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.

Based on AJCC/UICC TNM, 7th edition
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Procedure
- Biopsy
- Resection

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The College of American Pathologists offers these protocols to assist pathologists in providing clinically useful and relevant information when reporting results of surgical specimen examinations of surgical specimens. The College regards the reporting elements in the "Surgical Pathology Cancer Case Summary" portion of the protocols as essential elements of the pathology report. However, the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these protocols as an educational tool to assist pathologists in the useful reporting of relevant information. It did not issue the protocols for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the protocols might be used by hospitals, attorneys, payers, and others. Indeed, effective January 1, 2004, the Commission on Cancer of the American College of Surgeons mandated the use of the required data elements of the protocols as part of its Cancer Program Standards for Approved Cancer Programs. Therefore, it becomes even more important for pathologists to familiarize themselves with these documents. At the same time, the College cautions that use of the protocols other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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CAP Salivary Gland Protocol Revision History

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

Version: SalivaryGland 3.1.0.2

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

Incisional Biopsy, Excisional Biopsy, Resection

Specimen
Added the following elements:
___ Other (specify): _____
___ Not specified

Explanatory Notes

Scope of Guidelines
The word "checklist(s)" was changed to "case summary(ies)" or "protocol" as appropriate.

Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

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
___ 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)
___ Clear cell adenocarcinoma
___ Cystadenocarcinoma
___ Epithelial-myoepithelial carcinoma
___ Large cell carcinoma
___ Low-grade cribriform cystadenocarcinoma
___ Lymphoepithelial 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.

___ Metastasizing pleomorphic adenoma
___ Mucoepidermoid carcinoma
    ___ Low grade
    ___ Intermediate grade
    ___ High grade
___ Mucinous adenocarcinoma (colloid carcinoma)
___ Myoepithelial carcinoma (malignant myoepithelioma)
___ Oncocytic carcinoma
___ Polymorphous low-grade adenocarcinoma
___ Salivary duct carcinoma
___ Sebaceous adenocarcinomas
    ___ Sebaceous adenocarcinoma
    ___ Sebaceous lymphadenocarcinoma
___ Sialoblastoma
___ Small cell (neuroendocrine) carcinoma
___ 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 *or* ___ cm
    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

Number of Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): _____
+ Size (greatest dimension) of the largest positive lymph node: _____ cm (Note L)

[#] 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 oral cancer including the lip is facilitated by the provision of a case summary illustrating the features required for comprehensive patient care. However, there are many cases in which the individual practicalities of applying such a case summary may not be straightforward. Common examples include finding the prescribed number of lymph nodes, trying to determine the levels of the radical neck dissection, and determining if isolated tumor cells in a lymph node represent metastatic disease. Case summaries have evolved to include clinical, radiographic, morphologic, immunohistochemical, and molecular results in an effort to guide clinical management. Adjuvant and neoadjuvant therapy can significantly alter histologic findings, making accurate classification an increasingly complex and demanding task. This protocol tries to remain simple while still incorporating important pathologic features as proposed by the American Joint Committee on Cancer (AJCC) cancer staging manual, the World Health Organization classification of tumours, the TNM classification, the American College of Surgeons Commission on Cancer, and the International Union on Cancer (UICC). This protocol is to be used as a guide and resource, an adjunct to diagnosing and managing cancers of the oral cavity in a standardized manner. It should not be used as a substitute for dissection or grossing techniques and does not give histologic parameters to reach the diagnosis. Subjectivity is always a factor, and elements listed are not meant to be arbitrary but are meant to provide uniformity of reporting across all the disciplines that use the information. It is a foundation of practical information that will help to meet the requirements of daily practice to benefit both clinicians and patients alike.

A. Primary Site (Figure 1)
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, eg, oral cavity, pharynx, sinonasal tract.

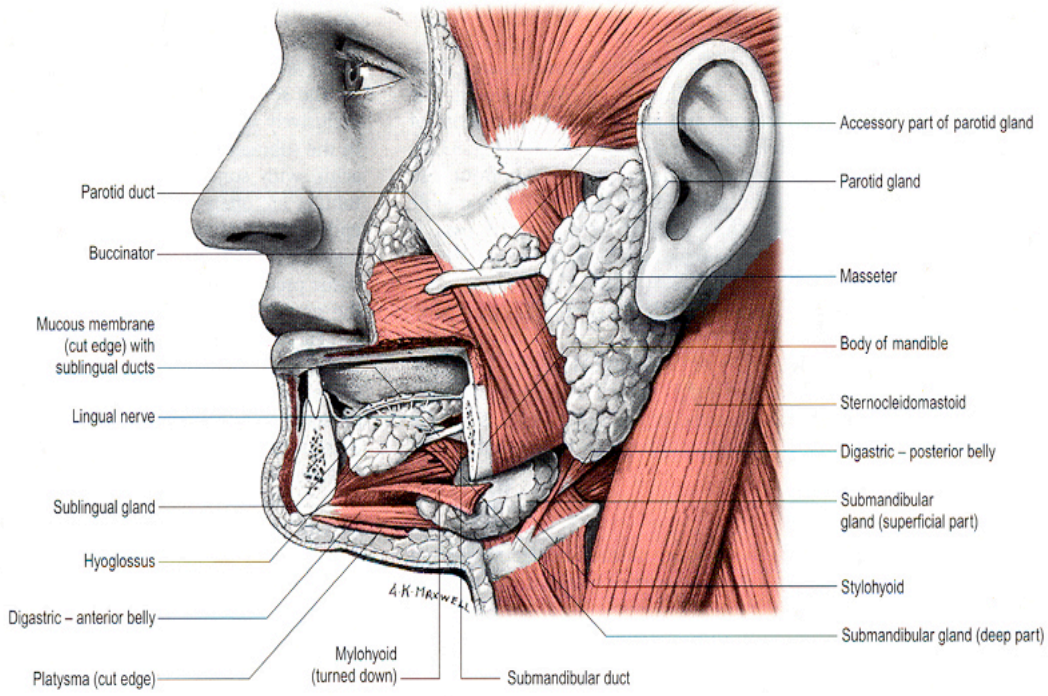

Figure 1. Anatomy of the major salivary glands. From: *Gray's Anatomy*. 39th ed. Edinburgh: Elsevier Churchill Livingstone; 2005. Reproduced with permission © Elsevier.

B. Histological Type

The histologic classification recommended is a modification of the World Health Organization (WHO) classification of salivary gland tumors.[2,3] 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)
Carcinoma, type cannot be determined
Carcinosarcoma (true malignant mixed tumor)
Clear cell adenocarcinoma
Cystadenocarcinoma
Epithelial-myoepithelial carcinoma
Large cell carcinoma
Low-grade cribriform cystadenocarcinoma
Lymphoepithelial carcinoma
Metastasizing pleomorphic adenoma#
Mucoepidermoid carcinoma
    Low grade

Intermediate grade
High grade
Mucinous adenocarcinoma (colloid carcinoma)
Myoepithelial carcinoma (malignant myoepithelioma)
Oncocytic carcinoma
Polymorphous low-grade adenocarcinoma
Salivary duct carcinoma
Sebaceous adenocarcinomas
Sebaceous adenocarcinoma
Sebaceous lymphadenocarcinoma
Sialoblastoma
Small cell (neuroendocrine) carcinoma
Squamous cell carcinoma, primary
Undifferentiated carcinoma, large cell type

Metastatic foci are histologically benign. Although not strictly considered a malignant neoplasm, this neoplasm is classified with other salivary gland carcinomas [2,3] 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%).[4]

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.[3,5-8] Further, there is often a positive correlation between histologic grade and clinical stage. For the majority of salivary gland carcinomas there is only a single histologic grade and classification alone determines the histologic grade (eg, acinic cell carcinoma is a histologically low-grade carcinoma; salivary duct carcinoma is a histologically high-grade carcinoma). With some exceptions, histologic grading is predicated on cytomorphologic features. In this histologic grading scheme, 3 histologic grades are suggested, as follows:

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

When a tumor manifests more than 1 grade of differentiation, the surgical report must designate both the highest and the most prevalent tumor grades. In some carcinomas, histologic grading may be based on growth pattern, such as in adenoid cystic carcinoma, for which a histologic high-grade variant has been recognized based on the percentage of solid growth.[3] Those adenoid cystic carcinomas showing 30% or greater of solid growth pattern are considered to be histologically high-grade carcinomas.[3,6,9] The histologic grading of mucoepidermoid carcinoma includes a combination of growth pattern characteristics (eg, cystic, solid, neurotropism) and cytomorphologic findings (eg, anaplasia, mitoses, necrosis). [10-12]

Carcinoma ex pleomorphic adenoma is subclassified by histologic grade (low-grade and high-grade) and extent of invasion, the latter including minimally invasive, invasive, and noninvasive cancers. Minimally invasive cancers measure less than or equal to 1.5 mm with penetration of the malignant component into extracapsular tissue; invasive carcinomas measure more than 1.5 mm of invasion; noninvasive cancers are completely confined within the capsule without evidence of penetration into extracapsular tissue. Prior to diagnosing a noninvasive carcinoma ex pleomorphic adenoma, sectioning of the entire lesion for histologic evaluation is recommended in order to exclude the presence of invasive growth. Prognosis has been linked to degree of invasion with noninvasive and minimally invasive cancers apparently having a better prognosis than invasive cancers.[13]

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.[14-18] 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. There is no category of carcinoma in situ relative to carcinomas of salivary glands (major, minor) with the exception of the rare, purely in situ, low-grade cribriform cystadenocarcinoma (also referred to as intraductal carcinoma).[3]

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

F. Perineural Invasion
The presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.[19] The 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.[3] Further, facial nerve involvement by carcinoma has been found to be predictive of occult metastases.[20,21] Among other prognostic indicators, perineural invasion in minor salivary gland tumors has been shown to be statistically significant to the outcome.[22] 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 extra-nodal extension (EE). This finding consists of extension of metastatic tumor, present within the confines of the lymph node, through the lymph node capsule into the surrounding connective tissue, with or without associated stromal reaction. If macroscopic examination suggests EE, this tissue should be submitted for microscopic confirmation. EE is a predictor of regional relapse and a criterion for postoperative radiotherapy.[23-25]

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.[1,26]

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[1] 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 IIT2		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.[1]

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
    a. Supraomohyoid neck dissection
    b. Posterolateral neck dissection
    c. Lateral neck dissection

d. Central compartment neck dissection
4. Selective neck dissection (SND), as specified by the surgeon -"SND" with levels and sublevels designated (Figure 2)[27-29]
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. Lymph nodes or distant sites with ITCs found by either histologic examination, immunohistochemistry, or non-morphologic techniques (eg, flow cytometry, DNA analysis, polymerase chain reaction [PCR] amplification of a specific tumor marker) should be classified as N0 or M0, respectively. Specific denotation of the assigned N category is suggested as follows for cases in which ITCs are the only evidence of possible metastatic disease.[30,31]

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

For purposes of pathologic evaluation, lymph nodes are organized by levels as shown in Figure 2.[32]

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 metastasis in a lymph node containing metastatic tumor is measured in the gross specimen at the time of macroscopic examination or, if necessary, on the histologic slide at the time of microscopic examination. There is conflicting data in the literature on the significance of the size of the largest metastatic lymph node on the risk of regional recurrence and a predictor of poor overall survival.[19] While the diameter of the largest positive lymph node may potentially serve as a predictor of outcome, it may not represent an independent predictor of outcome when other pathologic factors are considered.[19]

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 required other than routine histology for the assessment of salivary gland tumors. 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 fluorescence in-situ hybridization (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).[33] 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.[33]

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