Protocol for the Examination of Specimens From Patients With Carcinomas of the Major Salivary Glands

Version: 4.3.0.0
Protocol Posting Date: June 2023
CAP Laboratory Accreditation Program Protocol Required Use Date: March 2024
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 or containing parotid, submandibular, sublingual glands
Tumor Type	**Description**
Carcinoma	Includes primary salivary gland carcinoma and 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

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

Tumor Type
Minor salivary gland carcinoma (consider the Lip and Oral Cavity, Nasal Cavity and Paranasal Sinuses, Pharynx, or Larynx protocols)
Sarcoma (consider the Soft Tissue protocol)
Lymphoma (consider the Hodgkin or non-Hodgkin Lymphoma protocols)

Authors
Raja R. Seethala, MD*; 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; Jason Pettus, MD; Lindsay Williams, MD.
With guidance from the CAP Cancer and CAP Pathology Electronic Reporting Committees.
* Denotes primary author.

Accreditation Requirements

This protocol can be utilized for a variety of procedures and tumor types for clinical care purposes. For accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format.

- Core data elements are required in reports to adequately describe appropriate malignancies. For accreditation purposes, essential data elements must be reported in all instances, even if the response is "not applicable" or "cannot be determined."
- Conditional data elements are only required to be reported if applicable as delineated in the protocol. For instance, the total number of lymph nodes examined must be reported, but only if nodes are present in the specimen.
- Optional data elements are identified with "+" and although not required for CAP accreditation purposes, may be considered for reporting as determined by local practice standards.

The use of this protocol is not required for recurrent tumors or for metastatic tumors that are resected at a different time than the primary tumor. Use of this protocol is also not required for pathology reviews performed at a second institution (ie, secondary consultation, second opinion, or review of outside case at second institution).

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 ie, 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

- WHO 5th edition update to content and Explanatory Notes C and F
- pTNM classification update to content and Explanatory Note G
- LVI update from “Lymphovascular Invasion” to “Lymphatic and/or Vascular Invasion”

Reporting Template

Protocol Posting Date: June 2023
Select a single response unless otherwise indicated.

CASE SUMMARY: (MAJOR SALIVARY GLANDS)
Standard(s): AJCC-UICC 8

SPECIMEN (Note A)

Procedure (select all that apply)
___ Excision
___ Parotidectomy, superficial
___ Parotidectomy, deep
___ Parotidectomy, total
___ Parotidectomy, not specified
___ Resection, submandibular gland
___ Resection, sublingual gland
___ Neck (lymph node) dissection (specify type): _____
___ Other (specify): _____
___ Not specified

TUMOR

Tumor Focality
___ Unifocal
___ Multifocal: _____
___ Cannot be determined: _____

Tumor Site (Note B)
___ Parotid gland, superficial lobe: _____
___ Parotid gland, deep lobe: _____
___ Entire parotid gland: _____
___ Submandibular gland: _____
___ Sublingual gland: _____
___ Other (specify): _____
___ Not specified

Tumor Laterality
___ Right
___ Left
___ Bilateral
___ Not specified

Tumor Size
___ Greatest dimension in Centimeters (cm): _____ cm
+Additional Dimension in Centimeters (cm): ____ x ____ cm

___ Cannot be determined (explain): _____

Histologic Type (Note C)

Primary epithelial

___ Carcinoma ex pleomorphic adenoma

Architectural Type

Required in addition to carcinoma type

___ Carcinoma ex pleomorphic adenoma, minimally invasive
___ Carcinoma ex pleomorphic adenoma, invasive
___ Carcinoma ex pleomorphic adenoma, intracapsular (noninvasive)
___ Carcinoma ex pleomorphic adenoma, extent cannot be determined

Malignant Component Histologic Type(s) (select all that apply)

___ Intraductal pattern
___ Salivary duct carcinoma
___ Epithelial-myoepithelial carcinoma
___ Myoepithelial carcinoma
___ Carcinosarcoma (sarcomatoid carcinoma)
___ Other (specify): _____

___ Mucoepidermoid carcinoma
___ Adenoid cystic carcinoma tubular / cribriform

 # If multiple patterns are present, select the predominant pattern unless the solid pattern is greater than 30%, in which case the user should select the solid pattern.

___ Adenoid cystic carcinoma, solid#

+Percentage of Solid Component for Adenoid Cystic Carcinoma

___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined

___ Acinic cell carcinoma
___ Secretory carcinoma
___ Polymorphous adenocarcinoma, conventional
___ Polymorphous adenocarcinoma, cribriform subtype

+Percentage of Papillary Component for Polymorphous Adenocarcinoma

___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined

+Percentage of Cribriform Component for Polymorphous Adenocarcinoma

___ Specify percentage: _____ %
___ Other (specify): _____
___ Cannot be determined

___ Salivary duct carcinoma
___ Epithelial-myoepithelial carcinoma
___ Hyalinizing clear cell carcinoma
___ Microsecretory adenocarcinoma
___ Intraductal carcinoma (specify subtype): _____
___ Basal cell adenocarcinoma
___ Carcinosarcoma
___ Mucinous adenocarcinoma, not otherwise specified
___ Mucinous adenocarcinoma, intraductal papillary mucinous neoplasia subtype

___ Mucinous adenocarcinoma, colloid / signet ring subtype
___ Sclerosing microcystic adenocarcinoma
___ Lymphoepithelial carcinoma
___ Myoepithelial carcinoma
___ Sebaceous adenocarcinoma
___ Sialoblastoma
Neuroendocrine
___ Neuroendocrine tumor, grade 1
___ Neuroendocrine tumor, grade 2
 # This category is provisional and included solely based on the WHO intent to standardize terminology across organ sites. Evidence indicates that there is currently no use case for it.
___ Neuroendocrine tumor, grade 3#
___ Neuroendocrine carcinoma, small cell type
___ Neuroendocrine carcinoma, large cell type
Other
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined: _____
+Histologic Type Comment: _____

Grade / Intrinsic Biologic Potential (required only if applicable) (Note C)
___ Not applicable
___ Low
___ Intermediate
___ High / High-grade transformation
___ Cannot be assessed: _____

+Macroscopic Tumor Extent (select all that apply)
___ No evidence of extraparenchymal extension
pT3
___ Extraglandular soft tissue
pT4a
___ Facial nerve
___ Skin
___ Ear canal
___ Mandible
pT4b
___ Skull base
___ Pterygoid plates
___ Carotid artery encasement
Other
___ Other (specify): _____
___ Cannot be determined

Lymphatic and / or Vascular Invasion
___ Not identified
___ Present
___ Cannot be determined: _____

Perineural Invasion (Note D)
___ Not identified
___ Present
+Extent / Type of Perineural Invasion#
 # Select the most aggressive type
___ Intratumoral
___ Extratumoral
___ Intraneural
+Specify Diameter of Involved Nerve in Millimeters (mm): _____ mm
___ Cannot be determined: _____

+Tumor Comment: _____

MARGINS (Note E)

Margin Status
___ All margins negative for carcinoma
+Distance from Invasive Tumor to Closest Margin
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
+Closest Margin(s) to Carcinoma
___ Specify location(s) of closest margin(s): _____
___ Cannot be determined: _____
___ Carcinoma present at margin
Margin(s) Involved by Carcinoma
___ Specify involved margin(s): _____
___ Cannot be determined: _____
___ Other (specify): _____
___ Cannot be determined: _____

+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: _____

+Nodal Site(s) with Tumor (select all that apply)
___ Intra / 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)
___ Not applicable
___ Exact size: _____ cm
___ At least: _____ cm
___ Greater than: _____ cm
___ Less than: _____ cm
___ Other (specify): _____
___ Cannot be determined: _____

Extranodal Extension (ENE) (Note F)
___ Not identified
___ Present

+Distance of ENE from Lymph Node Capsule
Specify in Millimeters (mm)
___ Exact distance: _____ mm
___ Greater than 2 mm (macroscopic ENE)
___ Less than or equal to 2 mm (microscopic ENE)
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____

___ Cannot be determined: _____

___ 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: _____

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

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

pT Category
___ pT not assigned (cannot be determined based on available pathological information)
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma *in situ*
 # Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.
___ pT1: Tumor 2 cm or smaller in greatest dimension *without extraparenchymal extension*#
___ pT2: Tumor larger than 2 cm but not larger than 4 cm in greatest dimension *without extraparenchymal extension*#
___ pT3: Tumor larger than 4 cm and / or tumor *having extraparenchymal extension*#
pT4: Moderately advanced or very advanced disease
___ pT4a: Moderately advanced local disease. Tumor invades skin, mandible, ear canal, and / or facial nerve.
___ pT4b: Very advanced local disease. Tumor invades skull base and / or pterygoid plates and / or encases carotid artery
___ 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)

 # 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.

___ pN not assigned (no nodes submitted or found)
___ pN not assigned (cannot be determined based on available pathological information)
___ 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 metastasis in multiple ipsilateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
___ pN2a: Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); or a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
___ pN2b: Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
___ pN2c: Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)
___ pN2 (subcategory cannot be determined)
pN3: Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); or in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes any with ENE(+); or a single contralateral node of any size and ENE(+)
___ pN3a: Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)
___ pN3b: Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); or a single contralateral node of any size 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

ADDITIONAL FINDINGS

+Additional Findings (select all that apply)

___ None identified
___ Precursor lesions or tumors (aside from pleomorphic adenoma)
___ Other (specify): _____

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. Scope of Guidelines

The reporting of major salivary gland 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,[1] the World Health Organization (WHO) 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 oral cavity in a standardized manner. It should not be used as a substitute for dissection or grossing techniques and does not give histologic parameters to reach the diagnosis. Subjectivity is always a factor, and elements listed are not meant to be arbitrary but are meant to provide uniformity of reporting across all the disciplines that use the information. It is a foundation of practical information that will help to meet the requirements of daily practice to benefit both clinicians and patients alike.

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.

B. Primary Site

The classification applies only to carcinomas of the major salivary glands: parotid, submandibular (submaxillary), and sublingual glands.[1] Tumors arising in minor salivary glands (mucous-secreting glands in the lining membrane of the upper aerodigestive tract) are staged according to the classification schemes corresponding to the anatomic sites in which they reside, e.g., oral cavity, pharynx, sinonasal tract.

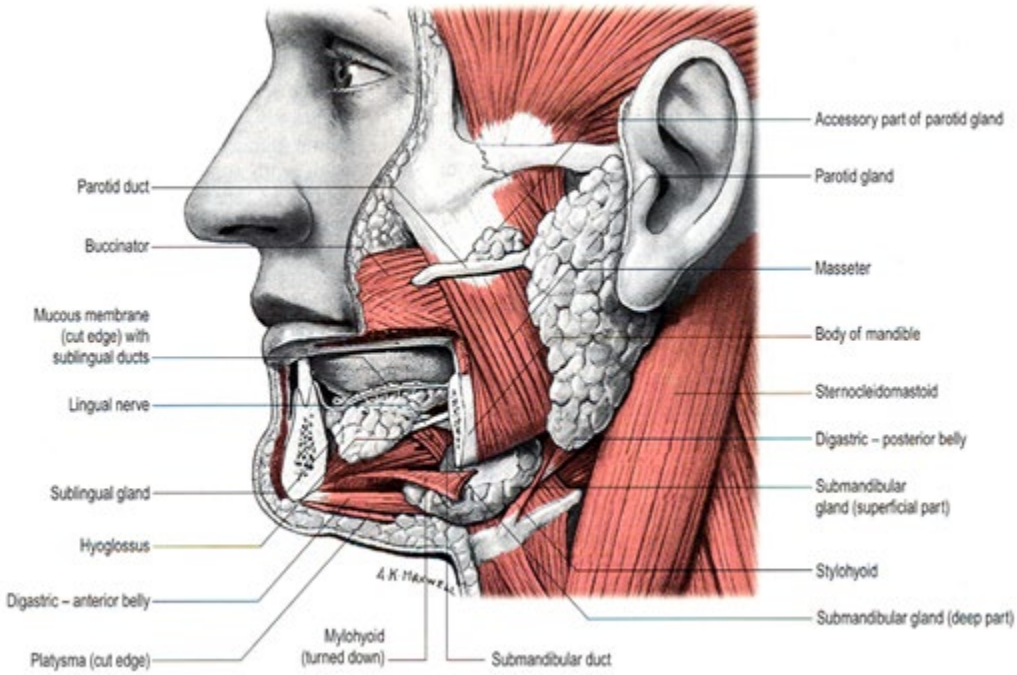

Figure 1. Anatomy of the major salivary glands. From: *Gray's Anatomy*. 39th ed. Edinburgh: Elsevier Churchill Livingstone; 2005. Reproduced with permission © Elsevier.

References

1. Lydiatt WM, Mukherji SK, O'Sullivan B, Patel SG, Shah JP. Major salivary glands. In: Amin MB, ed. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.

C. Histologic Type and Grade

The histologic classification recommended is the WHO classification of salivary gland tumors.[1]

- Mucoepidermoid carcinoma
- Adenoid cystic carcinoma
- Acinic cell carcinoma
- Secretory carcinoma
- Polymorphous adenocarcinoma, conventional (classic) and cribriform subtypes
- Salivary duct carcinoma
- Epithelial-myoepithelial carcinoma
- Hyalinizing clear cell carcinoma
- Microsecretory adenocarcinoma
- Intraductal carcinoma (with subtypes)
- Basal cell adenocarcinoma
- Carcinosarcoma
- Mucinous adenocarcinoma (with subtypes)
- Sclerosing microcystic adenocarcinoma
- Lymphoepithelial carcinoma

- Myoepithelial carcinoma (malignant myoepithelioma)
- Sebaceous adenocarcinoma
- Squamous cell carcinoma
- Sialoblastoma
- Carcinoma, not otherwise specified

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
- Merkel cell carcinoma

Histologic Grade

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. Further, there is often a positive correlation between histologic grade and clinical stage.[2,3,4,5] However, most salivary gland carcinoma types have an intrinsic biologic behavior, and attempted application of a universal grading scheme is suboptimal given tumor specific nuances.[4] Thus, a generic grading scheme is no longer recommended for salivary gland carcinomas.[6]

However, within a given tumor type, grade remains an important prognostic parameter. Carcinoma types for which grading systems exist and are relevant are incorporated into histologic type. The classic categories that are still graded using three tier schemes include mucoepidermoid carcinoma, and carcinoma, not otherwise specified. While adenoid cystic carcinoma was historically stratified into three tiers, current classification no longer advocates for this.[3,4,7] Additionally, several tumor types can at least be stratified into low and high grade. High grade transformation (historically designated as dedifferentiation) refers to the phenomenon of progression from a conventional, usually indolent phenotype, to a pleomorphic aggressive morphology.

As such carcinomas can alternatively be stratified by their risk for structural recurrence by a combination of category, subtype, and category specific grade[8] as in Table 1.

Table 1: Risk Stratification of Salivary Gland Carcinomas

Low Aggression	***High Aggression***
Mucoepidermoid carcinoma – Low grade	Mucoepidermoid carcinoma – High grade
Mucoepidermoid carcinoma – Intermediate grade*	
Acinic cell carcinoma – Conventional	Acinic cell carcinoma – High grade/HGT
Secretory carcinoma - Conventional	Secretory carcinoma – High grade/HGT
Microsecretory adenocarcinoma – Usual	Microsecretory adenocarcinoma – High grade/HGT
Polymorphous adenocarcinoma – Low grade, conventional	Polymorphous adenocarcinoma – High grade/HGT
Polymorphous adenocarcinoma – Low & intermediate grade, cribriform**	
Hyalinizing clear cell carcinoma – Conventional	Hyalinizing clear cell carcinoma – High grade/HGT
Basal cell adenocarcinoma – Conventional	Basal cell adenocarcinoma – High grade/HGT

Myoepithelial carcinoma – Low grade	Myoepithelial carcinoma – High grade
Epithelial-myoepithelial carcinoma – Conventional and subtypes	Epithelial-myoepithelial carcinoma – High grade/HGT
Sebaceous adenocarcinoma – Low grade	Sebaceous adenocarcinoma – High grade
	Adenoid cystic carcinoma – Solid/HGT
Adenoid cystic carcinoma – Tubular/cribriform^	
	Carcinosarcoma (sarcomatoid carcinoma)
	(Metastatic) Squamous cell carcinoma (usually cutaneous)
Intraductal carcinoma, oncocytic and intercalated duct	
Intraductal carcinoma, apocrine	Salivary duct carcinoma
Mucinous adenocarcinoma "intraductal papillary mucinous neoplasm" type	Mucinous adenocarcinoma (not otherwise specified, and with colloid/signet ring features
	Lymphoepithelial carcinoma
Sclerosing microcystic adenocarcinoma	
Sialoblastoma	
Carcinoma ex pleomorphic adenoma#	
Salivary carcinoma, NOS@	

Abbreviations: HGT-high grade transformation. NOS-not otherwise specified
*Behavior varies with grading system or criteria
**The cribriform subtype of polymorphous adenocarcinoma has a high propensity for regional recurrence
^Adenoid cystic carcinoma though highly aggressive locally with capacity for distant spread, has somewhat lower risk for regional recurrence
#Carcinoma ex pleomorphic adenoma behavior is determined by carcinoma type and extent
@Salivary carcinoma, NOS behavior is determined by grade

Adenoid cystic carcinomas were historically stratified into three tiers based on tubular, cribriform, and solid (>30%) patterns respectively.[7] However currently, while solid pattern remains an integral prognosticator, no standard grading scheme is endorsed. The histologic grading of mucoepidermoid carcinoma includes a combination of growth pattern characteristics (e.g., cystic, solid, neurotropism) and cytomorphologic findings (e.g., anaplasia, mitoses, necrosis).[9,10,11] Carcinomas, not otherwise specified, do not have a formalized grading scheme and are graded intuitively based on cytomorphologic features.[4] Polymorphous adenocarcinomas and intraductal carcinomas are to be graded as per current WHO recommendations. Polymorphous adenocarcinomas should be subtyped into conventional and cribriform types (i.e., cribriform adenocarcinoma of minor salivary gland). The latter is more frequently extrapalatal and locoregionally aggressive. Along these lines, papillary components (>10%) and cribriform components (>30%) regardless of subtype have been shown to be prognostically relevant and these can be recorded optionally.[12] Intraductal carcinomas can be subtyped and graded, as both influence biologic behavior.[13] Additionally, two-tier grading schema have shown prognostic relevance for other tumor types such as myoepithelial carcinoma,[14] and acinic cell carcinoma.[15] Low grade and high grade are generally separated by mitotic counts and/or necrosis.

The current protocol is thus structured to allow for provision of grade or biologic potential for almost every epithelial tumor type in at least a two-tier fashion as per Table 1. For instance, epithelial-myoepithelial carcinoma, basal cell adenocarcinoma, and hyalinizing clear cell carcinoma can be assigned a default low grade/biologic potential category. Conversely, salivary duct carcinoma and lymphoepithelial carcinoma can

be considered high grade/biologic potential category as a default. One key point is that adenoid cystic carcinoma should NEVER be assigned a low grade/biologic potential category. As this is one entity that does not fit into a standard risk of structural recurrence (i.e., discordant prevalence of local and regional aggression), this can be assigned N/A if non-solid and high grade if solid (>30%) or high grade transformed.

Carcinoma ex pleomorphic adenoma is subclassified by histologic type and/or grade and extent of invasion, the latter including minimally invasive, invasive, and intracapsular (noninvasive) cancers. Previously the cut-off for minimal invasion was designated as 1.5 mm; however, more recent studies have shown a favorable prognosis even with cut-offs of 4 mm to 6 mm.[16] Thus, there is no agreement on an optimal cut-off. However, from a practical standpoint, the terms *intracapsular* and *minimally invasive* should only be applied to uninodular tumors (as opposed to carcinomas arising in multinodular recurrent pleomorphic adenomas) with a well-delineated interface for which the entire lesional border has been microscopically evaluated. Prognosis has been linked to degree of invasion with noninvasive and minimally invasive cancers apparently having a better prognosis than invasive cancers.[4,16,17] Carcinosarcoma is a rare subtype morphology that while currently separated, appears to almost invariably arise in the setting of a precursor pleomorphic adenoma and should likely be regarded as a sarcomatoid carcinoma subtype ex pleomorphic adenoma.[18]

Aside from pleomorphic adenoma, other precursor lesions, most notably intercalated duct lesion/adenoma,[1,19] exist. Though biologically and diagnostically relevant, documentation of these precursors is currently optional (non-core) as there is limited literature[18] on these.

The WHO 5th edition has standardized the terminology for head and neck neuroendocrine neoplasms across all subsites.[20] 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 2. 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 2: 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.

Merkel cell carcinoma is a cutaneous neuroendocrine carcinoma, often driven by Merkel cell polyomavirus. Primary parotid Merkel cell carcinomas are described[21] and their definition is further obfuscated by the earlier description of a so called 'Merkel cell' subtype of primary parotid small cell neuroendocrine carcinoma that like Merkel cell carcinoma, expresses CK20 but are Merkel cell polyomavirus negative and do not show a UV molecular signature.[22] However, like squamous cell carcinoma of parotid, the idea of a primary parotid Merkel cell carcinoma should be viewed with heavy skepticism, and most are metastases from unknown primaries. This can often be resolved by a combination of detailed clinical history, and dermatologic examination.

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. Spiro RH, Thaler HT, Hicks WF, Kher UA, Huvos AH, Strong EW. The importance of clinical staging of minor salivary gland carcinoma. *Am J Surg*. 1991;162(4):330-336.
3. Spiro RH, Huvos AG, Strong EW. Adenocarcinoma of salivary origin. Clinicopathologic study of 204 patients. *Am J Surg*. 1982;144(4):423-431.
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6. Lydiatt WM, Mukherji SK, O'Sullivan B, Patel SG, Shah JP. Major salivary glands. In: Amin MB, ed. A*JCC Cancer Staging Manual. 8th ed.* New York, NY: Springer; 2017.
7. Szanto PA, Luna MA, Tortoledo ME, White RA. Histologic grading of adenoid cystic carcinoma of the salivary glands. *Cancer*. 1984;54(6):1062-1069.
8. Ramalingam N, Thiagarajan S, Chidambaranathan N, et al. Regression Derived Staging Model to Predict Overall and Disease Specific Survival in Patients With Major Salivary Gland Carcinomas With Independent External Validation. *JCO Glob Oncol* 2022;8:e2200150. doi:10.1200/GO.22.00150 [published Online First: 2022/08/19].
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D. Perineural Invasion

The presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.[1] The majority of studies evaluating the influence of perineural invasion on therapy and prognosis are limited to head and neck squamous cell carcinoma. However, relative to salivary gland carcinomas, facial nerve dysfunction, and perineural involvement are factors influencing the indication for neck dissection, postoperative radiation therapy, and survival rate. Perineural invasion

(neurotropism) in the primary salivary gland carcinomas, especially the facial nerve, is associated with recurrent tumor[2] and decreased survival. Further, facial nerve involvement by carcinoma has been found to be predictive of occult metastases.[3] Among other prognostic indicators, perineural invasion in minor salivary gland tumors has been shown to be statistically significant to the outcome.[4] Given the significance relative to prognosis and treatment, perineural invasion is a required data element in the reporting of salivary gland carcinomas.

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E. Surgical Margins

Complete surgical excision to include cancer-free surgical margins is the primary mode of therapy for salivary gland cancers, as retrospective studies have shown an increased risk for recurrence and decreased survival with positive surgical margins.[1,2,3] The need for additional surgery is determined on the basis of histopathologic review; positive surgical margins are an indication for additional resection to ensure total tumor removal.

Orientation of Specimen

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

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F. 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 nonmorphologic 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.

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 sternohyoid 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. For uniformity and based on existing evidence (albeit a much smaller scale),[9] these principles are applied to salivary gland carcinomas as well. 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),[10] 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).[11,12,13,14] 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, non-cystic (>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.[15.]

Other Elements

Emerging evidence suggests that positive lymph node number[16,17,18,19] and anatomic compartment/extent of nodal disease[20] may be better prognosticators than the current N classification. Positive lymph node number is already captured under the protocol, and indicating anatomic compartment location of positive lymph nodes is now a non-core element.

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G. TNM and Stage Groupings

The protocol recommends the TNM staging system of the American Joint Committee on Cancer and the International Union Against Cancer for salivary gland cancer.[1]

There are no significant changes to T stage in the AJCC 8th edition for major salivary gland. Carcinomas for which the Tis designation may be applied include some intracapsular carcinomas ex pleomorphic adenoma, and intraductal carcinomas. However, as with squamous cell carcinoma of the head and neck sites (excluding nasopharynx and human papillomavirus (HPV)-related carcinomas), N stage now incorporates extranodal extension.[1]

Tis

The concept of in-situ carcinoma of salivary gland is not well defined, and the categorization should be used sparingly. Intracapsular carcinoma ex pleomorphic adenoma, and intraductal carcinomas are the categories for which Tis can be considered. Even still, this should only be applied to intracapsular carcinoma ex pleomorphic adenoma with a ductal phenotype (i.e., not myoepithelial carcinoma) that is completely encapsulated/well demarcated and uninodular/unicystic for which the entire lesional border (preferably the entire lesion) has been sampled for histologic evaluation.

Extraparenchymal Extension
Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues or nerve (T1, T2, T3), except those listed under T4a and 4b. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.[1]

Intraparotid Lymph Nodes
By convention, a tumor arising from an intranodal parotid tissue should not be considered a metastasis (N0). However, if the tumor has spread via lymphatics into an intraparotid lymph node this would be considered positive with respect to determining N category.[2]

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 based on clinical stage information supplemented/modified by operative findings and gross and microscopic evaluation of the resected specimens.[3] 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 (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.

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.

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