



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

Protocol applies to all invasive carcinomas of the parotid, submandibular, and sublingual glands. Melanomas, lymphomas, and sarcomas are not included. Minor salivary gland carcinomas are detailed in upper aerodigestive tract site-specific protocols.

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Based on AJCC/UICC TNM, 7th edition

Protocol web posting date: October 2013

### Procedure

- Biopsy
- Resection

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## CAP Salivary Gland Protocol Revision History

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### Version Code

The definition of the version code can be found at [www.cap.org/cancerprotocols](http://www.cap.org/cancerprotocols).

**Version:** SalivaryGland 3.2.0.0

### Summary of Changes

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

### Incisional Biopsy, Excisional Biopsy, Resection

#### Histologic Type

Low, intermediate, and high grade were added to adenoid cystic carcinoma as follows:

- \_\_\_ Adenoid cystic carcinoma
  - \_\_\_ Low grade
  - \_\_\_ Intermediate grade
  - \_\_\_ High grade

"Clear cell adenocarcinoma" was changed to "(Hyalinizing) clear cell carcinoma"; "Mammary analogue secretory carcinoma" was added; "Large cell carcinoma" and "Small cell carcinoma" were replaced with "High-grade neuroendocrine carcinoma" with the subtypes of "Large cell neuroendocrine carcinoma" and "Small cell neuroendocrine carcinoma"; and "Cribriform adenocarcinoma of minor salivary origin" was added as a subtype of "Polymorphous low-grade adenocarcinoma."

#### Margins

Designation of distance of tumor from closest margin was changed from "mm or cm" to millimeters (mm).

#### Pathologic Staging (pTNM)

##### Regional Lymph Nodes (pN)

##### *Number of Lymph Nodes Involved*

Size (greatest dimension) of the largest "positive lymph node" was changed to largest "metastatic focus in the lymph node."

### Explanatory Notes

**Scope of Guidelines:** First sentence: "oral cancer including the lip" was changed to "major salivary gland cancer."

#### **B. Histologic Type**

Histologic types were updated.

#### **C. Histologic Grade; D. Surgical Margins; F. Perineural Invasion; G. Extranodal Extension; J. Classification of Neck Dissection; L. Lymph Nodes; M. Ancillary Testing**

Edits were made to these notes.

**K. Regional Lymph Nodes (pN0): Isolated Tumor Cells:** Classification scheme for ITCs was deleted.

**References:** References were updated.

## Surgical Pathology Cancer Case Summary

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Protocol web posting date: October 2013

### MAJOR SALIVARY GLANDS: Incisional Biopsy, Excisional Biopsy, Resection

Select a single response unless otherwise indicated.

#### Specimen (select all that apply) (Note A)

- Parotid gland
  - Superficial lobe only
  - Deep lobe only
  - Total parotid gland
- Submandibular gland
- Sublingual gland
- Other (specify): \_\_\_\_\_
- Not specified

Received:

- Fresh
- In formalin
- Other (specify): \_\_\_\_\_

#### Procedure (select all that apply)

- Incisional biopsy
- Excisional biopsy
- Resection, parotid gland
  - Superficial parotidectomy
  - Total parotidectomy
- Resection, submandibular gland
- Resection, sublingual gland
- Neck (lymph node) dissection (specify): \_\_\_\_\_
- Other (specify): \_\_\_\_\_
- Not specified

#### + Specimen Integrity

- +  Intact
- +  Fragmented

#### Specimen Size

Greatest dimensions: \_\_\_ x \_\_\_ x \_\_\_ cm

+ Additional dimensions (if more than 1 part): \_\_\_ x \_\_\_ x \_\_\_ cm

#### Specimen Laterality

- Right
- Left
- Bilateral
- Not specified

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

- Parotid gland  
      Superficial lobe  
      Deep lobe  
      Entire parotid gland  
 Submandibular gland  
 Sublingual gland  
 Other (specify): \_\_\_\_\_  
 Not specified

**Tumor Focality**

- Single focus  
 Bilateral  
 Multifocal (specify): \_\_\_\_\_

**Tumor Size**

- Greatest dimension: \_\_\_ cm  
 + Additional dimensions: \_\_\_ x \_\_\_ cm  
 Cannot be determined (see Comment)

**+ Tumor Description (select all that apply)**

- Encapsulated/circumscribed  
 Invasive  
 Solid  
 Cystic  
 Other (specify): \_\_\_\_\_

**+ Macroscopic Extent of Tumor (extent of invasion)**

- + Specify: \_\_\_\_\_

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

- Acinic cell carcinoma  
 Adenoid cystic carcinoma  
      Low grade  
      Intermediate grade  
      High grade  
 Adenocarcinoma, not otherwise specified (NOS)  
      Low grade  
      Intermediate grade  
      High grade  
 Basal cell adenocarcinoma  
 Carcinoma ex pleomorphic adenoma (malignant mixed tumor)  
      Low grade  
      High grade  
      Invasive  
          Minimally invasive (Note C)  
          Invasive (Note C)  
      Intracapsular (noninvasive)  
 Carcinosarcoma (true malignant mixed tumor)  
 (Hyalinizing) clear cell carcinoma  
 Cystadenocarcinoma  
 Epithelial-myoepithelial carcinoma

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

- Low-grade cribriform cystadenocarcinoma
- Lymphoepithelial carcinoma
- Mammary analogue secretory carcinoma
- Metastasizing pleomorphic adenoma
- Mucoepidermoid carcinoma
  - Low grade
  - Intermediate grade
  - High grade
- Mucinous adenocarcinoma (colloid carcinoma)
- High-grade neuroendocrine carcinoma
  - Large cell neuroendocrine carcinoma
  - Small cell neuroendocrine carcinoma
- Myoepithelial carcinoma (malignant myoepithelioma)
- Oncocytic carcinoma
- Polymorphous low-grade adenocarcinoma
  - Cribriform adenocarcinoma of minor salivary origin
- Salivary duct carcinoma
- Sebaceous adenocarcinoma
- Sebaceous lymphadenocarcinoma
- Sialoblastoma
- Squamous cell carcinoma, primary
- Undifferentiated carcinoma, large cell type
- Other (specify): \_\_\_\_\_
- Carcinoma, type cannot be determined

**Histologic Grade (Note C)**

- Not applicable
- GX: Cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- Other (specify): \_\_\_\_\_

**+ Microscopic Tumor Extension**

- + Specify: \_\_\_\_\_

**Margins (Notes D and E)**

- Cannot be assessed
- Margins uninvolved by carcinoma
  - Distance of tumor from closest margin: \_\_\_ mm
  - Specify margin, if possible: \_\_\_\_\_
- Margin(s) involved by carcinoma
  - Specify margin(s), if possible: \_\_\_\_\_

**+ Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy)**

- +  Not identified
- +  Present (specify): \_\_\_\_\_
- +  Indeterminate

**Lymph-Vascular Invasion**

- Not identified  
 Present  
 Indeterminate

**Perineural Invasion (Note F)**

- Not identified  
 Present  
 Indeterminate

**Lymph Nodes, Extranodal Extension (Note G)**

- Not identified  
 Present  
 Indeterminate

**Pathologic Staging (pTNM) (Note H)**

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

TNM Descriptors (required only if applicable) (select all that apply)

- m (multiple primary tumors)  
 r (recurrent)  
 y (posttreatment)

Primary Tumor (pT)

- pTX: Cannot be assessed  
 pT0: No evidence of primary tumor  
 pT1: Tumor 2 cm or less in greatest dimension *without extraparenchymal extension* (Note I)  
 pT2: Tumor more than 2 cm but not more than 4 cm in greatest dimension *without extraparenchymal extension* (Note I)  
 pT3: Tumor more than 4 cm and/or tumor *having extraparenchymal extension* (Note I)  
 pT4a: Moderately advanced 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

*Note: There is no category of carcinoma in situ (pTis) relative to carcinomas of salivary glands (major, minor).*

Regional Lymph Nodes (pN)# (Notes J through M)

- pNX: Cannot be assessed  
 pN0: No regional lymph node metastasis  
 pN1: Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension  
 pN2a: Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension  
 pN2b: Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension  
 pN2c: Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension  
 pN3: Metastasis in a lymph node, more than 6 cm in greatest dimension  
 No nodes submitted or found

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

*Number of Lymph Nodes Examined*

Specify: \_\_\_\_

\_\_\_ Number cannot be determined (explain): \_\_\_\_\_

*Number of Lymph Nodes Involved*

Specify: \_\_\_\_

+ Size (greatest dimension) of the largest metastatic focus in the lymph node: \_\_\_\_ cm (Note L)

\_\_\_ Number cannot be determined (explain): \_\_\_\_\_

*# Superior mediastinal lymph nodes are considered regional lymph nodes (level VII). Midline nodes are considered ipsilateral nodes.*

Distant Metastasis (pM)

\_\_\_ Not Applicable

\_\_\_ pM1: Distant metastasis

+ Specify site(s), if known: \_\_\_\_\_

**+ Additional Pathologic Findings (select all that apply)**

+ \_\_\_ Sialadenitis

+ \_\_\_ Tumor associated lymphoid proliferation (TALP)

+ \_\_\_ Other (specify): \_\_\_\_\_

**+ Ancillary Studies (Note N)**

+ Specify type(s): \_\_\_\_\_

+ Specify result(s): \_\_\_\_\_

**+ Clinical History (select all that apply)**

+ \_\_\_ Neoadjuvant therapy

+ \_\_\_ Yes (specify type): \_\_\_\_\_

+ \_\_\_ No

+ \_\_\_ Indeterminate

+ \_\_\_ Other (specify): \_\_\_\_\_

**+ Comment(s)**

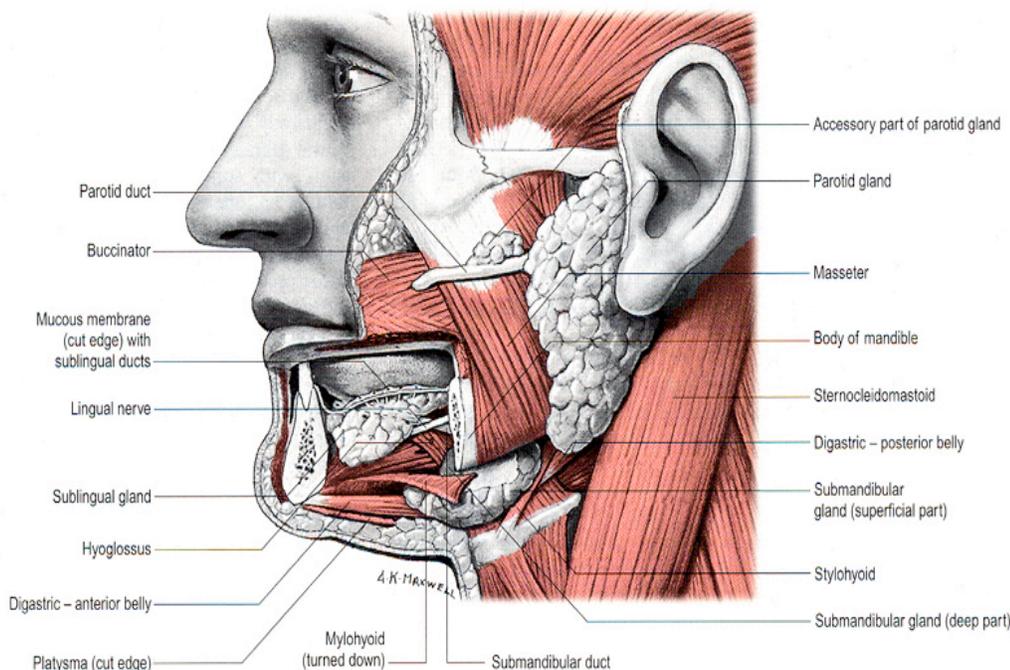
## Explanatory Notes

### Scope of Guidelines

The reporting of 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, the World Health Organization classification of tumours, the TNM classification, the American College of Surgeons Commission on Cancer, and the International Union on Cancer (UICC). This protocol is to be used as a guide and resource, an adjunct to diagnosing and managing cancers of the oral cavity in a standardized manner. It should not be used as a substitute for dissection or grossing techniques and does not give histologic parameters to reach the diagnosis. Subjectivity is always a factor, and elements listed are not meant to be arbitrary but are meant to provide uniformity of reporting across all the disciplines that use the information. It is a foundation of practical information that will help to meet the requirements of daily practice to benefit both clinicians and patients alike.

### A. Primary Site (Figure 1)

The classification applies only to carcinomas of the major salivary glands: parotid, submandibular (submaxillary), and sublingual glands.<sup>1</sup> 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, eg, 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.

**B. Histological Type**

The histologic classification recommended is a modification of the World Health Organization (WHO) classification of salivary gland tumors.<sup>2,3</sup> The listing is in alphabetical order and includes the following:

- Acinic cell carcinoma
- Adenoid cystic carcinoma
- Adenocarcinoma, not otherwise specified (NOS)
  - Low grade
  - Intermediate grade
  - High grade
- Basal cell adenocarcinoma
- Carcinoma ex pleomorphic adenoma (malignant mixed tumor)
  - Low grade
  - High grade
  - Invasive
    - Minimally invasive
    - Invasive
  - Intracapsular (noninvasive)
- Carcinosarcoma (true malignant mixed tumor)
- (Hyalinizing) clear cell carcinoma
- Cystadenocarcinoma
- Epithelial-myoeplithelial carcinoma
- Low-grade cribriform cystadenocarcinoma
- Lymphoepithelial carcinoma
- Mammary analogue secretory carcinoma<sup>#</sup>
- Metastasizing pleomorphic adenoma<sup>##</sup>
- Mucoepidermoid carcinoma
  - Low grade
  - Intermediate grade
  - High grade
- Mucinous adenocarcinoma (colloid carcinoma)
- High-grade neuroendocrine carcinoma
  - Large cell neuroendocrine carcinoma
  - Small cell neuroendocrine carcinoma
- Myoepithelial carcinoma (malignant myoepithelioma)
- Oncocytic carcinoma
- Polymorphous low-grade adenocarcinoma
  - Cribriform adenocarcinoma of minor salivary origin<sup>#</sup>
- Salivary duct carcinoma
- Sebaceous adenocarcinomas
  - Sebaceous adenocarcinoma
  - Sebaceous lymphadenocarcinoma
- Sialoblastoma
- Squamous cell carcinoma, primary
- Undifferentiated carcinoma, large cell type

<sup>#</sup> These entities were characterized as distinct tumor types subsequent to the WHO classification scheme.<sup>4,5</sup>

## Metastatic foci are histologically benign. Although not strictly considered a malignant neoplasm, this neoplasm is classified with other salivary gland carcinomas<sup>2,3</sup> given the fact that 40% of patients are reported to die of disease even though 60% are alive and well (47%) or are alive with disease (13%).<sup>6</sup>

### C. 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.<sup>3,7-11</sup> Further, there is often a positive correlation between histologic grade and clinical stage. Most salivary carcinomas have a biologic behavior defined by their categorization and do not require grading.<sup>11</sup> The 3 major categories that are amenable to grading include adenoid cystic carcinoma, mucoepidermoid carcinoma (the 2 most frequent histologic types seen in larynx), and adenocarcinoma, not otherwise specified.<sup>3,8,12</sup>

Generally, 3 histologic grades are suggested, as follows:

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

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

### D. 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.<sup>16-20</sup> 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. Carcinoma in situ of the salivary glands are exceptionally rare and constitute mainly salivary duct carcinoma in situ, low-grade cribriform cystadenocarcinoma (both of which have been referred to as intraductal carcinoma),<sup>21</sup> and possibly a subset of cystadenocarcinomas.

### E. Orientation of Specimen

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

### F. Perineural Invasion

The presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.<sup>22</sup> 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 and decreased survival.<sup>3</sup> Further, facial nerve involvement by carcinoma has been found to be predictive of occult metastases.<sup>23,24</sup> Among other prognostic indicators, perineural invasion in minor salivary gland tumors has been shown to be statistically significant to the outcome.<sup>25</sup> Given the significance relative to prognosis and treatment, perineural invasion is a required data element in the reporting of salivary gland carcinomas.

### G. Extranodal Extension

The status of cervical lymph nodes is the single most important prognostic factor in aerodigestive cancer. All macroscopically negative or equivocal lymph nodes should be submitted in toto. Grossly positive nodes may be partially submitted for microscopic documentation of metastasis. Reporting of lymph nodes containing metastasis should include whether there is presence or absence of extranodal extension (EE). This finding consists of extension of metastatic tumor, present within the confines of the lymph node, through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction. A distance of extension from the native lymph node capsule is optional and has not yet been shown to have a definitive impact on prognosis or treatment for head and neck subsites. If macroscopic examination suggests EE, this tissue should be submitted for microscopic confirmation. EE is a predictor of regional relapse and a criterion for postoperative radiotherapy.<sup>26-29</sup>

### H. TNM and Stage Groupings

The protocol recommends the TNM staging system of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) for salivary gland cancer.<sup>1,30</sup>

#### Primary Tumor

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less in greatest dimension without extraparenchymal extension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension without extraparenchymal extension
T3	Tumor more than 4 cm and/or tumor having extraparenchymal extension
T4a	Moderately advanced disease. Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease. Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

#### Regional Lymph Nodes #

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

#Superior mediastinal lymph nodes are considered regional lymph nodes (level VII).  
Midline nodes are considered ipsilateral nodes.

#### Distant Metastasis

M0	No distant metastasis
M1	Distant metastasis

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

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

Significant changes in the AJCC staging manual<sup>1</sup> include revision of T3 to include all tumors larger than 4cm and division of T4 lesions into T4a and T4b. T4a tumors invade skin, mandible, ear canal, and/or facial nerve. T4b tumors invade skull base and/or pterygoid plates and/or encases carotid artery. T4a are advanced tumors that can be resected with clear margins; T4b are advanced tumors that cannot be resected with clear margins.

### Stage Groupings

Stage I	T1	N0	M0
Stage II/2		N0	M0
Stage III	T3	N0	M0
	T1,T2,T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1,T2,T3,T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

### TNM Descriptors

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y,” “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 (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The “y” categorization is not an estimate of tumor prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

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

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

**Additional Descriptors**Residual Tumor (R)

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

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

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

**I. 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.<sup>1</sup>

**J. 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<sup>31-33</sup>:
  - 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<sup>34</sup>
5. Extended radical neck dissection, as specified by the surgeon

**K. Regional Lymph Nodes (pN0): Isolated Tumor Cells**

Isolated tumor cells (ITCs) are single cells or small clusters of cells not more than 0.2 mm in greatest dimension. While the generic recommendation is that for lymph nodes with ITCs found by either histologic examination, immunohistochemistry, or nonmorphologic techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker), they should be classified as N0 or M0, respectively,<sup>30,35</sup> 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.<sup>36</sup>

For purposes of pathologic evaluation, lymph nodes are organized by levels as shown in Figure 2.<sup>37</sup>



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

**L. Lymph Nodes****Lymph Node Number**

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

**Measurement of Tumor Metastasis**

The cross-sectional diameter of the largest lymph node metastasis (not the lymph node itself) is measured in the gross specimen at the time of macroscopic examination or, if necessary, on the histologic slide at the time of microscopic examination.<sup>22,31</sup>

**M. Special Procedures for Lymph Nodes**

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

**N. Ancillary Testing**

At the current time, no additional special techniques are mandatory other than routine histology for the assessment of salivary gland tumors. However the past few years, several salivary gland tumors have

been demonstrated to have unique fusion transcripts that may be considered optional for reporting purposes.

By both reverse transcriptase polymerase chain reaction (RT-PCR) and fluorescence in-situ hybridization (FISH), over 60% of mucoepidermoid carcinoma have been shown to demonstrate t(11;19) (q12;p13) translocation.<sup>15</sup> This aberration leads to a fusion gene comprised of exon 1 of the *CRTC1* (also known as *MECT1*) gene and exons 2-5 of the *MAML2* gene. The resultant *CRTC1-MAML2* fusion gene protein appears to activate both Notch signaling targets and cAMP/CREB targets.<sup>40-42</sup> An alternate fusion partner *CRTC3* has been documented as well.<sup>43</sup> This translocation is more frequent in low- and intermediate-grade mucoepidermoid carcinomas and is thus considered a more favorable prognosticator, even in the high-grade subgroup.<sup>11,15</sup>

A more recently described distinct primary salivary gland malignancy, mammary analogue secretory carcinoma, is now known to be defined by the unique translocation t(12;15)(p13;q25), leading to the *ETV6-NTRK3* fusion gene.<sup>4</sup> Historically many of these were grouped with acinic cell carcinoma or adenocarcinoma, not otherwise specified.<sup>44</sup> Prognosis is roughly similar to that of acinic cell carcinoma, though mammary analogue secretory carcinoma may have a slightly higher risk of nodal metastasis. Similarly, hyalinizing clear cell carcinoma is now known to harbor a defining *EWRS1-ATF1* translocation in 80% to 90% of cases.<sup>45</sup>

Approximately one-third of adenoid cystic carcinomas have been identified with t(6;9)(q22-23;p23-24), resulting in *MYB-NFIB* fusion transcript.<sup>38,39</sup> The prognostic and therapeutic value for this translocation is not yet established.

Additional ancillary testing that is not uncommonly used for hypothetical therapeutic applications includes immunohistochemical staining for HER2/*neu* can be identified in association with salivary duct carcinoma. However, at the present time there are no specific recommendations to perform confirmatory FISH analysis similar to mammary duct carcinoma; the utilization of FISH analysis in salivary duct carcinoma or any other salivary gland malignancy is considered an investigational technique at this time. Salivary duct carcinomas frequently express immunoreactivity for hormonal receptors, including androgen receptor and estrogen receptor-beta (usually negative for estrogen receptor-alpha, the more commonly used estrogen immunohistochemical stain).<sup>46</sup> Although there are no specific recommendations to perform confirmatory immunohistochemistry for hormonal receptors, the expression of androgen receptor and estrogen receptor-beta may potentially guide treatment with targeted multiagent chemotherapies.<sup>46</sup> More recently, *PIK3CA* mutations and *PTEN* loss in subsets of salivary duct carcinoma offer additional therapeutic targets, though again on an investigational basis.<sup>47</sup>

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