



Protocol for the Examination of Specimens From Patients With Carcinomas of the Nasal Cavity and Paranasal Sinuses

Protocol applies to all invasive carcinomas of the nasal cavity and paranasal sinuses. Mucosal melanoma is included. Lymphomas, neuroectodermal neoplasms, 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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Head and Neck • Nasal Cavity, Paranasal Sinuses

NasalCavityParanasalSinus 3.2.0.0

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CAP Nasal Cavity, Paranasal Sinuses Protocol Revision History

Version Code

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

Version: NasalCavityParanasalSinus 3.2.0.0

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

"Bilateral" was deleted.

Histologic Type

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

The following was added: Large cell carcinoma, neuroendocrine type (poorly differentiated neuroendocrine carcinoma)

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 E)
 - 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 E)
 - Specify margin(s), per orientation, if possible: _____

Applicable only to squamous cell carcinoma and histologic variants.

Pathologic Staging (pTNM)

Regional Lymph Nodes (pN)

Reporting on "Number of Lymph Nodes Examined" was modified and "Extracapsular Extension" was added, as follows:

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

Distant Metastasis

"Source of pathologic metastatic specimen (specify)" was deleted.

Explanatory Notes

Scope of Guidelines: First sentence: "oral cancer including the lip" was changed to "nasal cavity and paranasal sinus cancer." Third to last sentence: "oral cavity" was changed to "nasal cavity and paranasal sinus."

B. Histologic Type

Histologic types were updated.

C. Histologic Grade

D. Surgical Margins

E. Orientation of Specimen

F. Perineural Invasion

G. Extranodal Extension

I. Classification of Neck Dissection

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

K. Lymph Nodes, Measurement of Tumor Metastasis

Edits were made to these notes.

References

References were updated.

Surgical Pathology Cancer Case Summary

Protocol web posting date: October 2013

NASAL CAVITY AND PARANASAL SINUSES: Excisional Biopsy, Resection

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)

- Nasal cavity
 - Septum
 - Floor
 - Lateral wall
 - Vestibule
- Paranasal sinus(es), maxillary
- Paranasal sinus(es), ethmoid
- Paranasal sinus(es), frontal
- Paranasal sinus(es), sphenoid
- Other (specify): _____
- Not specified

Received:

- Fresh
- In formalin
- Other (specify): _____

Procedure (select all that apply)

- Excisional biopsy
- Resection (specify type)
 - Partial maxillectomy
 - Radical maxillectomy
- 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)

- Right
- Left
- Midline
- Not specified

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

- Nasal cavity
 Septum
 Floor
 Lateral wall
 Vestibule
 Paranasal sinus(es), maxillary
 Paranasal sinus(es), ethmoid
 Paranasal sinus(es), frontal
 Paranasal sinus(es), sphenoid
 Other (specify): _____
 Not specified

Tumor Focality (select all that apply)

- 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 Nasal Cavity and Paranasal Sinuses

- Squamous cell carcinoma, conventional
 Keratinizing
 Nonkeratinizing (formerly cylindrical cell, transitional cell)

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

 Giant cell carcinoma
 Lymphoepithelial carcinoma (non-nasopharyngeal)
 Sinonasal undifferentiated carcinoma (SNUC)

Adenocarcinoma, Non-Salivary Gland Type

- Intestinal type
 - Papillary-type
 - Colonic-type
 - Solid type
 - Mucinous type
 - Mixed type
- Non-intestinal type
 - Low grade
 - Intermediate grade
 - High grade

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
- Carcinoma ex pleomorphic adenoma (malignant mixed tumor)
- Clear cell adenocarcinoma
- Epithelial-myoepithelial carcinoma
- Mucoepidermoid carcinoma
 - Low grade
 - Intermediate grade
 - High grade
- 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 type):

- Mucosal melanoma
- Other (specify): _____
- Carcinoma, type cannot be determined

+ 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

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 E)
 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 E)
 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 MelanomaPrimary Tumor (pT): Maxillary Sinus

- pT1: Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
- pT2: Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
- pT3: Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
- pT4a: Moderately advanced local disease. Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
- pT4b: Very advanced local disease. Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V₂), nasopharynx, or clivus

Primary Tumor (pT): Nasal Cavity and Ethmoid Sinus

- pT1: Tumor restricted to any one subsite, with or without bone invasion
- pT2: Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bone invasion
- pT3: Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
- pT4a: Moderately advanced local disease. Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
- pT4b: Very advanced local disease. Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V₂), nasopharynx, or clivus

Regional Lymph Nodes (pN)# (Notes I through L)

- pNX: Cannot be assessed
- pN0: No regional lymph node metastasis
- 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 3cm 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 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: _____
 + Size (greatest dimension) of the largest metastatic focus in the lymph node: _____ cm (Note K)
 Number cannot be determined (explain): _____
 + Size of the associated metastatic focus: _____ (Note K)
 + Position of the involved node (level): _____ (Note K)

Extracapsular Extension (Note G)

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

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

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

+ 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

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
 + Carcinoma in situ (Note M)
 + Epithelial dysplasia (Note M)
 + Specify: _____
 + Inflammation (specify type): _____
 + Squamous metaplasia
 + Epithelial hyperplasia
 + Colonization
 + Fungal
 + Bacterial
 + Other (specify): _____

+ Ancillary Studies (Note N)

- + Specify type(s): _____
 + Specify result(s): _____

+ 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 nasal cavity and paranasal sinus 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 nasal cavity and paranasal sinus 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.¹

A. Anatomical Sites and Subsites for the Nasal Cavity and Paranasal Sinuses (Figure 1)

The nasal cavity is divided in the midline to right and left halves by the septum; each half opens on the face via the nares or nostrils and communicates behind with the nasopharynx through the posterior nasal apertures or the choanae. The nasal cavity is divided into 4 subsites including the septum, floor, lateral wall, and vestibule. The paranasal sinuses represent a grouping of 4 paired sinuses including the maxillary sinuses, ethmoid sinuses, frontal sinuses, and sphenoid sinuses. The nasoethmoidal complex is divided into 2 sites including the nasal cavity and the ethmoid sinuses.

Cancers of the maxillary sinuses are the most common sinonasal malignancies followed by cancers of the ethmoid sinuses, which are much less common.¹ Cancers of the frontal and sphenoid sinuses are rare. When considering the nasal cavity and paranasal sinuses, 60% of malignant neoplasms originate from the maxillary sinus, 20% to 30% from the nasal cavity, 10% to 15% from the ethmoid sinus and 1% from the sphenoid and frontal sinuses.² When only considering the paranasal sinuses, 77% of malignant neoplasms originate from the maxillary sinus, 22% from the ethmoid sinus, and 1% from the sphenoid and frontal sinuses.²

The location as well as the extent of the mucosal lesion in the maxillary sinus has prognostic importance. Ohngren's line, connecting the medial canthus of the eye to the angle of the mandible, divides the maxillary sinus into an anterioinferior portion (infrastructure) and superioposterior portion (suprastructure) structures. Carcinomas of the infrastructure are associated with a good prognosis; carcinomas of the suprastructure are associated with a poor prognosis. The poorer prognosis with carcinomas of the suprastructure reflects early access of these tumors to critical structures, including the eye, skull base, pterygoids, and infratemporal fossa.¹

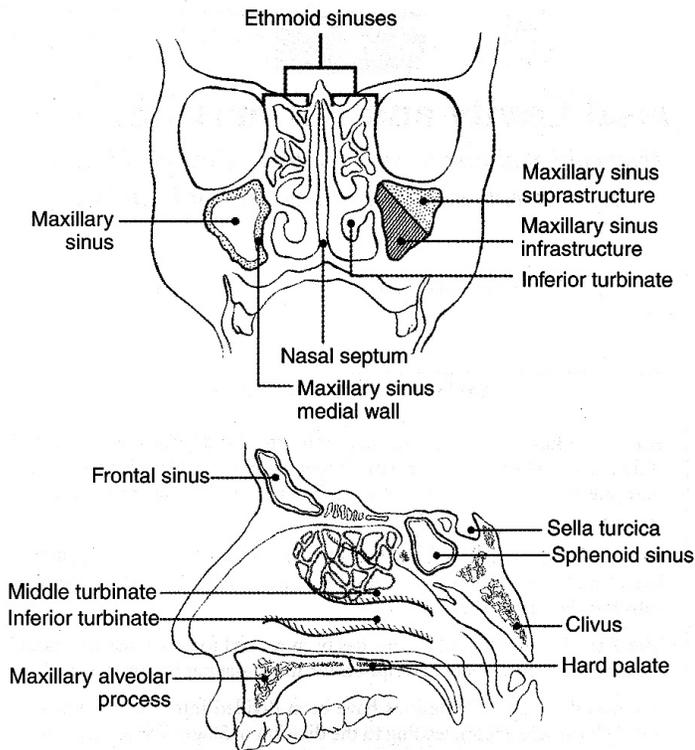


Figure 1. Anatomical sites and subsites for the nasal cavity and paranasal sinuses. From *AJCC Cancer Staging Manual*, 6th ed. New York: Springer; 2002. © American Joint Committee on Cancer. Reproduced with permission.

B. Histological Type

A modification of the World Health Organization (WHO) classification of carcinomas of the nasal cavity and paranasal sinuses is shown below.³ This list may not be complete. This protocol applies only to carcinomas and melanomas and does not apply to lymphomas, sarcomas or neuroectodermal tumors (eg, olfactory neuroblastoma, primitive neuroectodermal tumor [PNET], others).

Nasal Cavity and Paranasal Sinuses

- Squamous cell carcinoma, conventional
 - Keratinizing
 - Nonkeratinizing (formerly cylindrical cell, transitional cell)
- Variants of squamous cell carcinoma (*in alphabetical order*)
 - Acantholytic squamous cell carcinoma
 - Adenosquamous carcinoma
 - Basaloid squamous cell carcinoma
 - Papillary squamous cell carcinoma
 - Spindle cell squamous cell carcinoma
 - Verrucous carcinoma
- Giant cell carcinoma[#]
- Lymphoepithelial carcinoma (non-nasopharyngeal)
- Sinonasal undifferentiated carcinoma (SNUC)

Adenocarcinoma, Non-Salivary Gland Type

Intestinal-type
Non-intestinal type

Carcinomas of Minor Salivary Glands

Acinic cell carcinoma
Adenoid cystic carcinoma
Adenocarcinoma, not otherwise specified (NOS)
Carcinoma ex pleomorphic adenoma (malignant mixed tumor)
Clear cell adenocarcinoma
Mucoepidermoid carcinoma
Epithelial-myoepithelial carcinoma
Myoepithelial carcinoma (malignant myoepithelioma)
Oncocytic carcinoma
Polymorphous low-grade adenocarcinoma
Salivary duct carcinoma
Other

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##

Mucosal Melanoma

Not included in WHO classification.

Represents a carcinoma showing combined features of small cell neuroendocrine carcinoma associated with a squamous or adenocarcinomatous component.⁴

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

D. Surgical Margins

The definition of a positive margin is somewhat controversial given the varied results from prior studies.^{16,17} This is made even more challenging and nebulous for sinonasal tumors, which are often received piecemeal with margins submitted separately. But for squamous cell carcinoma, data is essentially extrapolated from other sites. Here, 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).¹⁶ 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.^{16,18,19} 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 glottic larynx.¹⁶ However, values ranging from 3 mm to 7 mm have been used with success,^{16,20} and for glottic tumors, as low as 1 mm.²¹ Thus distance of tumor from the nearest margin should be recorded when a specimen is sufficiently intact to allow for this.

Reporting of surgical margins for carcinomas of the minor salivary glands should follow those used for squamous cell carcinoma of oral cavity. While there is no standard recommendation for the other histologic types of carcinoma encountered, adherence to the recommendations for squamous cell carcinoma is acceptable.

E. Orientation of Specimen

Complex intact 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. For multipart piecemeal endoscopic resections, specimens should be clearly and precisely labeled. Parts that are margins should be designated explicitly as such. 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

Traditionally, the presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.²² 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.²² Further, perineural invasion is associated with decrease in disease-specific survival and overall survival.²² 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.²² The relationship between perineural invasion and prognosis is independent of nerve diameter.²³ Additionally, emerging evidence suggests that extratumoral perineural invasion may be more prognostically relevant.²⁴ 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).^{25,26} 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.²⁷⁻³⁰

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 nasal cavity and paranasal sinus cancer.^{1,31} 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 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.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 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: Maxillary Sinus

| | |
|-----|------------------------------|
| TX | Cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ |

- T1 Tumor limited to the maxillary sinus mucosa with no erosion or destruction of bone
- T2 Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
- T3 Tumor invades any of the following: bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
- T4a Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
- T4b Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V₂), nasopharynx, or clivus

Primary Tumor: Nasal Cavity and Ethmoid Sinus

- TX Cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- T1 Tumor restricted to any one subsite, with or without bone invasion
- T2 Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bone invasion
- T3 Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
- T4a Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
- T4b Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V₂), nasopharynx, or clivus

Regional Lymph Nodes#

- 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
- N2 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 nodes, none more than 6 cm 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 nodes are considered ipsilateral nodes.

Distant Metastasis

- M0 No distant metastasis
- M1 Distant metastasis

For Mucosal MelanomaPrimary Tumor

- T3 Mucosal disease
- T4a Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone, 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.

Stage Groupings – For All Cancers Except Mucosal Melanoma

| | | | |
|-----------|----------|----------|----|
| Stage 0 | Tis | N0 | M0 |
| Stage I | T1 | N0 | M0 |
| Stage II | T2 | N0 | M0 |
| Stage III | T1 | N1 | M0 |
| | T2 | N1 | M0 |
| | T3 | N0,N1 | M0 |
| Stage IVA | T1,T2,T3 | N2 | M0 |
| | T4a | N0,N1,N2 | M0 |
| Stage IVB | T4b | Any N | M0 |
| | Any T | N3 | 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 2), defined by dissection of less than the 5 traditional levels of a radical and modified radical neck dissection. The following dissections are now under this category³²⁻³⁴:
 - 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 levels³⁵
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 nonmorphologic 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,^{31,36} 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.³⁷

For purposes of pathologic evaluation, lymph nodes are organized by levels as shown in Figure 2.³⁸



Figure 2. 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 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. 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.^{22,32}

L. Special Procedures for Lymph Nodes

At the current time, no additional special techniques should be used other than routine histology for the assessment of nodal metastases. Immunohistochemistry and PCR to detect isolated tumor cells are considered investigational techniques at this time.

M. Dysplasia of the Upper Aerodigestive Tract (UADT)

Epithelial dysplasias of the nasal cavity and paranasal sinuses as a precursor lesion for sinonasal carcinomas are less common and less well defined as compared to epithelial dysplasias of the oral cavity and the larynx.³⁹ Further, unlike dysplastic lesions of the oral cavity and/or the larynx, precursor lesions of the nasal cavity and paranasal sinuses are generally asymptomatic and therefore are not biopsied. Instead, they are identified more often in association with another lesion, such as an invasive carcinoma.

N. Ancillary Studies

At the current time, no additional special techniques are required other than routine histology for the assessment of nasal cavity and paranasal sinus carcinomas. Immunohistochemistry and in situ hybridization (ISH) to detect the presence of viruses (eg, human papillomavirus, Epstein-Barr virus) are considered investigational techniques at this time.

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