Protocol for the Examination of Specimens from Patients with Cancers of the Nasal Cavity and Paranasal Sinuses

Version: 4.3.0.0
Protocol Posting Date: April 2026

CAP Laboratory Accreditation Program Protocol Required Use Date: January 2027
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

For accreditation purposes, this protocol should be used for the following procedures AND tumor types:

Procedure	Description
Resection	Includes specimens designated nasal cavity and paranasal sinuses
Tumor Type	**Description**
Carcinoma	Includes squamous cell carcinoma, sinonasal carcinomas including: sinonasal adenocarcinoma and sinonasal neuroendocrine carcinoma

This protocol is NOT required for accreditation purposes for the following:

Procedure
Biopsy
Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy)
Cytologic specimens
Squamous cell carcinoma in situ (Tis)

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

Tumor Type
Olfactory Neuroblastoma
Sarcoma (consider the Soft Tissue or Bone protocol)
Minor salivary gland carcinoma (consider the Salivary Gland protocol)
Mucosal melanoma (consider the Head and Neck Mucosal Melanoma protocol)
Hematologic malignancies (consider the Precursor and Mature Lymphoid Malignancies, Myeloid and Mixed / Ambiguous Lineage Neoplasms, and Plasma Cell Malignancies protocols)

Version Contributors
Committee Authors: Raja R. Seethala, MD, FCAP*, Nicole A. Cipriani, MD, FCAP*, Lananh Nguyen, MD, MSc, FCAP, Rashmi Samdani, MD, FCAP, Michael A. Berman, MD, FCAP, Jason R. Pettus, MD, FCAP
Expert Panel Contributors: Justin A. Bishop, MD, William C. Faquin, MD, PhD, Shao Hui Huang, MD, Nora Katabi, MD, William Lydiatt, MD, Brian O'Sullivan, MB BCh, Snehal Patel, MD, Lindsay Williams, MD, Keluo Yao, MD, FCAP

** Denotes primary author.*
For any questions or comments, contact: cancerprotocols@cap.org.

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

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

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

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

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

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

Summary of Changes

v 4.3.0.0

- Updates to cover page, content, and explanatory notes reflecting the separation of select Head and Neck protocols
- Addition of “Middle Ear” to Tumor Site question
- Histologic Type question updates
- Removal of Grade / Intrinsic Biologic Potential, Extent / Type of Perineural Invasion questions, and ADDITIONAL FINDINGS section
- Addition of Tumor Bed Margin Status section
- Separation of “Intraparotid” and “Periparotid” terms to Nodal Site(s) with Tumor question
- Modification to pTNM Classification pT, pN, and pM categories to remove mucosal melanoma staging and make minor typographical updates

Reporting Template

Protocol Posting Date: April 2026
Select a single response unless otherwise indicated.
CASE SUMMARY: (NASAL CAVITY AND PARANASAL SINUSES)
Standard(s): AJCC 8

SPECIMEN

Procedure (select all that apply)
___ Endoscopic endonasal resection
___ Excision
___ Partial maxillectomy
___ Radical maxillectomy
___ Neck (lymph node) dissection (specify type): _____
___ Other (specify): _____
___ Not specified

TUMOR

Multiple Primary Sites (e.g., nasal cavity and paranasal sinus, maxillary) (required only if applicable)#
 # Please complete a separate checklist for each primary site
___ Not applicable (no additional primary site(s) present)
___ Present: _____

Tumor Focality
___ Unifocal
___ Multifocal: _____
___ Cannot be determined (explain): _____

Tumor Site (Note A) (select all that apply)
___ Nasal septum
___ Nasal floor
___ Nasal lateral wall
___ Nasal vestibule
___ Nasal cavity, NOS
___ Middle ear
___ Paranasal sinus(es), maxillary
___ Paranasal sinus(es), ethmoid
___ Paranasal sinus(es), frontal
___ Paranasal sinus(es), sphenoid
___ Other (specify): _____
___ Not specified

Tumor Laterality (select all that apply)
___ Right
___ Left

___ Midline
___ Not specified

Tumor Size
___ Greatest dimension in Centimeters (cm): _____ cm
___ Cannot be determined (explain): _____

Histologic Type (Note B)
Carcinomas
___ Squamous cell carcinoma and subtypes
Select all that apply
___ Squamous cell carcinoma, keratinizing
___ Squamous cell carcinoma, non-keratinizing, HPV-independent
___ Squamous cell carcinoma, non-keratinizing, HPV-associated
___ Squamous cell carcinoma, non-keratinizing, DEK::AFF2 translocated
___ Lymphoepithelial carcinoma
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Papillary squamous cell carcinoma
___ Spindle cell [sarcomatoid] squamous cell carcinoma
___ Verrucous carcinoma
___ Carcinoma cuniculatum
___ Other subtype (specify): _____
___ NUT carcinoma
___ SWI / SNF complex-deficient sinonasal carcinoma
___ Sinonasal undifferentiated carcinoma (SNUC)
___ Teratocarcinosarcoma
___ HPV-associated multiphenotypic sinonasal carcinoma
___ Intestinal-type sinonasal adenocarcinoma
___ Non-intestinal-type sinonasal adenocarcinoma
Neuroendocrine
___ Neuroendocrine tumor, grade 1
___ Neuroendocrine tumor, grade 2
___ Neuroendocrine tumor, grade 3
___ Neuroendocrine carcinoma, small cell type
___ Neuroendocrine carcinoma, large cell type
___ Combined (or composite) small cell carcinoma, neuroendocrine type
Type of Combined Histology# (select all that apply)
 # Please note that the user must select at least one neuroendocrine type and at least one carcinoma type from the list below.
___ Squamous cell carcinoma: _____
___ Adenocarcinoma: _____
___ Neuroendocrine carcinoma, small cell type
___ Neuroendocrine carcinoma, large cell type
___ Other (specify): _____
Other
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined: _____

+Histologic Type Comment: _____

Histologic Grade (Note C)
___ G1, well-differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ Other (specify): _____
___ GX, cannot be assessed: _____
___ Not applicable

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

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

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

+Tumor Comment: _____

MARGINS (Note E)

Specimen Margin Status for Invasive Tumor
___ All specimen margins negative for invasive tumor
Distance from Invasive Tumor to Closest Specimen Margin
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined (explain): _____
Closest Specimen Margin(s) to Invasive Tumor (use orientation when provided)
___ Specify location(s) of closest specimen margin(s): _____
___ Cannot be determined (explain): _____
+Other Close Specimen Margin(s) to Invasive Tumor
___ Specify location(s) and distance(s) of other close specimen margin(s): _____
___ Cannot be determined: _____
___ Invasive tumor present at specimen margin(s)
Specimen Margin(s) Involved by Invasive Tumor (use orientation when provided)
___ Specify involved specimen margin(s): _____
___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

Specimen Margin Status for Non-invasive Tumor (High-grade Dysplasia) (required only if applicable)#

 # Applicable only to squamous cell carcinoma and its histologic subtypes and required only when closer than invasive carcinoma.

___ Not applicable
___ All specimen margins negative for high-grade dysplasia / in situ disease

+Distance from Non-invasive Tumor to Closest Specimen Margin

Specify in Millimeters (mm)

___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____

+Closest Specimen Margin(s) to Non-invasive Tumor (use orientation when provided)

___ Specify location(s) of closest specimen margin(s): _____
___ Cannot be determined: _____

___ High-grade dysplasia / in situ disease present at specimen margin

Specimen Margin(s) Involved by Non-invasive Tumor (use orientation when provided)

___ Specify involved specimen margin(s): _____
___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

+Tumor Bed Margin Status (separately submitted)

___ Tumor bed margins assessed

Tumor Bed Margin Orientation

___ Oriented to true margin surface
___ Unoriented to true margin surface
___ Cannot be determined (explain): _____

Tumor Bed Margin Status for Invasive Tumor

___ All tumor bed margins negative for invasive tumor

+Distance from Invasive Tumor to True Margin Surface (pertinent to oriented specimens which are sectioned perpendicularly)

Specify in Millimeters (mm)

___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____

___ Invasive tumor present at tumor bed margin(s)

Tumor Bed Margin(s) Involved by Invasive Tumor (per part labeling)

___ Specify involved tumor bed margin(s): _____
___ Cannot be determined (explain): _____

+Tumor Bed Margin Status for Non-invasive Tumor

___ All tumor bed margins negative for high-grade dysplasia / in situ disease
+Distance from Non-invasive Tumor to True Margin Surface (pertinent to oriented specimens which are sectioned perpendicularly)
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
___ High-grade dysplasia / in situ disease present at tumor bed margin(s)
Tumor Bed Margin(s) Involved by Non-invasive Tumor (per part labeling)
___ Specify involved tumor bed margin(s): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Other (specify): _____
___ Cannot be determined: _____
___ Not applicable

+Margin Comment: _____

REGIONAL LYMPH NODES (Note F)

Regional Lymph Node Status
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)
Number of Lymph Nodes with Tumor
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____
Laterality of Lymph Node(s) with Tumor
___ Ipsilateral (including midline): _____
___ Contralateral: _____
___ Bilateral: _____
___ Cannot be determined (explain): _____
+Nodal Site(s) with Tumor (select all that apply)
___ Intraparotid: _____
___ Periparotid: _____
___ Level I: _____
___ Level II: _____
___ Level III: _____
___ Level IV: _____
___ Level V: _____
___ Other (specify): _____

___ Cannot be determined: _____

Size of Largest Nodal Metastatic Deposit

Specify in Centimeters (cm)

___ Exact size: _____ cm
___ At least: _____ cm
___ Greater than: _____ cm
___ Less than: _____ cm
___ Other (specify): _____
___ Cannot be determined (explain): _____

Extranodal Extension (ENE)

___ Not identified
___ Present

+Distance of ENE from Lymph Node Capsule

Specify in Millimeters (mm)

___ Exact distance: _____ mm
___ Greater than 2 mm (major ENE)
___ Less than or equal to 2 mm (minor ENE)
___ Less than 1 mm (minor ENE)
___ Other (specify): _____
___ Cannot be determined: _____

___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

Number of Lymph Nodes Examined

___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

+Regional Lymph Node Comment: _____

DISTANT METASTASIS

Distant Site(s) Involved, if applicable (select all that apply)

___ Not applicable
___ Lung: _____
___ Bone: _____
___ Brain: _____
___ Liver: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

pTNM CLASSIFICATION (AJCC 8th Edition) (Note G)

Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

Modified Classification (required only if applicable) (select all that apply)
___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

pT Category
___ Maxillary sinus
pT Category (maxillary sinus)
___ pT not assigned (cannot be determined based on available pathological information)
___ pTis: Carcinoma in situ
___ pT1: Tumor limited to the 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
pT4: Moderately advanced or very advanced local disease
___ 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
___ pT4 (subcategory cannot be determined)

___ Nasal cavity and ethmoid sinus
pT Category (nasal cavity and ethmoid sinus)
___ pT not assigned (cannot be determined based on available pathological information)
___ pTis: Carcinoma in situ
___ pT1: Tumor restricted to any one subsite, with or without bony invasion
___ pT2: Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
___ pT3: Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
pT4: Moderately advanced or very advanced local disease
___ 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 (V2), nasopharynx, or clivus
___ pT4 (subcategory cannot be determined)

T Suffix (required only if applicable)
___ Not applicable
___ (m) multiple primary synchronous tumors in a single organ

pN Category# (Note F)
___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
 # Midline nodes are considered ipsilateral nodes.

Pathological ENE should be recorded as ENE(−) or ENE(+).
Measurement of the metastatic focus in the lymph nodes is based on the largest metastatic deposit size, which may include matted or fused lymph nodes.

___ pN0: No regional lymph node metastasis
___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
pN2: Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); OR larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); OR metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); OR in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)
___ pN2a: Metastasis in single ipsilateral node 3 cm or less in greatest dimension and ENE(+); OR a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
___ pN2b: Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
___ pN2c: Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)
___ pN2 (subcategory cannot be determined)
pN3: Metastases in a lymph node larger than 6 cm in greatest dimension and ENE(-); OR in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); OR multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+); OR a single contralateral node of any size and ENE(+)
___ pN3a: Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)
___ pN3b: Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); OR multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); OR a single contralateral node of any size and ENE(+)
___ pN3 (subcategory cannot be determined)

pM Category (required only if confirmed pathologically)
___ Not applicable - pM cannot be determined from the submitted specimen(s)
___ pM1: Distant metastasis

SPECIAL STUDIES
For reporting molecular testing and other cancer biomarker testing results, the CAP Head and Neck Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.

COMMENTS

Comment(s): _____

Explanatory Notes

A. Anatomic Sites and Subsites for the Nasal Cavity and Paranasal Sinuses

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]

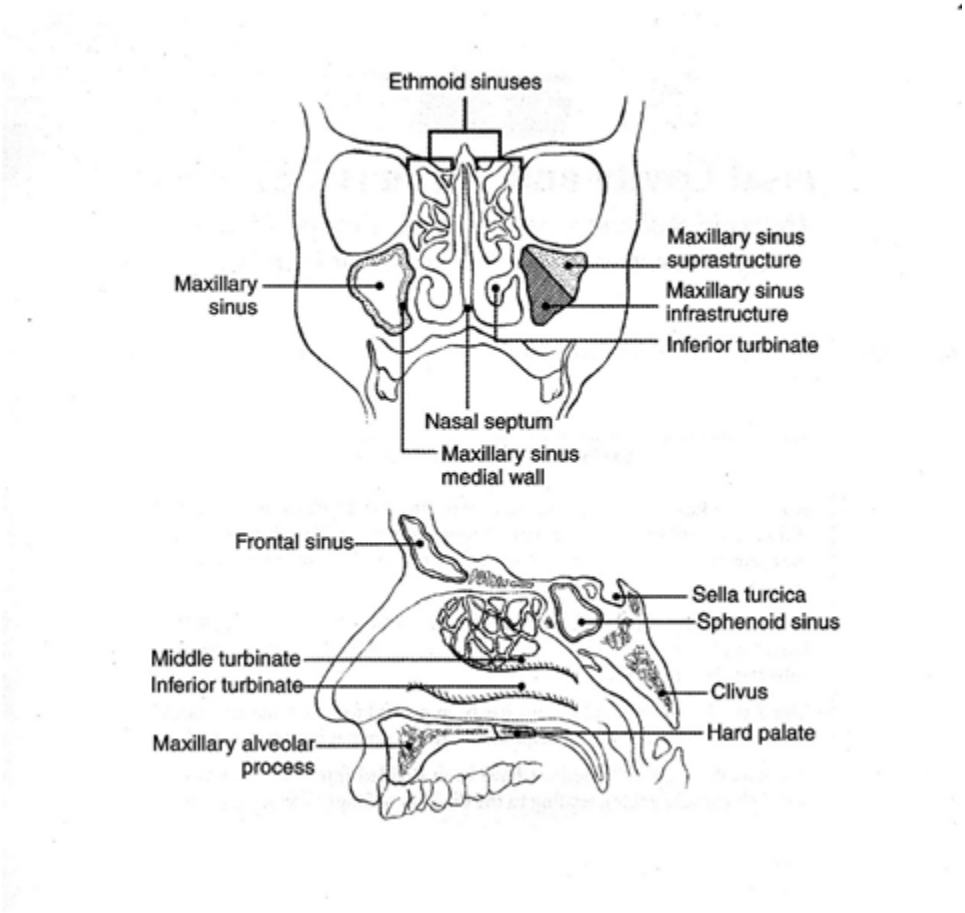

Figure 1. Anatomic sites and subsites for the nasal cavity and paranasal sinuses. From *AJCC Cancer Staging Manual.* 6th ed. New York: Springer; 2002. © American Joint Committee on Cancer. Reproduced with permission.

References

1. Gress DM, Edge SB, Greene FL, et al. Principles of cancer staging. In: Amin MB, ed. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
2. Kraus DH, Lydiatt WM, Patel SG, et al. Nasal cavity paranasal sinuses. In: Amin MB, ed. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.

B. Histologic Type

A modification of the WHO classification of carcinomas[1] of the nasal cavity and paranasal sinuses is shown below to include subtypes of squamous cell carcinoma seen at all head and neck sites and key molecular subtypes.[2,3] This protocol applies only to carcinomas and does not apply to melanomas, lymphomas, sarcomas, or neuroectodermal tumors (e.g., olfactory neuroblastoma, primitive neuroectodermal tumor [PNET], others).

Nasal Cavity and Paranasal Sinuses

- Keratinizing squamous cell carcinoma
- Non-keratinizing squamous cell carcinoma
    - HPV-independent
    - HPV-associated

    - *DEK::AFF2* translocated
- Lymphoepithelial carcinoma
- Adenosquamous carcinoma
- Basaloid squamous cell carcinoma
- Papillary squamous cell carcinoma
- Spindle cell squamous cell carcinoma
- Verrucous carcinoma
- Carcinoma cuniculatum
- NUT carcinoma
- SWI/SNF complex deficient carcinoma
- Sinonasal undifferentiated carcinoma
- Teratocarcinosarcoma
- HPV-associated multiphenotypic sinonasal carcinoma

Adenocarcinoma

- Intestinal-type
- Non-intestinal-type

Neuroendocrine Carcinomas

The recommended histologic classification for neuroendocrine neoplasms has been standardized across all head and neck sites.[1] The entities relevant to this protocol are listed below:

- Neuroendocrine tumor, grade 1-3
- Neuroendocrine carcinoma, small cell type
- Neuroendocrine carcinoma, large cell type

Additionally, composite tumors with non-neuroendocrine CA components exist throughout the upper aerodigestive tract. The carcinoma component can then be captured in this protocol accordingly.

References

1. WHO Classification of Tumours Editorial Board. *Head and neck tumours* [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2023, Jan 26]. (WHO classification of tumours series, 5th ed.; vol. 9). Available from: https://tumourclassification.iarc.who.int/chapters/52
2. Oliver JR, Lieberman SM, Tam MM, Liu CZ, Li Z, Hu KS, Morris LGT, Givi B. Human papillomavirus and survival of patients with sinonasal squamous cell carcinoma. *Cancer.* 2020 Apr 1;126(7):1413-1423.
3. Ruangritchankul K, Sandison A. DEK::AFF2 Fusion Carcinomas of Head and Neck. *Adv Anat Pathol.* 2023 Mar 1;30(2):86-94.

C. Histologic Grade

For histologic types of carcinomas that are amenable to grading, three histologic grades are suggested, as shown below. For conventional squamous cell carcinoma, histologic grading as a whole does not perform well as a prognosticator.[1] Nonetheless, it should be recorded when applicable, as it is a basic tumor characteristic. For sinonasal intestinal type adenocarcinomas, pattern-based grading is commonly employed: papillary tumors can be considered grade I, colonic and mixed grade II, solid and mucinous

grade III.[2] Non-intestinal type (seromucinous) adenocarcinomas are graded intuitively into low, intermediate, and high-grade tumors.

Selecting either the most prevalent grade or the highest grade for this synoptic protocol is acceptable. Some subtypes of squamous cell carcinoma (i.e., verrucous, basaloid, etc.) have an intrinsic biologic potential. Newer subtypes with distinctive molecular alterations[3,4,5] do not currently require grading as data are still emerging regarding biologic behavior.

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

The WHO 5th edition has standardized the terminology for head and neck neuroendocrine neoplasms across all subsites.[6] Tumors previously designated as carcinoid and well-differentiated neuroendocrine carcinoma would now be considered grade 1 neuroendocrine tumors while atypical carcinoids/moderately-differentiated neuroendocrine carcinomas are now considered grade 2 neuroendocrine tumors. Grade 3 neuroendocrine tumor is a provisional category with no historical analogue. *It must be emphasized that this category in head and neck sites is provisional with no current evidence to support its use in head and neck sites.* Practically speaking, tumors that exceed the mitotic rate for grade 2 neuroendocrine tumors are usually more in keeping with neuroendocrine carcinomas (see below). Grading of neuroendocrine tumors is summarized in Table 1. Ki-67 proliferation indices are recommended for neuroendocrine tumors of head and neck, but are not required elements, and delineation of grade 1 and 2 at this site by proliferation index is not yet established.

Table 1: WHO Classification of Head and Neck Neuroendocrine Tumors

Neuroendocrine Tumor Grade	Mitoses per two mm^2	Necrosis
1	Less than 2	Absent
2	2-10	Present
3	*Undefined*	

Neuroendocrine carcinoma, small cell types and large cell types on the other hand, have not changed much in terms of their designation and reflect poorly differentiated neuroendocrine malignancies that were previously labeled small cell and large cell neuroendocrine carcinomas respectively. These characteristically show necrosis and have mitotic counts that exceed 10 per two mm^2. While neuroendocrine tumors and carcinomas are defined by neuroendocrine marker expression (synaptophysin, chromogranin, and/or INSM-1), other tumor types at each head and neck subsite may express these. Morphologic, other immunophenotypic, and molecular features would then supersede this neuroendocrine marker expression for classification.

References

1. WHO Classification of Tumours Editorial Board. *Head and neck tumours* [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2023, Jan 26]. (WHO classification of tumours series, 5th ed.; vol. 9). Available from: https://tumourclassification.iarc.who.int/chapters/52
2. Barnes L. Intestinal-type adenocarcinoma of the nasal cavity and paranasal sinuses. *Am J Surg Pathol.* 1986;10(3):192-202.

3. Oliver JR, Lieberman SM, Tam MM, Liu CZ, Li Z, Hu KS, Morris LGT, Givi B. Human papillomavirus and survival of patients with sinonasal squamous cell carcinoma. *Cancer.* 2020 Apr 1;126(7):1413-1423.
4. Ruangritchankul K, Sandison A. DEK::AFF2 Fusion Carcinomas of Head and Neck. *Adv Anat Pathol.* 2023 Mar 1;30(2):86-94.
5. Dogan S, Frosina D, Geronimo JA, Hernandez E, Mohanty A, Bale T, Hechtman JF, Arcila ME, Hameed MR, Jungbluth AA. Molecular epidemiology of IDH2 hotspot mutations in cancer and immunohistochemical detection of R172K, R172G, and R172M variants.*Hum Pathol.* 2020 Dec;106:45-53.
6. Mete O, Gill A, and Nosé V. *Neuroendocrine neoplasms and paraganglioma: Introduction*. In: WHO Classification of Tumours Editorial Board. Head and neck tumours [Internet; beta version ahead of print]. Lyon (France): International Agency for Research on Cancer; 2022 [cited 2023 Jan 26]. (WHO classification of tumours series, 5th ed.; vol. 9). Available from: https://tumourclassification.iarc.who.int/chapters/52

D. 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.[1] 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.[1] Further, perineural invasion is associated with decrease in disease-specific survival and overall survival.[1] 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.[1] The relationship between perineural invasion and prognosis is independent of nerve diameter.[2] Additionally, emerging evidence suggests that extratumoral perineural invasion may be more prognostically relevant.[3] 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 (i.e., 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).[4,5] Given the significance relative to prognosis and treatment, perineural invasion is a required data element in the reporting of head and neck cancers.

References

1. Smith BD, Haffty BG. Prognostic factoris in patients with head and neck cancer. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and Neck Cancer: A Multidisciplinary Approach.* Philadelphia, PA: Lippincott Williams and Wilkins; 2009:51-75.
2. Fagan JJ, Collins B, Barnes L, D'Amico F, Myers EN, Johnson JT. Perineural invasion in squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg*. 1998;124(6):637-640.
3. Miller ME, Palla B, Chen Q, et al. A novel classification system for perineural invasion in noncutaneous head and neck squamous cell carcinoma: histologic subcategories and patient outcomes. *Am J Otolaryngol.* 2012;33(2):212-215.
4. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med.* 2004;350(19):1937-1944.
5. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med.* 2004;350(19):1945-1952.

E. Surgical Margins

The definition of a positive margin is somewhat controversial given the varied results from prior studies.[1,2] 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).[2] 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.[2,3] 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.[2] However, values ranging from 3 mm to 7 mm have been used with success,[2,4] and for glottic tumors as low as 1 mm.[5] Thus, distance of tumor from the nearest margin should be recorded.

Reporting of surgical margins for all types of carcinomas should follow those used for squamous cell carcinoma of the 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.

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.

References

1. Brandwein-Gensler M, Teixeira MS, Lewis CM, et al. Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. *Am J Surg Pathol.* 2005;29(2):167-178.
2. Hinni ML, Ferlito A, Brandwein-Gensler MS, et al. Surgical margins in head and neck cancer: a contemporary review. *Head Neck.* 2012.
3. Alicandri-Ciufelli M, Bonali M, Piccinini A, et al. Surgical margins in head and neck squamous cell carcinoma: what is 'close'? *Eur Arch Otorhinolaryngol.* 2012.
4. Liao CT, Chang JT, Wang HM, et al. Analysis of risk factors of predictive local tumor control in oral cavity cancer. *Ann Surg Oncol.* 2008;15(3):915-922.
5. Ansarin M, Santoro L, Cattaneo A, et al. Laser surgery for early glottic cancer: impact of margin status on local control and organ preservation. *Arch Otolaryngol Head Neck Surg.* 2009;135(4):385-390.

F. Regional Lymph Nodes

Direct Extension of Tumor to Lymph Node

While data are essentially nonexistent for defining N status for lymph nodes involved by tumor via direct extension for head and neck cancers, the general convention, based on other organ sites, is to consider

these positive for N categorization and counting purposes. It is recommended, however, to denote in the report the number of lymph nodes involved in this manner, as it may influence more nuanced management decisions.

Measurement of Tumor Metastasis
The cross-sectional diameter of the largest lymph node metastasis (not the lymph node itself) is measured in the gross specimen at the time of macroscopic examination or, if necessary, on the histologic slide at the time of microscopic examination.[1,2]

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 polymerase chain reaction (PCR) to detect isolated tumor cells are considered investigational techniques at this time.

Lymph Node Number
For assessment of pN, a selective neck dissection will ordinarily include 10 or more lymph nodes, and a comprehensive neck dissection (radical or modified radical neck dissection) will ordinarily include 15 or more lymph nodes. Examination of fewer tumor-free nodes still mandates a pN0 designation.

Regional Lymph Nodes (pN0): Isolated Tumor Cells
Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. While the generic recommendation is that for lymph nodes with ITCs found by either histologic examination, immunohistochemistry, or non-morphologic techniques (e.g., flow cytometry, DNA analysis, PCR amplification of a specific tumor marker), they should be classified as N0 or M0, respectively.[3,4] 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.[5]
For purposes of pathologic evaluation, lymph nodes are organized by levels, as shown in Figure 2.

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 category:[2,6,7]
    a. Supraomohyoid neck dissection
    b. Posterolateral neck dissection
    c. Lateral neck dissection
    d. Central compartment neck dissection

4. Superselective neck dissection (SSND), a relatively new term defined by dissection of the fibrofatty elements of 2 or less levels.[8]
5. Extended radical neck dissection, as specified by the surgeon

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, e.g., scalene, suboccipital, and retropharyngeal, should be identified and reported from all levels separately. Midline nodes are considered ipsilateral nodes.

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, particularly if there is gross extranodal extension. However, generous sampling of the lymph node periphery is recommended if there is no gross extranodal extension to adequately assess microscopic extranodal extension. Reporting of lymph nodes containing metastasis should include whether there is presence or absence of extranodal extension (ENE),[9] which is now part of N staging. 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 now suggested (but not yet required) with the proposed stratification of ENE into ENEma (>2 mm) and ENEmi (≤2 mm).[10,11,12,13] However, pitfalls in the measurement (i.e., in larger, matted lymph nodes, in nodes post fine-needle aspiration, and in nodes with near total replacement of lymph node

architecture), and the disposition of soft tissue deposits is still not resolved. In general, absence of ENE in a large (>3 cm) lymph node, especially with traversing fibrous bands, should be viewed with skepticism. Soft tissue deposits for lymph node metastases based on limited studies appear to be the equivalent of a positive lymph node with ENE and should be recorded as such.[14]

Other Elements

Anatomic compartment location of positive lymph nodes is now a non-core element.

References

1. Smith BD, Haffty BG. Prognostic factoris in patients with head and neck cancer. In: Harrison LB, Sessions RB, Hong WK, eds. *Head and Neck Cancer: A Multidisciplinary Approach.* Philadelphia, PA: Lippincott Williams and Wilkins; 2009:51-75.
2. Seethala RR. Current state of neck dissection in the United States. *Head Neck Pathol.* 2009;3(3):238-245.
3. Sobin LH, Gospodarowicz MK, Wittekind CH, eds. *TNM Classification of Malignant Tumours.* New York: Wiley-Liss; 2009.
4. Singletary SE, Greene FL, Sobin LH. Classification of isolated tumor cells: clarification of the 6th edition of the American Joint Committee on Cancer Staging Manual. *Cancer.* 2003;98(12):2740-2741.
5. Broglie MA, Haerle SK, Huber GF, Haile SR, Stoeckli SJ. Occult metastases detected by sentinel node biopsy in patients with early oral and oropharyngeal squamous cell carcinomas: impact on survival. *Head Neck.* 2013;35(5):660-666.
6. Ferlito A, Robbins KT, Shah JP, et al. Proposal for a rational classification of neck dissections. *Head Neck.* 2011;33(3):445-450.
7. Robbins KT, Shaha AR, Medina JE, et al. Consensus statement on the classification and terminology of neck dissection. *Arch Otolaryngol Head Neck Surg.* 2008;134(5):536-538.
8. Suarez C, Rodrigo JP, Robbins KT, et al. Superselective neck dissection: rationale, indications, and results. *Eur Arch Otorhinolaryngol.* 2013.
9. Ebrahimi A, Gil Z, Amit M. International Consortium for Outcome Research (ICOR) in Head and Neck Cancer. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. JAMA *Otolaryngol Head Neck Surg.* 2014;140(12):1138-1148.
10. Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In: Amin MB, ed. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.
11. Ebrahimi A, Clark JR, Amit M, et al. Minimum nodal yield in oral squamous cell carcinoma: defining the standard of care in a multicenter international pooled validation study. *Ann Surg Oncol.* 2014;21(9):3049-3055.
12. Prabhu RS, Hanasoge S, Magliocca KR, et al. Extent of pathologic extracapsular extension and outcomes in patients with nonoropharyngeal head and neck cancer treated with initial surgical resection. *Cancer.* 2014;120(10):1499-1506.
13. Dunne AA, Muller HH, Eisele DW, Kessel K, Moll R, Werner JA. Meta-analysis of the prognostic significance of perinodal spread in head and neck squamous cell carcinomas (HNSCC) patients. *Eur J Cancer.* 2006;42(12):1863-1868.
14. Jose J, Moor JW, Coatesworth AP, Johnston C, MacLennan K. Soft tissue deposits in neck dissections of patients with head and neck squamous cell carcinoma: prospective analysis of prevalence, survival, and its implications. *Arch Otolaryngol Head Neck Surg.* 2004;130(2):157-160.

G. pTNM Classification

The protocol recommends the TNM staging system of the American Joint Committee on Cancer and the International Union Against Cancer for nasal cavity and paranasal sinus cancer.[1,2] Of note, in the 7th edition of the AJCC staging of head and neck cancers[1] is the division of T4 lesions into T4a (moderately advanced local disease) and T4b (very advanced local disease), leading to the stratification of stage IV into stage IVA (moderately advanced local/regional disease), stage IVB (very advanced local/regional disease), and stage IVC (distant metastatic disease).

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 (e.g., when technically unfeasible) and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y”, “r”, and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis. Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician’s responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

The “m” suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy).

The “r” prefix indicates a recurrent tumor when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

The “a” prefix designates the stage determined at autopsy: aTNM.

References

1. Gress DM, Edge SB, Greene FL, et al. Principles of cancer staging. In: Amin MB, ed. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.
2. Jose J, Moor JW, Coatesworth AP, Johnston C, MacLennan K. Soft tissue deposits in neck dissections of patients with head and neck squamous cell carcinoma: prospective analysis of prevalence, survival, and its implications. *Arch Otolaryngol Head Neck Surg.* 2004;130(2):157-160.