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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 malignant melanoma is included. Lymphomas and sarcomas are not included.

Based on AJCC/UICC TNM, 7th edition

Protocol web posting date: June 2012

Procedures

- Biopsy
- Resection

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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 3.2.0.0

Summary of Changes

The following changes have been made since the November 2011 release.

Incisional Biopsy, Excisional Biopsy, Resection

Ancillary Studies

Requirement was clarified. Reporting on p16 was added, reporting on HPV was changed, and “present” was changed to “positive” in reporting on Epstein-Barr virus, as follows:

Ancillary Studies (required only for oropharynx [p16, HPV] and nasopharynx [EBV] if available at time of report completion) (select all that apply)

p16

Positive

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

Explanatory Notes

Scope of Guidelines

The word “checklist(s)” was changed to “case summary(ies)” or “protocol” as appropriate.

O. Ancillary Testing

Information on p16 immunochemistry was added.

References

Reference #47 was added.

Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

PHARYNX (OROPHARYNX, HYPOPHARYNX, NASOPHARYNX): Incisional Biopsy, 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)

- Incisional biopsy
 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
 Bilateral
 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
- Bilateral
- Midline
- Not specified

Tumor Focality

- Single focus
- Bilateral
- 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, conventionalVariants of Squamous Cell Carcinoma Acantholytic squamous cell carcinoma Adenosquamous carcinoma Basaloid squamous cell carcinoma Papillary squamous cell carcinoma Spindle cell squamous carcinoma Verrucous carcinoma Lymphoepithelial carcinoma (non-nasopharyngeal)Carcinomas of the Nasopharynx Keratinizing squamous cell carcinoma (formerly WHO-1) Nonkeratinizing carcinoma Differentiated carcinoma (formerly WHO-2; transitional carcinoma) Undifferentiated carcinoma (formerly WHO-3; lymphoepithelioma) Basaloid squamous cell carcinomaAdenocarcinomas (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 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

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

- Salivary duct carcinoma
 Other (specify): _____

Neuroendocrine Carcinoma

- Typical carcinoid tumor (well differentiated neuroendocrine carcinoma)
 Atypical carcinoid tumor (moderately differentiated neuroendocrine carcinoma)
 Small cell carcinoma (poorly differentiated neuroendocrine carcinoma)
 Combined (or composite) small cell carcinoma, neuroendocrine type
- Mucosal malignant 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: ___ mm or ___ cm
 Specify margin(s), per orientation, if possible: _____
 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: ___ mm or ___ cm
 Specify margin(s), per orientation, if possible: _____
 Margins involved by carcinoma in situ (includes moderate and severe dysplasia#) (Note D)
 Specify margin(s), per orientation, if possible: _____
 Not applicable

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)

Note: The phrases in italics include clinical findings required for AJCC staging. This clinical information may not be available to the pathologist. However, if known, these findings should be incorporated into the pathologic staging.

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 Malignant MelanomaPrimary 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 *without fixation of hemilarynx*
 pT3: Tumor more than 4 cm in greatest dimension *or with fixation of hemilarynx* 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

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

- 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 prelaryngeal 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 positive lymph node: (Note K)

[#] 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

+ Data elements preceded by this symbol are not required. However, these elements may be clinically important but are not yet validated or regularly used in patient management.

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 positive lymph node: ____ (Note K)

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: _____

+ Source of pathologic metastatic specimen (specify): _____

For Mucosal Malignant MelanomaPrimary 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: _____

+ Source of pathologic metastatic specimen (specify): _____

+ 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] if available at time of report completion) (select all that apply) (Notes M and O)

- p16
 - Positive
 - 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 oral cancer including the lip is facilitated by the provision of a case summary illustrating the features required for comprehensive patient care. However, there are many cases in which the individual practicalities of applying such a case summary may not be straightforward. Common examples include finding the prescribed number of lymph nodes, trying to determine the levels of the radical neck dissection, and determining if isolated tumor cells in a lymph node represent metastatic disease. Case summaries have evolved to include clinical, radiographic, morphologic, immunohistochemical, and molecular results in an effort to guide clinical management. Adjuvant and neoadjuvant therapy can significantly alter histologic findings, making accurate classification an increasingly complex and demanding task. This protocol tries to remain simple while still incorporating important pathologic features as proposed by the American Joint Committee on Cancer (AJCC) cancer staging manual, the World Health Organization classification of tumours, 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 oral cavity 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).

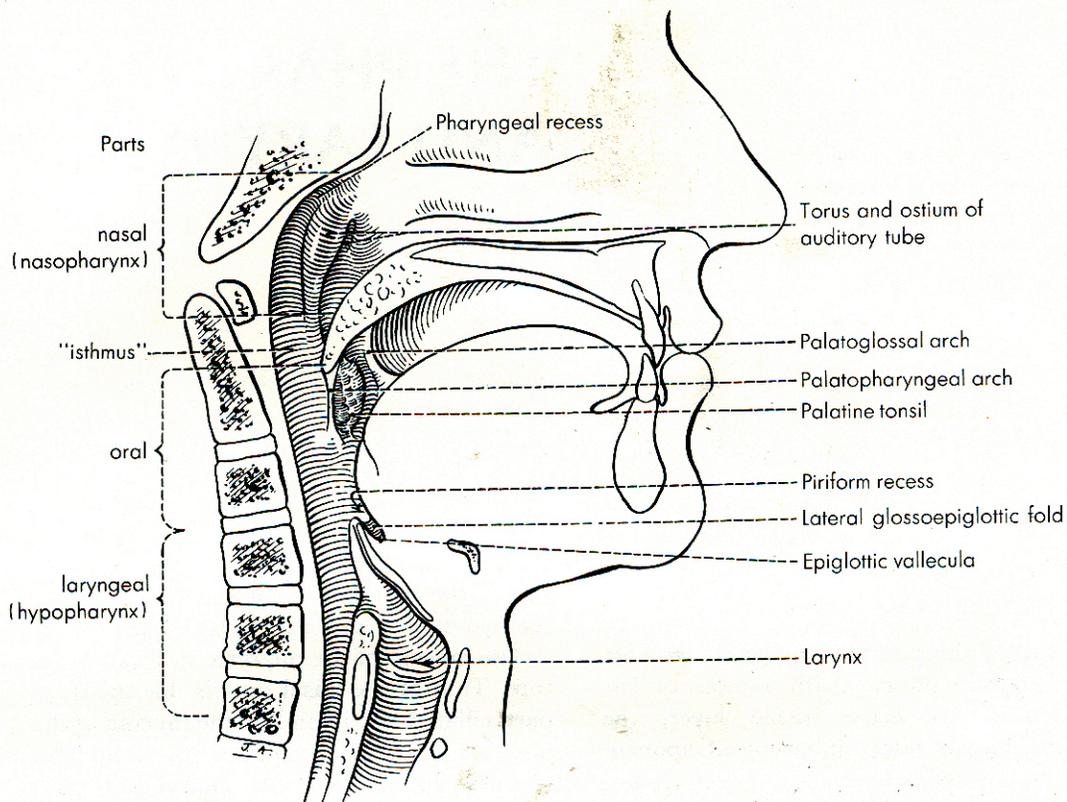


Figure 1. Anatomical subdivisions and "contents" of the pharynx. From Hollinshead WH. *Anatomy for Surgeons: The Head and Neck*. 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 1982. Reproduced with permission (<http://lww.com>).

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's 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

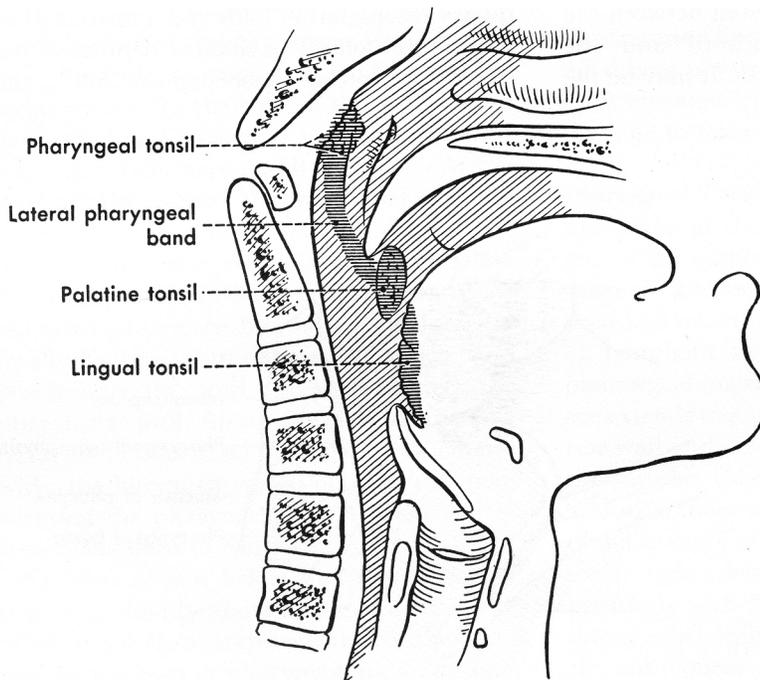


Figure 2. Waldeyer's tonsillar tissues. From Hollinshead WH. *Anatomy for Surgeons: The Head and Neck*. 3rd ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 1982. Reproduced with permission (<http://lww.com>).

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 hypopharynx⁴ 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

Squamous cell carcinoma, variant (*in alphabetical order*)

Acantholytic squamous cell carcinoma

Adenosquamous carcinoma

Basaloid squamous cell carcinoma

Papillary squamous cell carcinoma

Spindle cell squamous carcinoma

Verrucous carcinoma

Lymphoepithelial carcinoma (non-nasopharyngeal)

Carcinomas of the Nasopharynx

Keratinizing squamous cell carcinoma (formerly WHO-1)

Non-keratinizing carcinoma

Differentiated type (formerly WHO-2; transitional carcinoma)

Undifferentiated type (formerly WHO-3; lymphoepithelioma; note designations of

Schmincke and Regaud refer to growth patterns, including cohesive and dyscohesive, respectively, and are not diagnostic terms)

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-myoeplithelial 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)

Small cell (undifferentiated) carcinoma (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.⁶

Mucosal Malignant Melanoma

C. Histologic Grade

For histologic types of carcinomas that are amenable to grading, 3 histologic grades are suggested, as shown below. When a tumor manifests more than 1 grade of differentiation, the surgical report must designate both the highest and the most prevalent tumor grades.^{5,6}

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

This grading system does not apply to all salivary gland tumors. 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.⁷⁻¹¹ Further, there is often a positive correlation between histologic grade and clinical stage. For the majority of salivary gland carcinomas there is only a single histologic grade and classification alone determines the histologic grade (eg, acinic cell carcinoma is a histologically low-grade carcinoma; salivary duct carcinoma is a histologically high-grade carcinoma). With some exceptions, histologic grading is predicated on cytomorphologic features. In this histologic grading scheme, 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

When a tumor manifests more than 1 grade of differentiation, the surgical report must designate both the highest and the most prevalent tumor grades. 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.⁷ Those adenoid cystic carcinomas showing 30% or greater of solid growth pattern are considered to be histologically high-grade carcinomas.^{7,9,12} 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

D. Surgical Margins

Reporting of surgical margins should include information regarding the distance of invasive carcinoma, carcinoma in situ, or high-grade dysplasia (moderate to severe) from the surgical margin. Closeness of the above, microscopically less than 5 mm, from the surgical border should be noted in the report. Presence of the above lesions found within 5 mm of the surgical border carry a significant risk for subsequent local recurrence.¹⁶⁻¹⁸ Reporting of surgical margins for carcinomas of the minor salivary glands should follow those used for squamous cell carcinoma of oral cavity. There is no category of carcinoma in situ relative to carcinomas of salivary glands (major, minor).

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 attending surgeons. 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 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

The presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.¹⁹ 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.¹⁹ Further, perineural invasion is associated with decrease in disease-specific survival and overall survival.¹⁹ 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 but other studies not showing any correlation with distant metastasis.¹⁹ The relationship between perineural invasion and prognosis is independent of nerve diameter.²⁰ 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).^{21,22} 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 extra-nodal 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. If macroscopic examination suggests EE, this tissue should be submitted for microscopic confirmation. EE is a predictor of regional relapse and a criterion for post-operative radiotherapy.²³⁻²⁶

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.^{1,27} Of note in the 7th edition of the AJCC staging of head and neck cancers¹ 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 malignant melanomas.¹ Approximately two-thirds of mucosal malignant 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.¹ 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 malignant melanomas does not provide for the histologic definition of a T3 lesion; as

the majority of mucosal malignant 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 Malignant 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

[#] 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: 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, hypharynx, 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 prelaryngeal 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.

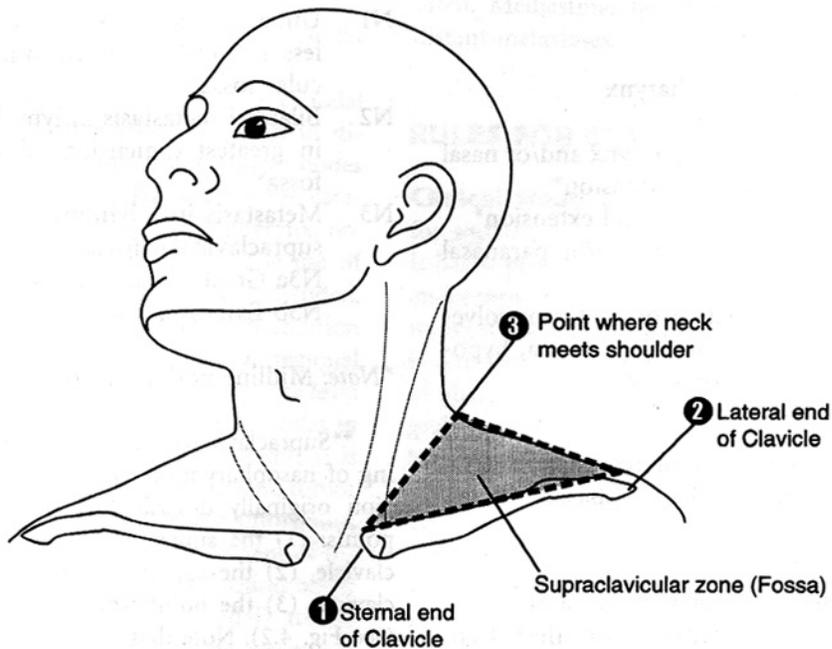


Figure 3. Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma. From *AJCC Cancer Staging Manual*. 6th ed. New York: Springer; 2002. Reproduced with permission.

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

For Mucosal Malignant 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 Malignant 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 Malignant 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
 - a. Supraomohyoid neck dissection
 - b. Posterolateral neck dissection
 - c. Lateral neck dissection
 - d. Central compartment neck dissection
4. Selective neck dissection (SND), as specified by the surgeon -“SND” with levels and sublevels designated (Figure 4)²⁸⁻³⁰
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. Lymph nodes or distant sites 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) should be classified as N0 or M0, respectively. Specific denotation of the assigned N category is suggested as follows for cases in which ITCs are the only evidence of possible metastatic disease.^{27,31,32}

pN0	No regional lymph node metastasis histologically, no examination for isolated tumor cells (ITCs)
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pN0(i-)	No regional lymph node metastasis histologically, negative morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(i+)	No regional lymph node metastasis histologically, positive morphologic (any morphologic technique, including hematoxylin-eosin and immunohistochemistry) findings for ITCs
pN0(mol-)	No regional lymph node metastasis histologically, negative non-morphologic (molecular) findings for ITCs
pN0(mol+)	No regional lymph node metastasis histologically, positive non-morphologic (molecular) findings for ITCs

For purposes of pathologic evaluation, lymph nodes are organized by levels as shown in Figure 4.³³



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 metastasis in a lymph node containing metastatic tumor 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. There is conflicting data in the literature on the significance of the size of the largest metastatic lymph node on the risk of regional recurrence and a predictor of poor overall survival.¹⁹ While the diameter of the largest positive lymph node may potentially serve as a predictor of outcome, it may not represent an independent predictor of outcome when other pathologic factors are considered.¹⁹

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.³⁴ Cervical nodal metastases may occur in the setting of an unknown primary carcinoma referred to as metastatic cervical carcinoma with an unknown primary (MCCUP).³⁵ The most common histologic subtypes of MCCUP include squamous cell carcinoma and nonkeratinizing carcinomas, differentiated and undifferentiated.³⁵ The most common clinical manifestation of MCCUP is that of a unilateral, fixed neck mass. The pharynx, in particular the oropharynx and nasopharynx (Waldeyer's tonsillar tissues), represents the more common primary sites giving rise MCCUP.³⁴ 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).³⁶⁻³⁸ 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).^{39,40} As such, the use of p16 (ISH or IHC; see also Note O) is advocated in the evaluation of MCCUP either by biopsy³⁹ or fine-needle aspiration.⁴⁰

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.⁴¹ The most reliable detection method for EBV is in situ hybridization for EBV encoded early RNA (EBER) present in cells latently infected by EBV.⁴¹ Practically all tumor cells should show nuclear staining.⁴¹ 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 nasopharynx⁴¹ or other tissues in which such tumor types may originate (ie, Waldeyer's 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.⁴² 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.⁴³ Further, carcinoma in situ of the oropharynx and nasopharynx as confirmed by biopsy to rule out an invasive carcinoma component is very rare.⁴³ 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

There is increasing evidence that human papillomavirus plays a pathogenic role in a subset of head and neck cancers, termed HPV-associated head and neck squamous cell carcinoma (HPV-HNSCC).⁴⁴ HPV, in particular the high-risk type 16 (HPV-16), is present in most oropharyngeal carcinomas, and for those oropharyngeal cancers positive for high-risk HPV, HPV-16 was detected in 93% of cases.⁴⁵ 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 basaloid cell type.³⁶ 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.³⁶ 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). The International Agency for Research of Cancer (IARC) recently concluded that there is sufficient evidence that HPV-16 is causal for a subset of oropharyngeal cancers.⁴⁶ 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 immunostaining 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.⁴⁷ Additionally, p16 immunostaining 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.⁴¹ 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.⁴¹ 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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