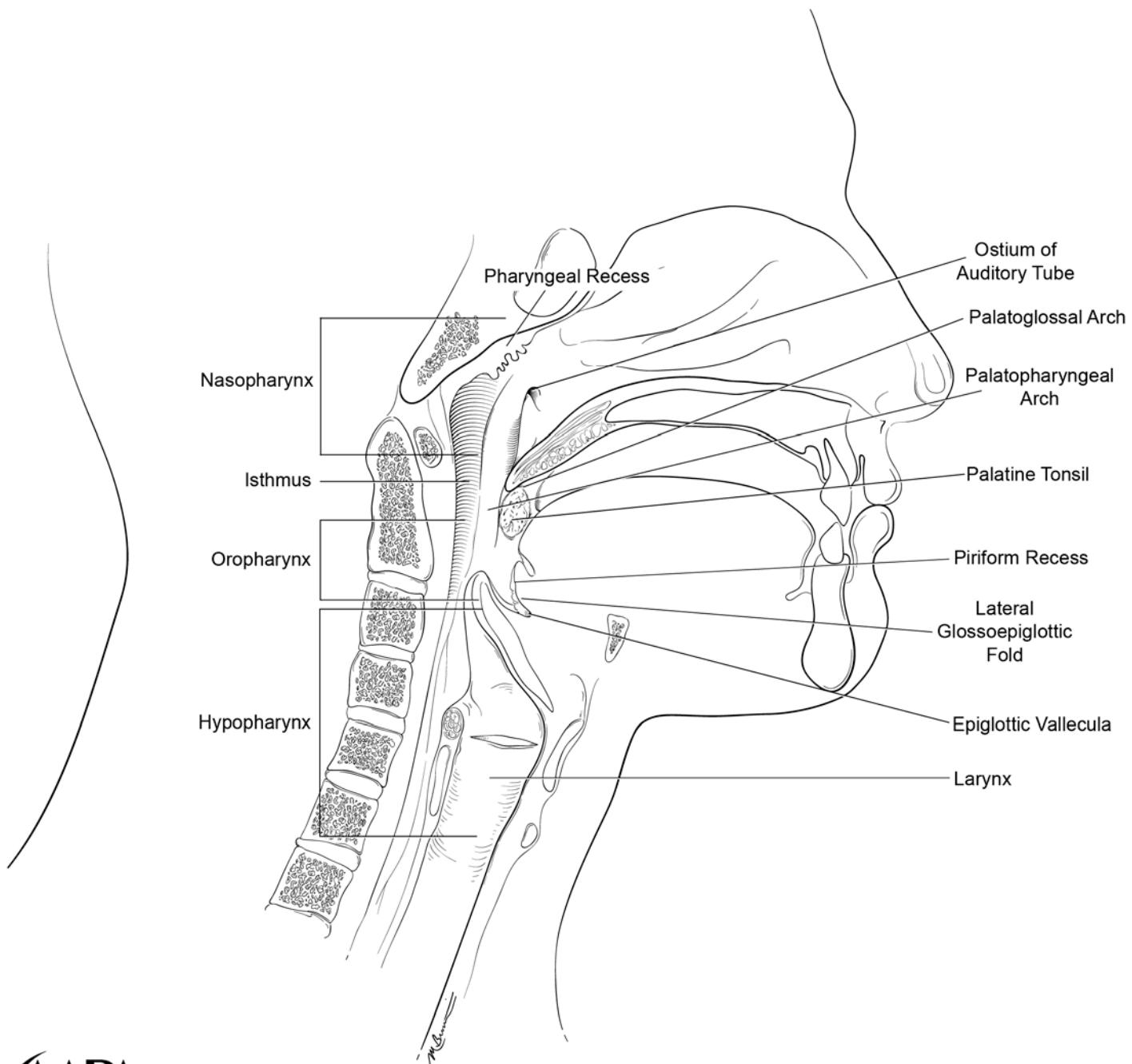


Figure 1: Pharynx General Anatomy

■ **Specimen Integrity and Adequacy:**

- Provide an assessment of the specimen integrity.
 - Specify if the specimen is intact or fragmented.
 - If fragmented, count and provide an aggregate measurement of tissue fragments.
- Identify and describe any defects or disruptions.*

** Statements should include the location of any defects in relation to surrounding anatomical structures and the tumor. Disruptions of margins must also be noted. Surgical disruptions should be differentiated from tumor breach by consultation with the surgeon and pathologist. The defect may need to be specifically identified and applied with ink. It may be critical to determine the breach of a particular margin, especially if such a margin constitutes an increase in staging.*

TUMOR ("T" of TNM):

■ **Tumor Size:**

- State if unifocal or multifocal.
- Provide three dimensions for each tumor in cm.
- Use descriptors for tumor (e.g., polypoid, ulcerated, exophytic, endophytic, sessile, other).

Note: Size is important in staging based on the anatomic site of primary tumor.

■ **Tumor Site(s):**

- Specify laterality and anatomic site
 - Left
 - Right
 - Midline
- Nasopharynx
 - Nasopharyngeal tonsils (adenoids)
- Oropharynx
 - Palatine tonsil
 - Base of tongue, including lingual tonsil
 - Soft palate
 - Uvula
 - Pharyngeal wall (posterior)
- Hypopharynx
 - Piriform sinus
 - Postcricoid
 - Pharyngeal wall (posterior and/or lateral)

Note: Carefully review T stage criteria as anatomic site is critical for appropriate staging.

■ **Tumor Depth of Invasion and Relationship to Attached Organs / Structures:**

For tumors of the nasopharynx, oropharynx, and hypopharynx, the most significant prognostic factors are the status of cervical lymph nodes and perineural invasion. Perineural invasion is a required data element in the reporting of head and neck cancers, and the presence of perineural invasion also guides therapy. Perineural invasion is associated with decrease in disease-specific survival and overall survival.

Superficial erosion alone of bone/tooth socket by primary gingival tumor is not sufficient to classify a tumor as T4.

Definition of Primary Tumor (pT)

Nasopharynx:

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pT0	No tumor identified, but EBV-positive cervical node(s) involvement
pT1	Tumor confined to nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension
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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com.

Oropharynx (p16+)

pT Category	pT Criteria
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 or epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com.

Oropharynx (p16-)

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pTis	Carcinoma <i>in situ</i>
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
pT4a	Moderately advanced local disease. Tumor invades the 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

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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com.

Hypopharynx:

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pTis	Carcinoma <i>in situ</i>
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.

*Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com.

Pathologic staging requires the use of all information obtained in clinical staging and in histologic study of the surgically resected specimen. Vocal cord mobility/fixation (immobility) of the larynx may only be determined clinically.

TNM Criteria for mucosal melanoma:

Mucosal melanoma is an aggressive neoplasm that calls for separate consideration. Approximately two-thirds of these lesions arise in the nasal cavity and paranasal sinuses; 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 advanced initial presentation, high rates of recurrence and death. To reflect this aggressive behavior, primary cancers limited to the mucosa are considered T3 lesions.

Definition of Primary Tumor (pT)

pT Category	pT Criteria
pT3	Tumor 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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com.

TNM Descriptors:

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

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.

Residual Tumor (R) Category

The absence or presence of residual tumor at the primary tumor site after treatment is denoted by the symbol R. The R categories for the primary tumor site are as follows:

R	R Definition
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor at the primary cancer site or regional nodal sites

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com.

■ **Margins:**

- Apply ink to the appropriate margins and evaluate mucosal and soft tissue margins.
- Margins may be evaluated by either shave (parallel) or radial (perpendicular) sections, depending on the nature of the specimen.
 - If the tumor is relatively distant from a margin, shave (parallel) sections may be taken, however, radial (perpendicular) sections are preferred. *
 - If the tumor approximates a margin to <1 to 2 mm, radial sections (perpendicular; showing relationship of the tumor to the margin) should be taken.
- If margins are uninvolved by invasive carcinoma/carcinoma in situ:
 - Specify the distance from the closest margin in mm.
 - Specify the location of the closest margin, if possible.
 - Specify the location and distance of other close margins.
- If margins are involved by invasive carcinoma/carcinoma in situ, specify the margin.

**It is recommended to take radial (perpendicular) margins whenever possible, even when margins are distant from the tumor. With this technique, the distance to occult tumor or dysplasia, if present, can still be measured. Bone margins may be taken en face.*

■ **Explanatory Notes:**

The definition of a positive margin is somewhat controversial. Many studies support the definition of a positive margin to be invasive carcinoma or carcinoma in situ/high-grade dysplasia present at the margins. Tumors with "close" margins also carry an increased risk for local recurrence. Commonly used cut points to define close margins are 5 mm in general and 2 mm with respect to glottis larynx. Values ranging from 3 mm to 7 mm have been used with success, and for glottic tumors, as low as 1 mm.

Advanced lesion depths of 4 mm at presentation and lack of research renders depth of invasion of limited value in the oropharynx.

LYMPH NODES ("N" of TNM)

- **Lymph Nodes:**

The status of cervical lymph nodes is the single most important prognostic factor in aerodigestive cancer. The risk of regional (cervical neck) nodal spread from cancers of the head and neck is high. Squamous cell carcinoma (SCC), the most common histologic type of cervical neck metastasis, often derives from a metastatic cervical carcinoma with an unknown primary (MCCUP) which may not be detected endoscopically or radiographically. Waldeyer's tonsillar tissue (nasopharynx) and the oropharynx represent common sites giving rise to MCCUP as a unilateral neck mass.

Definition of Regional Lymph Node (pN)

Nasopharynx

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Unilateral metastasis in cervical lymph node(s), and/or unilateral or bilateral metastases in retropharyngeal lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
pN2	Bilateral metastases in cervical lymph node(s), 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage
pN3	Unilateral or bilateral metastases in cervical lymph node(s), larger than 6 cm in greatest dimension, and/or extension below the caudal border of cricoid cartilage

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com.

Note: Midline nodes are considered ipsilateral nodes.

Oropharynx (p16+)

Pathological N (pN)

N Category	N Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Oropharynx (p16-) and Hypopharynx

Pathological N (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE (-)
pN2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest

	dimension and ENE(+); or larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); or metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); or in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)
pN2a	Metastasis in a single ipsilateral node, 3 cm or smaller in greatest dimension and ENE(+); or 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(-)
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 with ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).

Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+).

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Note: Midline nodes are considered ipsilateral nodes.

Definition of Regional Lymph Node for Mucosal Melanoma (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastases
pN1	Regional lymph node metastases present

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com

Regional Lymph Nodes:

- Nasopharynx
 - Retropharyngeal nodes
 - Cervical nodes (jugular and spinal accessory chains)
- Oropharynx
 - Upper and midjugular nodes
 - Submental/submandibular nodes (less common)
- Hypopharynx
 - Parapharyngeal nodes
 - Paratracheal nodes
 - Mid and lower jugular nodes

Lymph Node Examination:

Macroscopically positive:

- Count and submit representative sections of all macroscopically positive lymph nodes.
- Measure the lymph nodes in three dimensions.
- Section the lymph node along the long axis.
- Take steps to ensure that an accurate lymph node count can be rendered.
- Additional sections should be submitted to assess for extranodal extension.*
 - 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.
 - If extranodal extension is macroscopically identified, measure the distance from lymph node capsule in mm.

**Extranodal extension is metastatic tumor present within the confines of the lymph node, through the lymph node capsule into the surrounding connective tissue.*

Macroscopically negative:

- Count and submit macroscopically negative or equivocal smaller nodes in toto and larger nodes entirely.
- Measure the lymph nodes in three dimensions.
- Section the lymph nodes along the long axis.
- Take steps to ensure that an accurate lymph node count can be rendered.

Note: All midline lymph nodes are considered ipsilateral.

Non-regional lymph nodes:

Delineation as to what constitutes non-regional is still unspecified. The above procedure may be employed for more distant level lymph nodes.

Extranodal Extension:

For HPV-unrelated/p16 negative oro- and hypo-pharyngeal cancers, reporting of lymph node metastasis should include whether there is presence (ENE+) or absence (ENE-) of extranodal

extension, which is now part of N staging for these tumor types. This finding consists of extension of metastatic tumor, present within the lymph node, through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction. Absence of ENE in a large (>3 cm) lymph node, especially with traversing fibrous bands, should be viewed with skepticism and therefore thoroughly sampled grossly.

Classification of Neck Dissection:

- Radical neck dissection

Includes 22 or more lymph nodes
- Modified radical neck dissection, internal jugular vein and/or sternocleidomastoid muscle spared

Includes 15 or more lymph nodes
- Selective neck dissection (SND), as specified by surgeon, defined by dissection of less than the 5 traditional levels of a radical and modified radical neck dissection

Includes 15 or more lymph nodes

 - Supraomohyoid neck dissection
 - Posterolateral neck dissection
 - Lateral neck dissection
 - Central compartment neck dissection
- Superselective neck dissection (SSND), as specified by the surgeon – “SSND”, defined by dissection of the fibrofatty elements of 2 or less levels
- Extended radical neck dissection, as specified by surgeon

For purposes of pathologic evaluation, lymph nodes are organized by levels. (Figure 2)

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.

Other Lymph Nodes

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.

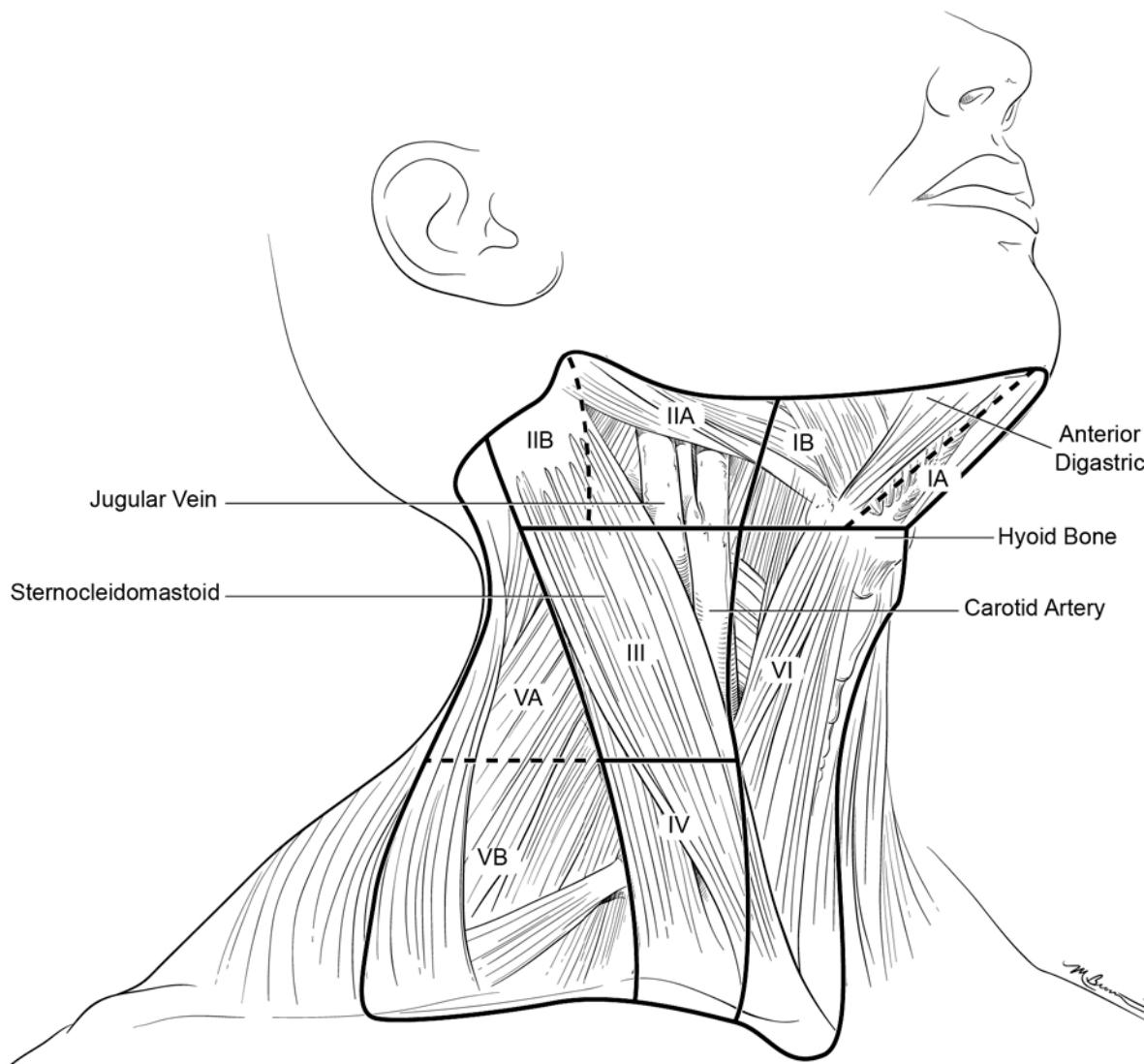


Figure 2: The Six Levels of the Neck with Sublevels

- Level IA: Submental group
- Level IB: Submandibular group
- Level IIA: Upper jugular nodes along the carotid sheath, including the subdigastic group
- Level IIB: Upper jugular nodes in the submuscular recess
- Level III: Middle jugular group
- Level IV: Lower jugular group
- Level VA: Spinal accessory nodes
- Level VB: Supraclavicular and transverse cervical nodes
- Level VI: Anterior (central) compartment

Note:

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*

METASTASIS ("M" of TNM)

- **Metastasis:**

Definition of Distant Metastasis (pM) (required only if confirmed pathologically)

pM Category	pM Criteria
M0	No distant metastasis
pM1	Distant metastasis

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com.

- Specify site of distant metastasis, if known.
- M1 constitutes very advanced local disease involving nerve, mediastinal structures, brain, dura, and skull, along with any amount of positive lymph nodes.
- Nasopharyngeal carcinoma is notorious for a high risk of distant metastasis.
 - The most common sites include lung, bone, liver, and distant lymph nodes.
 - Involvement of lymph nodes below the clavicle is considered as distant metastasis.
- The most common site of distant metastases for oropharynx and hypopharynx are the lungs, with skeletal or hepatic metastases occurring less often.
 - Mediastinal lymph node metastases are considered distant metastases except level VII lymph nodes.

Mucosal Melanoma

pM Category	pM Criteria
M0	No distant metastasis
pM1	Distant metastasis present

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer Science and Business Media LLC, www.springer.com.

- Specify site of distant metastasis, if known.

REFERENCE REVIEW:

1. Seethala RR, Bullock MJ, Carlson DL, et al. Protocol for the Examination of Specimens from Patients with Cancers of the Pharynx. *CAP Cancer Protocol Pharynx* 4.0.0.1. 2017.
2. Amin MB, Edge SB, Greene FL, Byrd DR, et al. (Eds.) *AJCC Cancer Staging Manual*, 8th ed. New York, NY: Springer; 2017.
3. Barnes L, et al. WHO histological classification of tumors of the oral cavity and oropharynx. In: Barnes, et al. eds. *Pathology and Genetics of Head and Neck Tumours*. Lyon, France: IARC Press;2005:206-208. *World Health Organization Classification of Tumours*.
4. Barnes L, et al. WHO histological classification of tumors of the nasopharynx. In: Barnes, et al. eds. *Pathology and Genetics of Head and Neck Tumours*. Lyon, France: IARC Press;2005:85-91. *World Health Organization Classification of Tumours*.
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.
6. Carlson D, et al. Protocol for Examination of the Specimens from Patients with Carcinoma of the Pharynx. *CAP Cancer Protocol* 3.2.0.0. 2012.
7. 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.
8. Hinni ML, Ferlito A, Brandwein-Gensler MS, et al. Surgical margins in head and neck cancer: a contemporary review. *Head Neck*. 2013;35(9):1362-70.
9. Humphrey P. *The Washington manual of surgical pathology*. Philadelphia: Lippincott Williams & Wilkins; 2008.
10. Robbins KT, Shaha AR, Medina JE, Califano JA, Wolf GT, Ferlito A, Som PM, Day TA. Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg*. 2008;134(5):536-538.
11. Seethala RR. Current state of neck dissection in the United States. *Head Neck Pathol*. 2009;3(3):238- 245.
12. Woolgar JA, Rogers SN, Lowe D, Brown JS, Vaughan ED. Cervical lymph node metastasis in oral cancer: the importance of even microscopic extracapsular spread. *Oral Oncol*. 2003;39(2):130-137.