COLLEGE of AMERICAN PATHOLOGISTS

Protocol for the Examination of Specimens From Patients With Carcinomas of the Pharynx

Protocol applies to all invasive carcinomas of the pharynx (oropharynx, nasopharynx, hypopharynx) including the base of tongue, tonsils, soft palate, and uvula. Mucosal melanoma is included. Lymphomas and sarcomas are not included.

Based on AJCC/UICC TNM, 7th edition
Protocol web posting date: October 2013

Procedures

- Biopsy
- Resection

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For the Members of the Cancer Committee, College of American Pathologists

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the "Surgical Pathology Cancer Case Summary" portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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CAP Pharynx Protocol Revision History

Version Code
The definition of the version code can be found at www.cap.org/cancerprotocols.

Version: Pharynx 3.3.0.0

Summary of Changes
The following changes have been made since the June 2012 release.

Entire Document
"Mucosal malignant melanoma" was changed to "Mucosal melanoma."

Excisional Biopsy, Resection

Procedure
"Incisional biopsy" was deleted.

Specimen Laterality
Tumor Laterality
Tumor Focality
"Bilateral" was deleted as a choice for these data elements.

Histologic Type
Carcinomas of the Oropharynx and Hypopharynx
"Keratinizing" and "Nonkeratinizing" were added under "Squamous cell carcinoma, conventional" as follows:

___ Squamous cell carcinoma, conventional
- ___ Keratinizing
- ___ Nonkeratinizing

Carcinomas of the Nasopharynx
The former WHO designations were deleted.
Carcinomas of Minor Salivary Glands
Low, intermediate, and high grade were added to adenoid cystic carcinoma as follows:

___ Adenoid cystic carcinoma
- ___ Low grade
- ___ Intermediate grade
- ___ High grade

Neuroendocrine Carcinoma
"Large cell carcinoma, neuroendocrine type (poorly differentiated neuroendocrine carcinoma)" was added.

Margins
Reporting on margins was updated, as follows:

___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
- Distance from closest margin:
- Specify distance: ____ mm
- ___ Cannot be determined
- Specify location of closest margin, per orientation, if possible: _____
- + Location and distance of other close margins (Note D): _____

___ Margins involved by invasive carcinoma
- Specify margin(s), per orientation, if possible: _____

___ Margins uninvolved by carcinoma in situ (includes moderate and severe dysplasia#) (Note D)
Distance from closest margin:
Specify distance: ____ mm
___ Cannot be determined
Specify location of closest margin, per orientation, if possible: _____
___ Margins involved by carcinoma in situ (includes moderate and severe dysplasia#) (Note D)
Specify margin(s), per orientation, if possible: _____

 # Applicable only to squamous cell carcinoma and histologic variants.

Pathologic Staging (pTNM)

For All Carcinomas Excluding Mucosal Melanoma

Primary Tumor (pT): Oropharynx

Definitions of pT2 and pT3 were updated, as follows:

___ pT2: Tumor more than 2 cm but not more than 4 cm in greatest dimension
___ pT3: Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis

Regional Lymph Nodes (pN)

Number of Lymph Nodes Involved

Size was changed from "largest positive lymph node" to largest metastatic focus in the lymph node."
Extracapsular extension was added, as follows:

Extracapsular Extension

___ Not identified
___ Present
+ Distance from lymph node capsule: _____ mm
___ Indeterminate

Distant Metastasis (pM)

Deleted "Source of pathologic metastatic specimen (specify)."

Ancillary Studies

Deleted "if available at time of report completion" from heading, and added "(>70% nuclear and cytoplasmic staining)" to p16, as follows:

Ancillary Studies (required only for oropharynx [p16, HPV] and nasopharynx [EBV]) (select all that apply)

___ p16
___Positive (>70% nuclear and cytoplasmic staining)
___ Negative

Explanatory Notes

Scope of Guidelines: First sentence: "oral cancer including the lip" was changed to "pharyngeal cancer." Third to last sentence: "oral cavity" was changed to "pharynx."

B. Histologic Type: Carcinomas of the Oropharynx and Hypopharynx were updated.
Neuroendocrine Carcinoma: added "Large cell carcinoma, neuroendocrine type (poorly differentiated neuroendocrine carcinoma)."

C. Histologic Grade; D. Surgical Margins; E. Orientation of Specimen; F. Perineural Invasion;
G. Extracapsular Extension; J. Regional Lymph Nodes (pN0): Isolated Tumor Cells; K. Lymph Nodes;
O. Ancillary Testing: Edits were made to these notes.

References: References were updated.

Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

PHARYNX (OROPHARYNX, HYPOPHARYNX, NASOPHARYNX): Excisional Biopsy, Resection

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)

___ Oropharynx
___ Nasopharynx
___ Hypopharynx
___ Other (specify): _____
___ Not specified

Received:
___ Fresh
___ In formalin
___ Other (specify): _____

Procedure (select all that apply)

___ Excisional biopsy
___ Resection
    ___ Tonsillectomy
    ___ Laryngopharyngectomy
    ___ Other (specify): _____
___ Neck (lymph node) dissection (specify): _____
___ Other (specify): _____
___ Not specified

+ Specimen Integrity

+ ___Intact
+ ___Fragmented

Specimen Size

Greatest dimensions: ___ x ___ x ___ cm
+ Additional dimensions (if more than one part): ___ x ___ x ___ cm

Specimen Laterality (select all that apply)

___ Left
___ Right
___ Midline
___ Not specified

Tumor Site (select all that apply) (Note A)

___Oropharynx
- ___ Palatine tonsil
- ___ Base of tongue, including lingual tonsil
- ___ Soft palate
- ___ Uvula
- ___ Pharyngeal wall (posterior)
- ___ Other

___ Nasopharynx
- ___ Nasopharyngeal tonsils (adenoids)

___ Hypopharynx
- ___ Piriform sinus
- ___ Postcricoid
- ___ Pharyngeal wall (posterior and/or lateral)
- ___ Other

___ Other (specify): _____
___ Not specified

Tumor Laterality (select all that apply)

___ Left
___ Right
___ Midline
___ Not specified

Tumor Focality

___ Single focus
___ Multifocal (specify): _____

Tumor Size

Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

+ Tumor Description (select all that apply)

+ Gross subtype:
+ ___ Polypoid
+ ___ Exophytic
+ ___ Endophytic
+ ___ Ulcerated
+ ___ Sessile
+ ___ Other (specify): _____

+ Macroscopic Extent of Tumor

+ Specify: _____

Histologic Type (select all that apply) (Note B)

Carcinomas of the Oropharynx and Hypopharynx
___ Squamous cell carcinoma, conventional
    ___ Keratinizing
    ___ Nonkeratinizing
Variants of Squamous Cell Carcinoma
___ Acantholytic squamous cell carcinoma
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Papillary squamous cell carcinoma
___ Spindle cell squamous cell carcinoma
___ Verrucous carcinoma

___ Lymphoepithelial carcinoma (non-nasopharyngeal)

Carcinomas of the Nasopharynx
___ Keratinizing squamous cell carcinoma
___ Nonkeratinizing carcinoma
    ___ Differentiated carcinoma
    ___ Undifferentiated carcinoma
___ Basaloid squamous cell carcinoma

Adenocarcinomas (Non-Salivary Gland Type)
___ Nasopharyngeal papillary adenocarcinoma
___ Adenocarcinoma, not otherwise specified (NOS)
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Other (specify): _____

Carcinomas of Minor Salivary Glands
___ Acinic cell carcinoma
___ Adenoid cystic carcinoma
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Adenocarcinoma, not otherwise specified (NOS)
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Basal cell adenocarcinoma
___ Carcinoma ex pleomorphic adenoma (malignant mixed tumor)
___ Carcinoma, type cannot be determined
___ Clear cell adenocarcinoma
___ Cystadenocarcinoma
___ Epithelial-myoepithelial carcinoma
___ Mucoepidermoid carcinoma
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Mucinous adenocarcinoma (colloid carcinoma)

___ Myoepithelial carcinoma (malignant myoepithelioma)
___ Oncocytic carcinoma
___ Polymorphous low-grade adenocarcinoma
___ Salivary duct carcinoma
___ Other (specify): _____

Neuroendocrine Carcinoma
___ Typical carcinoid tumor (well differentiated neuroendocrine carcinoma)
___ Atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma)
___ Large cell carcinoma, neuroendocrine type (poorly differentiated neuroendocrine carcinoma)
___ Small cell carcinoma, neuroendocrine type (poorly differentiated neuroendocrine carcinoma)
___ Combined (or composite) small cell carcinoma, neuroendocrine type with (specify):
___ Mucosal melanoma

___ Other carcinoma (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade (Note C)
___ Not applicable
___ GX: Cannot be assessed
___ G1: Well differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ Other (specify): _____

+ Microscopic Tumor Extension
+ ___ Specify: _____

Margins (select all that apply) (Notes D and E)
___ Cannot be assessed
___ Margins uninvolved by invasive carcinoma
    Distance from closest margin:
    Specify distance: _____ mm
    ___ Cannot be determined
    Specify location of closest margin, per orientation, if possible: _____
    + Location and distance of other close margins (Note D): _____
___ Margins involved by invasive carcinoma
    Specify margin(s), per orientation, if possible: _____
___ Margins uninvolved by carcinoma in situ (includes moderate and severe dysplasia[#]) (Note D)
    Distance from closest margin:
    Specify distance: _____ mm
    ___ Cannot be determined
    Specify location of closest margin, per orientation, if possible: _____
___ Margins involved by carcinoma in situ (includes moderate and severe dysplasia[#]) (Note D)
    Specify margin(s), per orientation, if possible: _____

[#] Applicable only to squamous cell carcinoma and histologic variants

+ Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)
+ ___ Not identified
+ ___ Present (specify): _____
+ ___ Indeterminate

Lymph-Vascular Invasion
___ Not identified
___ Present
___ Indeterminate

Perineural Invasion (Note F)
___ Not identified
___ Present
___ Indeterminate

Lymph Nodes, Extranodal Extension (Note G)
___ Not identified
___ Present
___ Indeterminate

Pathologic Staging (pTNM) (Note H)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ

For All Carcinomas Excluding Mucosal Melanoma

Primary Tumor (pT): Oropharynx
___ pT1: Tumor 2 cm or less in greatest dimension
___ pT2: Tumor more than 2 cm but not more than 4 cm in greatest dimension
___ pT3: Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
___ pT4a: Moderately advanced local disease. Tumor invades larynx, deep/extrinsic muscle of tongue, medial pterygoid muscles, hard palate, or mandible#
___ pT4b: Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery

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

Primary Tumor (pT): Nasopharynx
___ pT1: Tumor confined to nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension#
___ pT2: Tumor with parapharyngeal extension#
___ pT3: Tumor invades bony structures of skull base and/or paranasal sinuses
___ pT4: Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space

 # Parapharyngeal extension denotes posterolateral infiltration of tumor.

Primary Tumor (pT): Hypopharynx

___ pT1: Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
___ pT2: Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of hemilarynx
___ pT3: Tumor measures more than 4 cm in greatest dimension *or* with fixation of hemilarynx or extension to esophagus
___ pT4a: Moderately advanced local disease. Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, 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 prelarnygeal strap muscles and subcutaneous fat.

Regional Lymph Nodes (pN) (Notes I through M)

___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis

Regional Lymph Nodes (pN): Oropharynx and Hypopharynx#

___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
___ pN2: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
___ pN2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
___ pN2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
___ pN3: Metastasis in a lymph node more than 6 cm in greatest dimension

___ No nodes submitted or found

Number of Lymph Nodes Examined

Specify: ____
___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved

Specify: ____
___ Number cannot be determined (explain): _____
+ Size (greatest dimension) of the largest metastatic focus in the lymph node: ____ cm (Note K)

Extracapsular Extension (Note G)

___ Not identified
___ Present
+ Distance from lymph node capsule: _____ mm
___ Indeterminate

 # Note: Metastases at level VII are considered regional lymph node metastases. Midline nodes are considered ipsilateral nodes.

Regional Lymph Nodes (pN): Nasopharynx[#] (Note L)
___ pN1: Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[##]
___ pN2: Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[##]
___ pN3: Metastasis in a lymph node greater than 6 cm and/or to supraclavicular fossa[##]
___ pN3a: Greater than 6 cm in dimension
___ pN3b: Extension to the supraclavicular fossa[##]

___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved
Specify: ____
+ Size (greatest dimension) of the largest metastatic focus in the lymph node: ____ (Note K)
___ Number cannot be determined (explain): _____

[#] Metastases at level VII are considered regional lymph node metastases. Midline nodes are considered ipsilateral nodes.

[##] Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder (see Figure 3, no. 2). Note that this would include caudal portions of Levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
+ Specify site(s), if known: _____

For Mucosal Melanoma

Primary Tumor (pT)
___pT3: Mucosal 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.

Regional Lymph Nodes (pN)
___pNX: Regional lymph nodes cannot be assessed
___pN0: No regional lymph node metastases
___pN1: Regional lymph node metastases present

Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis present
+ Specify site(s), if known: _____

+ Additional Pathologic Findings (select all that apply)

+ ___ None identified
+ ___ Keratinizing dysplasia (Note N)
    + ___ Mild
    + ___ Moderate
    + ___ Severe (carcinoma in situ)
+ ___ Nonkeratinizing dysplasia (Note N)
    + ___ Mild
    + ___ Moderate
    + ___ Severe (carcinoma in situ)
+ ___ Inflammation (specify type): _____
+ ___ Squamous metaplasia
+ ___ Epithelial hyperplasia
+ ___ Colonization
    + ___ Fungal
    + ___ Bacterial
+ ___ Other (specify): _____

Ancillary Studies (required only for oropharynx [p16, HPV] and nasopharynx [EBV]) (select all that apply) (Notes M and O)

___ p16
    ___Positive (>70% nuclear and cytoplasmic staining)
    ___ Negative
___ Human papillomavirus (HPV), in situ hybridization (ISH)
    Type (specify): _____
    ___ Positive
        Pattern:
        ___ Punctate
        ___ Diffuse
        ___ Mixed
    ___ Negative
    ___ Indeterminate (explain): _____
___ HPV, polymerase chain reaction (PCR)
    Type (specify): _____
    ___ Positive
    ___ Negative
___ Epstein-Barr virus (Epstein Barr virus encoded RNA [EBER], other)
    ___ Positive
    ___ Negative
___ Other (specify): _____
___ Not specified

+ Clinical History (select all that apply)

+ ___ Neoadjuvant therapy
    + ___ Yes (specify type): _____
    + ___ No
    + ___Indeterminate
+ ___ Other (specify): _____

+ Comment(s)

Explanatory Notes

Scope of Guidelines

The reporting of pharyngeal cancer is facilitated by the provision of a case summary illustrating the features required for comprehensive patient care. However, there are many cases in which the individual practicalities of applying such a case summary may not be straightforward. Common examples include finding the prescribed number of lymph nodes, trying to determine the levels of the radical neck dissection, and determining if isolated tumor cells in a lymph node represent metastatic disease. Case summaries have evolved to include clinical, radiographic, morphologic, immunohistochemical, and molecular results in an effort to guide clinical management. Adjuvant and neoadjuvant therapy can significantly alter histologic findings, making accurate classification an increasingly complex and demanding task. This protocol tries to remain simple while still incorporating important pathologic features as proposed by the American Joint Committee on Cancer (AJCC) cancer staging manual, the World Health Organization classification of tumors, the TNM classification, the American College of Surgeons Commission on Cancer, and the International Union on Cancer (UICC). This protocol is to be used as a guide and resource, an adjunct to diagnosing and managing cancers of the pharynx in a standardized manner. It should not be used as a substitute for dissection or grossing techniques and does not give histologic parameters to reach the diagnosis. Subjectivity is always a factor, and elements listed are not meant to be arbitrary but are meant to provide uniformity of reporting across all the disciplines that use the information. It is a foundation of practical information that will help to meet the requirements of daily practice to benefit both clinicians and patients alike.

A. Anatomical Sites and Subsites for Pharynx

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

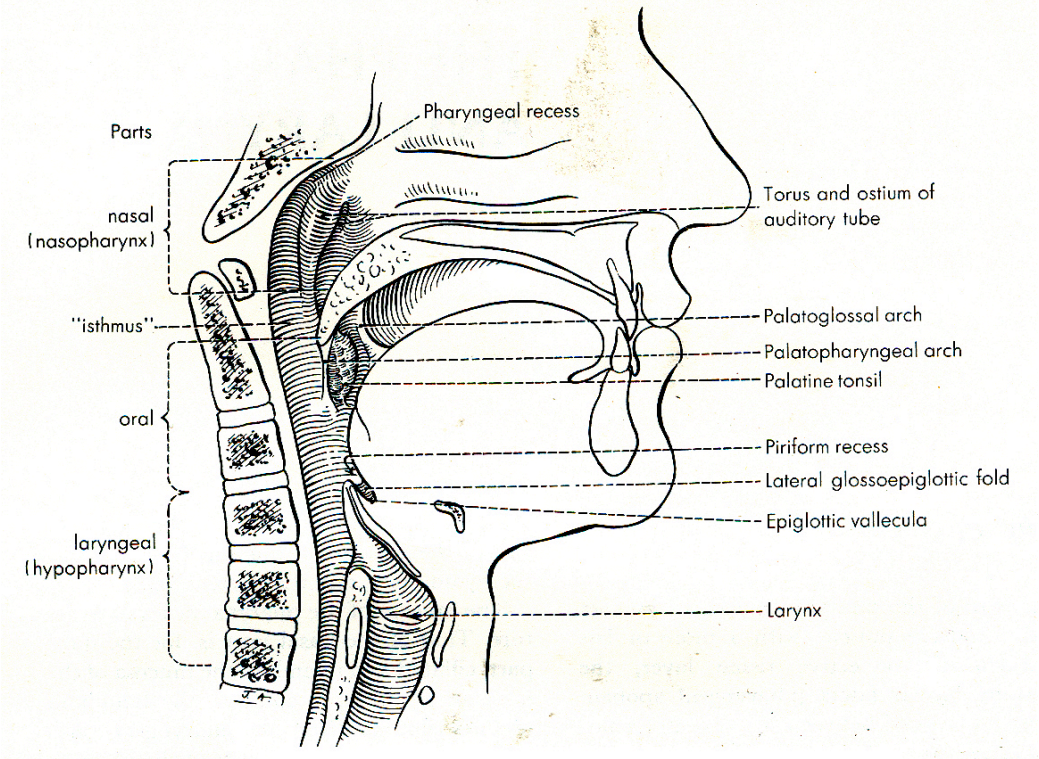

Figure 1. Anatomical subdivisions and "contents" of the pharynx. From Hollinshead WH. *Anatomy for Surgeons: The Head and Neck*. 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 1982. Reproduced with permission (http://lww.com).

Oropharynx (Figure 1)
The oropharynx is the portion of the continuity of the pharynx extending from the plane of the superior surface of the soft palate to the superior surface of the hyoid bone or floor of the vallecula.[1] The contents of the oropharynx include:
- soft palate
- palatine tonsils
- anterior and posterior tonsillar pillars
- tonsillar fossa and tonsillar (faucial) pillars
- uvula
- base of tongue, including the lingual tonsils
- vallecula
- posterior oropharyngeal wall

Nasopharynx (Figure 1)
The nasopharynx is situated behind the nasal cavity and above the soft palate; it begins anteriorly at the posterior choana and extends along the plane of the airway to the level of the free border of the soft palate.[1] The contents of the nasopharynx include:
- nasopharyngeal tonsils (adenoids) lie along the posterior and lateral of the nasopharynx
- orifice of Eustachian tube lies along the lateral aspects of the nasopharyngeal wall
- fossa of Rosenmüller

Hypopharynx (Figure 1)
The hypopharynx is the portion of the pharynx extending from the plane of the superior border of the hyoid bone (or floor of the vallecula) to the plane corresponding to the lower border of the cricoid cartilage.[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

Waldeyer ring is formed by a ring or group of extranodal lymphoid tissues about the upper end of the pharynx (Figure 2) which consists of the:
- palatine tonsils
- pharyngeal tonsils (adenoids)
- base of tongue/lingual tonsils
- adjacent submucosal lymphatics

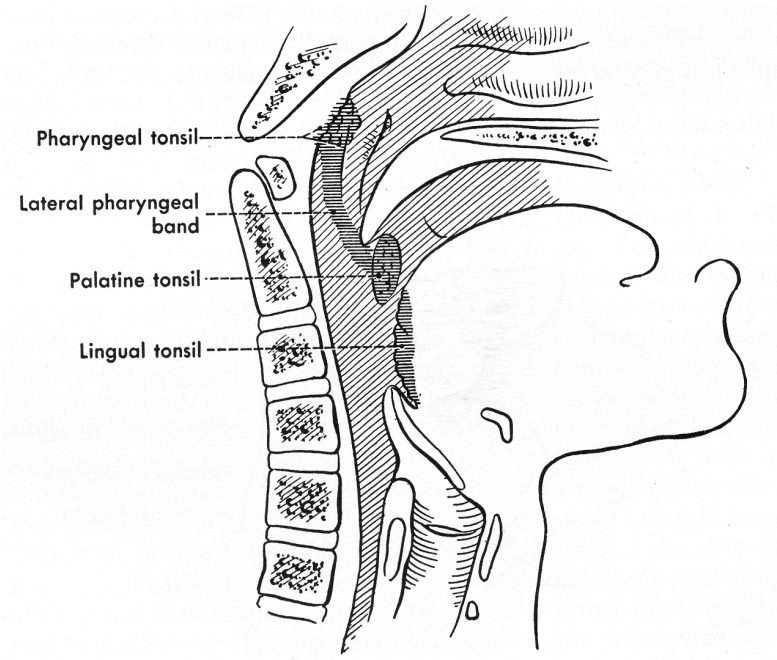

Figure 2. Waldeyer tonsillar tissues. From Hollinshead WH. *Anatomy for Surgeons: The Head and Neck.* 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 1982. Reproduced with permission (http://lww.com).

B. Histological Type

A modification of the World Health Organization (WHO) classification of carcinomas of the oral cavity and oropharynx,[2] the nasopharynx,[3] and the hypopharynx[4] is shown below. This list may not be complete. This protocol applies only to carcinomas and melanomas and does not apply to lymphomas or sarcomas.

Carcinomas of the Oropharynx and Hypopharynx

- Squamous cell carcinoma, conventional
  - Keratinizing
  - Nonkeratininizing
- Squamous cell carcinoma, variant
  - Acantholytic squamous cell carcinoma
  - Adenosquamous carcinoma
  - Basaloid squamous cell carcinoma
  - Carcinoma cuniculatum
  - Papillary squamous cell carcinoma
  - Spindle cell squamous carcinoma
  - Verrucous carcinoma
- Lymphoepithelial carcinoma (non-nasopharyngeal)

Carcinomas of the Nasopharynx

- Keratinizing squamous cell carcinoma
- Nonkeratinizing carcinoma
  - Differentiated type
  - Undifferentiated type
- Basaloid squamous cell carcinoma

Adenocarcinomas Non-salivary Gland Type

Nasopharyngeal papillary adenocarcinoma, low-grade

Carcinomas of the Minor Salivary Glands

The histologic classification recommended is a modification of the WHO classification of salivary gland tumors.

Acinic cell carcinoma
Adenoid cystic carcinoma
Adenocarcinoma, not otherwise specified (NOS)
Basal cell adenocarcinoma
Carcinoma ex pleomorphic adenoma (malignant mixed tumor)
Carcinoma, type cannot be determined
Clear cell carcinoma, not otherwise specified
Cystadenocarcinoma
Epithelial-myoepithelial carcinoma
Mucoepidermoid carcinoma,
Mucinous adenocarcinoma (colloid carcinoma)
Myoepithelial carcinoma (malignant myoepithelioma)
Oncocytic carcinoma
Polymorphous low-grade adenocarcinoma
Salivary duct carcinoma

Neuroendocrine Carcinoma

Typical carcinoid tumor (well differentiated neuroendocrine carcinoma)
Atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma)
Large cell carcinoma, neuroendocrine type (poorly differentiated neuroendocrine carcinoma)
Small cell carcinoma, neuroendocrine type (poorly differentiated neuroendocrine carcinoma)
Combined (or composite) small cell carcinoma, neuroendocrine type#

Represents a carcinoma showing combined features of small cell neuroendocrine carcinoma associated with a squamous or adenocarcinomatous component.[5]

Mucosal Melanoma

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.[5] Nonetheless, it should be recorded when applicable as it is a basic tumor characteristic. Selecting either the most prevalent grade or the highest grade for this synoptic protocol is acceptable. Variants of squamous cell carcinoma (ie verrucous, basaloid, etc) have an intrinsic biologic potential and currently do not appear to require grading.

Grade 1 Well differentiated
Grade 2 Moderately differentiated
Grade 3 Poorly differentiated
Grade X Cannot be assessed

The histologic (microscopic) grading of salivary gland carcinomas has been shown to be an independent predictor of behavior and plays a role in optimizing therapy.[6-11] Further, there is often a positive correlation between histologic grade and clinical stage. Most salivary carcinomas have a biologic behavior defined by their categorization and do not require grading.[11] The 3 major categories

that are amenable to grading include adenoid cystic carcinoma, mucoepidermoid carcinoma (the 2 most frequent histologic types seen in larynx) and adenocarcinoma , not otherwise specified.[6,8,12]

Generally, 3 histologic grades are suggested, as follows:

Grade 1 Well differentiated = Low-grade
Grade 2 Moderately differentiated = Intermediate-grade
Grade 3 Poorly differentiated = High-grade
Grade X Cannot be assessed

In some carcinomas, histologic grading may be based on growth pattern, such as in adenoid cystic carcinoma, for which a histologic high-grade variant has been recognized based on the percentage of solid growth.[8] Those adenoid cystic carcinomas showing 30% or greater of solid growth pattern are considered to be histologically high-grade carcinomas. The histologic grading of mucoepidermoid carcinoma includes a combination of growth pattern characteristics (eg, cystic, solid, neurotropism) and cytomorphologic findings (eg, anaplasia, mitoses, necrosis).[13-15] Adenocarcinomas, not otherwise specified, do not have a formalized grading scheme and are graded intuitively, based on cytomorphologic features.[11]

Carcinoma ex pleomorphic adenoma is subclassifed by histologic grade (low grade and high grade) and extent of invasion, the latter including minimally invasive, invasive, and noninvasive cancers. Minimally invasive cancers measure less than or equal to 1.5 mm with penetration of the malignant component into extracapsular tissue; invasive carcinomas measure more than 1.5 mm of invasion; noninvasive cancers are completely confined to within the capsule without evidence of penetration into extracapsular tissue. Prior to diagnosing a noninvasive carcinoma ex pleomorphic adenoma, sectioning of the entire lesion for histologic evaluation is recommended in order to exclude the presence of invasive growth. Prognosis has been linked to degree of invasion with noninvasive and minimally invasive cancers apparently having a better prognosis than invasive cancers.[11,16]

D. Surgical Margins

The definition of a positive margin is somewhat controversial given the varied results from prior studies.[17,18] However, overall, several studies support the definition of a positive margin to be invasive carcinoma *or* carcinoma in situ/high-grade dysplasia present at margins (microscopic cut-through of tumor).[17] Furthermore, reporting of surgical margins should also include information regarding the distance of invasive carcinoma, carcinoma in situ, or high-grade dysplasia (moderate to severe) from the surgical margin. Tumors with "close" margins also carry an increased risk for local recurrence.[17,19,20] The definition of a "close" margin is not standardized as the effective cut-off varies between studies and between anatomic subsites. Commonly used cut points to define close margins are 5 mm in general, and 2 mm with respect to glottis larynx.[17] However, values ranging from 3 mm to 7 mm have been used with success,[17,21] and for glottic tumors, as low as 1 mm.[22] Thus distance of tumor from the nearest margin should be recorded.

Reporting of surgical margins for carcinomas of the minor salivary glands should follow those used for squamous cell carcinoma of oral cavity.

While intraepithelial dysplasias including nonkeratinizing and keratinizing dysplasias as well as carcinoma in situ of the pharynx, including oropharyngeal sites (base of tongue, tonsils), nasopharynx, and hypopharynx, may occur as an isolated (clinical and/or histopathologic) lesion, they are less common as compared to than the oral cavity and larynx. When such lesions are identified in pharyngeal sites it usually occurs in association with an invasive carcinoma. In this setting, the same criteria detailed in the oral cavity and laryngeal protocols apply (see Protocol for the Examination of Specimens from

Patients with Carcinomas of the Lip and Oral Cavity and Protocol for the Examination of Specimens from Patients with Carcinomas of the Larynx).

E. Orientation of Specimen

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

F. 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.[23] 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.[23] Further, perineural invasion is associated with decrease in disease-specific survival and overall survival.[23] 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.[23] The relationship between perineural invasion and prognosis is independent of nerve diameter.[24] Additionally, emerging evidence suggests that extratumoral perineural invasion may be more prognostically relevant.[25] 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 (ie, 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).[26,27] Given the significance relative to prognosis and treatment, perineural invasion is a required data element in the reporting of head and neck cancers.

G. Extranodal Extension

The status of cervical lymph nodes is the single most important prognostic factor in aerodigestive cancer. All macroscopically negative or equivocal lymph nodes should be submitted in toto. Grossly positive nodes may be partially submitted for microscopic documentation of metastasis. Reporting of lymph nodes containing metastasis should include whether there is presence or absence of extranodal extension (EE). This finding consists of extension of metastatic tumor, present within the confines of the lymph node, through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction. A distance of extension from the native lymph node capsule is optional and has not yet been shown to have a definitive impact on prognosis or treatment for head and neck subsites. If macroscopic examination suggests EE, this tissue should be submitted for microscopic confirmation. EE is a predictor of regional relapse and a criterion for postoperative radiotherapy.[28-31]

H. TNM and Stage Groupings

The protocol recommends the TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) for the pharynx.[1,32] Of note in the 7th edition of the AJCC staging of head and neck cancers[1] is the division of T4 lesions into T4a (moderately advanced local disease) and T4b (very advanced local disease), leading to the stratification of stage IV into stage IVA (moderately advanced local/regional disease), stage IVB (very advanced local/regional disease), and stage IVC (distant metastatic disease).

The 7th edition of the AJCC staging of head and neck cancers includes mucosal melanomas.[1] Approximately two-thirds of mucosal melanomas arise in the sinonasal tract, one-quarter are found in

the oral cavity and the remainder occur only sporadically in other mucosal sites of the head and neck. Even small cancers behave aggressively with high rates of recurrence and death.[1] To reflect this aggressive behavior, primary cancers limited to the mucosa are considered T3 lesions. Advanced mucosal melanomas are classified as T4a and T4b. The anatomic extent criteria to define *moderately advanced* (T4a) and *very advanced* (T4b) disease are given below. The AJCC staging for mucosal melanomas does not provide for the histologic definition of a T3 lesion; as the majority of mucosal melanomas are invasive at presentation, mucosal based melanomas (T3 lesions) include those lesions that involve either the epithelium and/or lamina propria of the involved site. Rare examples of in situ mucosal melanomas occur but in situ mucosal melanomas are excluded from staging, as they are extremely rare.[1]

For All Carcinomas Excluding Mucosal Melanoma

Primary Tumor: Oropharynx

TX	Cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension or extension to the lingual surface of epiglottis
T4a	Moderately advanced local disease. Tumor invades larynx, deep/extrinsic muscle of tongue, medial pterygoid muscles, hard palate, or mandible[#]
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery

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

Primary Tumor: Nasopharynx

TX	Cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension[#]
T2	Tumor with parapharyngeal extension[#]
T3	Tumor involves bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hyphpharynx, orbit, or with extension to the infratemporal fossa/masticator space

[#] Parapharyngeal extension denotes posterolateral infiltration of tumor.

Primary Tumor: Hypopharynx

TX	Cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to 1 subsite of hypopharynx and 2 cm or less in greatest dimension
T2	Tumor invades more than 1 subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of hemilarynx
T3	Tumor measures more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4a	Moderately advanced local disease. Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, esophagus, or central compartment soft tissue[#]

T4b Very advanced local disease. Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures

[#] Central compartment soft tissue includes prelarnygeal strap muscles and subcutaneous fat.

Regional Lymph Nodes: Oropharynx and Hypopharynx[#]

NX Cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension
N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3 Metastasis in a lymph node more than 6 cm in greatest dimension

[#] Metastases at level VII are considered regional lymph node metastases; midline lymph nodes are considered ipsilateral nodes.

Regional Lymph Nodes: Nasopharynx[#]

NX Cannot be assessed
N0 No regional lymph node metastasis
N1 Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[##]
N2 Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa[##]
N3 Metastasis in a lymph node greater than 6 cm and/or to supraclavicular fossa
N3a Greater than 6 cm in dimension
N3b Extension to the supraclavicular fossa[##]

[#] Metastases at level VII are considered regional lymph node metastases; midline lymph nodes are considered ipsilateral nodes.

[##] Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region defined as follows (Figure 3):

- superior margin of the sternal end of the clavicle
- superior margin of the lateral end of the clavicle
- point where the neck meets the shoulder

All cases with lymph nodes (whole or in part) in the fossa are considered N3b.

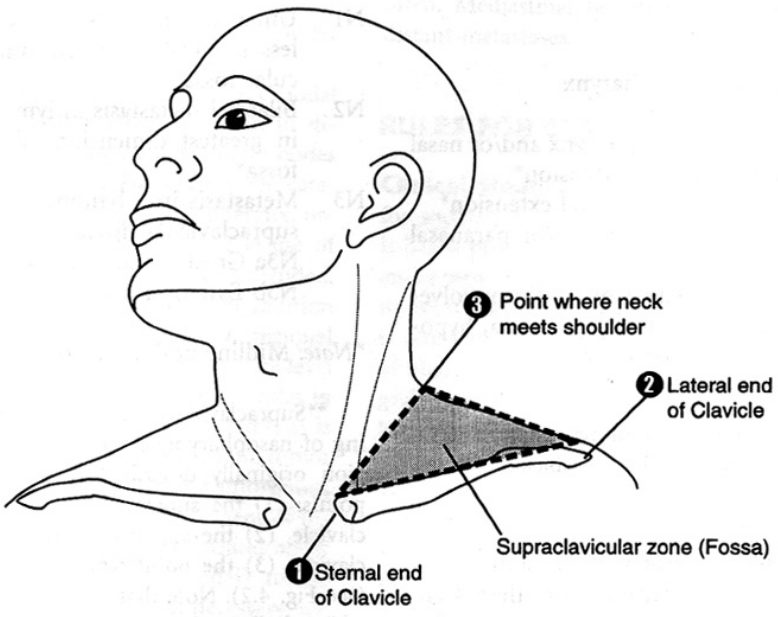

Figure 3. Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma. From *AJCC Cancer Staging Manual.* 6th ed. New York: Springer; 2002. Reproduced with permission.

Distant Metastasis (M)

M0 No distant metastasis
M1 Distant metastasis

For Mucosal Melanoma

Primary Tumor

T3 Mucosal disease
T4a Moderately advanced disease. Tumor involving deep soft tissue, cartilage, one, or overlying skin.
T4b 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.

Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastases
N1 Regional lymph node metastases present

Distant Metastasis

M0 No distant metastasis
M1 Distant metastasis present

By AJCC/UICC convention, the designation "T" refers to a primary tumor that has not been previously treated. The symbol "p" refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical

classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathologic staging is usually performed after surgical resection of the primary tumor. Pathologic staging depends on pathologic documentation of the anatomic extent of disease, whether or not the primary tumor has been completely removed. If a biopsied tumor is not resected for any reason (eg, when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

T Category Considerations

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

Stage Groupings – For All Cancers Except Mucosal Melanoma

Oropharynx and Hypopharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1,T2	N1	M0
	T3	N0,N1	M0
Stage IVA	T1,T2,T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Nasopharynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1,T2	N1	M0
	T3	N0,N1	M0
Stage IVA	T1,T2,T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Stage Groupings – For Mucosal Melanoma

Stage III	T3	N0	M0
Stage IVA	T4a	N0	M0
	T3-T4a	N1	M0
Stage IVB	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

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 (ie, 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 (ie, 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.

Additional Descriptors

Residual Tumor (R)
Tumor remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumor involving the resection margin on pathologic examination may be assumed to correspond to residual tumor in the patient and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

I. Classification of Neck Dissection

1. Radical neck dissection
2. Modified radical neck dissection, internal jugular vein and/or sternocleidomastoid muscle spared
3. Selective neck dissection (SND), as specified by the surgeon (Figure 4), defined by dissection of less than the 5 traditional levels of a radical and modified radical neck dissection. The following dissections are now under this category[33-35]:
   a. Supraomohyoid neck dissection
   b. Posterolateral neck dissection
   c. Lateral neck dissection
   d. Central compartment neck dissection
4. Superselective neck dissection (SSND), a relatively new term defined by dissection of the fibrofatty elements of 2 or less levels[36]
5. Extended radical neck dissection, as specified by the surgeon

J. Regional Lymph Nodes (pN0): Isolated Tumor Cells

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. While the generic recommendation is that for lymph nodes with ITCs found by either histologic examination, immunohistochemistry, or non-morphologic techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) they should be classified as N0 or M0, respectively,[32,37] evidence for the validity of this practice in head and neck squamous cell carcinoma and other histologic subtypes is lacking. In fact, rare studies relevant to head and neck sites indicate that isolated tumor cells may actually be a poor prognosticator in terms of local control.[38]

For purposes of pathologic evaluation, lymph nodes are organized by levels as shown in Figure 4.[34]

Figure 4. The six sublevels of the neck for describing the location of lymph nodes within levels I, II, and V. Level IA, submental group; level IB, submandibular group; level IIA, upper jugular nodes along the carotid sheath, including the subdigastric group; level IIB, upper jugular nodes in the submuscular recess; level VA, spinal accessory nodes; and level VB, the supraclavicular and transverse cervical nodes. From Flint PW et al, eds. *Cummings Otolaryngology: Head and Neck Surgery*. 5th ed. Philadelphia, PA; Saunders: 2010. Reproduced with permission © Elsevier.

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

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

Level I. Submental Group (Sublevel IA)
Lymph nodes within the triangular boundary of the anterior belly of the digastric muscles and the hyoid bone.

Level I. Submandibular Group (Sublevel IB)
Lymph nodes within the boundaries of the anterior and posterior bellies of the digastric muscle and the body of the mandible. The submandibular gland is included in the specimen when the lymph nodes within this triangle are removed.

Level II. Upper Jugular Group (Sublevels IIA and IIB)
Lymph nodes located around the upper third of the internal jugular vein and adjacent spinal accessory nerve extending from the level of the carotid bifurcation (surgical landmark) or hyoid bone (clinical

landmark) to the skull base. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the stylohyoid muscle.

Level III. Middle Jugular Group
Lymph nodes located around the middle third of the internal jugular vein extending from the carotid bifurcation superiorly to the omohyoid muscle (surgical landmark), or cricothyroid notch (clinical landmark) inferiorly. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the sternohyoid muscle.

Level IV. Lower Jugular Group
Lymph nodes located around the lower third of the internal jugular vein extending from the omohyoid muscle superiorly to the clavicle inferiorly. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the sternohyoid muscle.

Level V. Posterior Triangle Group (Sublevels VA and VB)
This group comprises predominantly the lymph nodes located along the lower half of the spinal accessory nerve and the transverse cervical artery. The supraclavicular nodes are also included in this group. The posterior boundary of the posterior triangle is the anterior border of the trapezius muscle, the anterior boundary of the posterior triangle is the posterior border of the sternocleidomastoid muscle, and the inferior boundary of the posterior triangle is the clavicle.

Level VI. Anterior (Central) Compartment
Lymph nodes in this compartment include the pre- and paratracheal nodes, precricoid (Delphian) node, and the perithyroidal nodes, including the lymph nodes along the recurrent laryngeal nerve. The superior boundary is the hyoid bone, the inferior boundary is the suprasternal notch, the lateral boundaries are the common carotid arteries, and the posterior boundary by the prevertebral fascia.

Level VII. Superior Mediastinal Lymph Nodes
Metastases at level VII are considered regional lymph node metastases; all other mediastinal lymph node metastases are considered distant metastases.

Lymph node groups removed from areas not included in the above levels, eg, 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.

K. Lymph Nodes

Lymph Node Number
Histological examination of a selective neck dissection specimen will ordinarily include 6 or more lymph nodes. Histological examination of a radical or modified radical neck dissection specimen will ordinarily include 10 or more lymph nodes in the untreated neck.

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.[23,33]

L. Nodal Metastasis in Nasopharyngeal Nonkeratinizing Carcinomas

The prognostic impact of regional lymph node metastases from nasopharyngeal cancer, particularly nasopharyngeal nonkeratinizing carcinomas (differentiated and undifferentiated), differs from and is not necessarily comparable to the prognoses of other head and neck mucosal carcinomas. Therefore, a different N classification scheme is used for nasopharyngeal carcinoma.

M. Special Procedures for Lymph Nodes

The risk of regional (cervical neck) nodal spread from cancers of the pharynx is high.[1] The majority of metastatic carcinomas to the cervical lymph nodes take origin from a head and neck primary carcinoma. The most common histologic type of carcinoma to metastasize to cervical neck lymph nodes is squamous cell carcinoma.[39] Cervical nodal metastases may occur in the setting of an unknown primary carcinoma referred to as metastatic cervical carcinoma with an unknown primary (MCCUP).[40] The most common histologic subtypes of MCCUP include squamous cell carcinoma and nonkeratinizing carcinomas, differentiated and undifferentiated.[40] The most common clinical manifestation of MCCUP is that of a unilateral, fixed neck mass. The pharynx, in particular the oropharynx and nasopharynx (Waldeyer tonsillar tissues), represents the more common primary sites giving rise MCCUP.[39] Advances in diagnostic techniques, including imaging studies (eg, positron emission tomography and computed tomography [PET-CT]) have improved the detection of the "unknown" primary carcinoma. However, despite thorough physical evaluation, panendoscopic biopsy, and radiologic imaging, the primary carcinoma may be so small and/or be located within crypt epithelium as to defy clinical detection. Recent addition to the diagnostic armament in the detection of the primary carcinoma in the setting of MCCUP is evaluation for human papillomavirus (HPV), in particular the high risk type 16 (HPV-16). HPV-16 has been implicated as a causative agent in a subset of head and neck squamous cell carcinoma (HNSCC).[41-43] In situ hybridization (ISH) for HPV-16 and/or p16 immunohistochemical (IHC) staining correlate(s) with the presence of HPV-16. Furthermore, the presence of p16 represents a reliable predictor of origin from the oropharynx (ie, tonsil and base of tongue).[44,45] As such, the use of p16 (ISH or IHC; see also Note O) is advocated in the evaluation of MCCUP either by biopsy[44] or fine-needle aspiration.[45]

Epstein-Barr virus (EBV) is associated with the nonkeratinizing types of nasopharyngeal carcinomas, including both differentiated and undifferentiated subtypes in practically 100% of cases irrespective of the ethnic background of the patient.[46] The most reliable detection method for EBV is in situ hybridization for EBV encoded early RNA (EBER) present in cells latently infected by EBV.[46] Practically all tumor cells should show nuclear staining.[46] The detection of EBV by ISH for EBER can facilitate the diagnosis of nasopharyngeal carcinoma and can also be utilized in the setting of MCCUP where the presence of strong positive staining for EBER in a nonkeratinizing carcinoma (differentiated and undifferentiated subtypes) suggests origin from the nasopharynx[46] or other tissues in which such tumor types may originate (ie, Waldeyer tonsillar tissues).

At the current time, 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.

N. Dysplasia of the Upper Aerodigestive Tract (UADT)

In contrast to the uterine cervix, in which the nonkeratinizing ("classic") form of epithelial dysplasia is most common resulting in a reproducible and clinically useful grading scheme of mild, moderate, and severe dysplasia (ie, carcinoma in situ), the majority of the UADT mucosal lesions fall under the designation of keratinizing dysplasias. The criteria for evaluating keratinizing dysplasias are less defined, and the diagnosis of severe keratinizing (intraepithelial) dysplasia remains controversial. In particular, the definition of severe dysplasia in the setting of keratosis is broader than the highly reproducible pattern seen in the uterine cervix and includes a microscopically heterogeneous group of lesions. In the setting of keratinizing dysplasia where surface maturation is retained with only partial replacement of the

epithelium by atypical cells, severe dysplasia includes those lesions in which the epithelial alterations are so severe that there would be a high probability for the progression to an invasive carcinoma if left untreated. The evaluation of keratinizing dysplasia includes cellular abnormalities (ie, cytomorphology) and maturation abnormalities (ie, architectural alterations). The histopathologic interpretation and grading of epithelial dysplastic lesions in the UADT are imprecise and subjective. At present, the preferred grading for keratinizing dysplasias of the UADT include mild, moderate, and severe dysplasia, depending on the degree and extent of cellular and maturation alterations that are present.[43] Using the definition of carcinoma in situ (CIS) as applied to the uterine cervix requires loss of maturation of squamous epithelium; therefore, by this definition most keratotic lesion would not be classified as CIS because keratinization would represent a type of maturation. Therefore, the use of the specific term CIS in keratinizing dysplasias of the UADT has been questioned and is likely inappropriate in this setting; a more appropriate designation is keratinizing severe dysplasia.

Several points should be stressed relative to keratinizing dysplasia of the UADT:
- Invasive carcinoma can develop from keratinizing dysplasia that is limited in extent and in the absence of full thickness dysplasia (ie, "classic" carcinoma in situ) progression can occur even in the setting of lesions with atypia limited to the lower third (basal zone region) of the surface epithelium.
- Keratinizing severe dysplasia is often multifocal and frequently occurs adjacent to or near synchronous foci of invasive carcinoma.
- Keratinizing severe dysplasia has a rate of progression to invasive carcinoma that is greater than that of "classic" carcinoma in situ.
- A diagnosis of severe dysplasia requires therapeutic intervention, as well as clinical evaluation of the entire upper aerodigestive tract to exclude the possible presence of additional foci of dysplasia or carcinoma that may exist from field effect.

The concept of epithelial precursor lesions, including dysplasia and carcinoma in situ of the oropharyngeal (base of tongue and tonsils) and nasopharyngeal mucosa are not well defined. In biopsies of nasopharyngeal carcinoma, only a minority of cases (less than 10%) will have an in situ component.[46] Further, carcinoma in situ of the oropharynx and nasopharynx as confirmed by biopsy to rule out an invasive carcinoma component is very rare.[46] Histologically, carcinoma in situ of the oropharynx and nasopharynx may be confined to the surface or crypt epithelium without invasive carcinoma and, when present, are most often of the nonkeratinizing type. Hypopharyngeal precursor lesions are rarely identified as hypopharyngeal cancers by virtue of their anatomic site often remain clinically quiescent commonly presenting as invasive carcinomas.

O. Ancillary Testing

It is now well established that human papillomavirus (HPV) plays a pathogenic role in a subset of head and neck cancers, termed HPV-associated head and neck squamous cell carcinoma (HPV-HNSCC).[47,48] HPV, in particular the high risk type 16 (HPV-16), is present in most oropharyngeal carcinomas.[47] These carcinomas arise predominantly from the palatine tonsil and lingual tonsils of the oropharynx (ie, tonsil or base of tongue) and are nonkeratinizing carcinomas characterized by a somewhat basaloid morphology recapitulating tonsillar crypt epithelium (not to be confused with the specific variant basaloid squamous cell carcinoma).[49] A similar association has been suggested but not confirmed for oral cavity carcinoma. To date, there are no data linking HPV with laryngeal carcinoma, and the utility of testing for the presence of HPV in laryngeal carcinomas is unproven.

Such oropharyngeal carcinomas may be small and clinically/radiographically difficult to detect, and may present as metastatic cancer to a cervical neck lymph node from an unknown primary site (see discussion under Note L). HPV-associated oropharyngeal carcinoma represents a unique subtype of HNSCC.[37] HPV-positive oropharyngeal carcinomas frequently occur in patients with no known risk factors for HNSCC (ie, nonsmokers and nondrinkers), in younger aged patients, and is associated with a better outcome (better overall and disease-specific survival). For this reason, it is becoming evident that

specific reporting of HPV is a critical diagnostic parameter in the HNSCC, in particular oropharyngeal carcinomas.

There are many methods for testing HPV status including p16 immunohistochemistry, in situ hybridization, and PCR for HPV-DNA. DNA testing is generally directed towards the high-risk subtypes, particularly HPV-16. Specific assays for integrated HPV exist. Integration of HPV into the host genome is regarded as an important tumorigenic event. Additionally, with in situ hybridization, a punctate pattern of HPV positivity suggests integration. There is still, however, no consensus on the best methodology for HPV testing.

p16 immunohistochemical staining is validated and can be used as a useful surrogate marker for HPV status, though only for oropharyngeal sites, and mainly for tumors that have a nonkeratinizing morphology.[50] Additionally, p16 immunohistochemical staining in a lymph node metastasis can suggest an oropharyngeal primary site. A commonly used criterion for positivity as a surrogate marker is 70% strong diffuse nuclear and cytoplasmic staining, with the caveat that the correlation with HPV status is not 100%. It is important to note also that the morphologic appearance (keratinizing versus nonkeratinizing) also impacts the predictive value of p16 immunostaining as a surrogate for HPV status. The table below lists common conditional scenarios in which HPV DNA testing would be required to confirm a p16 result.

Recommendations for HPV DNA Testing in Oropharyngeal Squamous Cell Carcinoma Based on Morphology and p16 Staining Profile

Morphology	p16	Requires HPV DNA Testing Confirmation
Nonkeratinizing or predominantly nonkeratinizing	Strong and diffuse (cytoplasmic and nuclear, ie, >70%)	No
Nonkeratinizing or predominantly nonkeratinizing	Negative or only focally positive	Yes
Keratinizing	Strong and diffuse (cytoplasmic and nuclear, ie, >70%)	Yes
Keratinizing	Negative or only focally positive	No

As previously discussed under Note M, Epstein-Barr virus is associated with the nonkeratinizing types of nasopharyngeal carcinomas, including both differentiated and undifferentiated subtypes in practically 100% of cases irrespective of the ethnic background of the patient.[46] The most reliable detection method for EBV is in situ hybridization for EBV encoded early RNA (EBER) present in cells latently infected by EBV, and can facilitate the diagnosis of nasopharyngeal carcinoma.[46] In a similar manner as head and neck squamous cell carcinomas associated with HPV have been termed HPV-associated head and neck squamous cell carcinoma (HPV-HNSCC), carcinomas associated with EBV can be referred to as EBV-associated head and neck squamous cell carcinoma (EBV-HNSCC). Such designations for these carcinomas, while not as yet universally accepted, have merit given their unique clinical, pathologic, therapeutic, and prognostic implications as compared to non–viral-associated head and neck squamous cell carcinomas. Recent studies suggest that a minor subset of nasopharyngeal carcinomas (nonkeratinizing differentiated and undifferentiated types) are associated with HPV rather than EBV. Thus it would be desirable to test nasopharyngeal carcinoma for HPV if EBV is negative.

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