Protocol for Examination of Specimens from Patients with Carcinomas of the Major Salivary Glands

Protocol applies to carcinoma of the primary salivary glands and neuroendocrine carcinoma. This protocol does not apply to minor salivary gland carcinoma, sarcoma, or lymphoma.

Based on:

AJCC/UICC TNM, 8th edition
CAP Cancer Protocol version: SalivaryGland 4.0.0.1
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Revision History:

None

Summary of Changes:

This protocol is revised to the 8th edition of the AJCC Cancer Staging Manual and the current version of the CAP Cancer Protocol SalivaryGland 4.0.0.1.

Procedures Covered in this Protocol:

- Excision
- Parotidectomy, superficial
- Parotidectomy, deep
- Parotidectomy, total
- Resection, submandibular gland
- Resection, sublingual gland
- Lymph node dissection (specify)

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Molecular and Immunohistochemistry Considerations:

Immunohistochemical staining for HER2/neu can be identified in association with salivary duct, mucoepidermoid carcinomas, adenoid cystic carcinomas and adenocarcinomas. However, at the present time there are no specific recommendations to perform confirmatory fluorescence in-situ hybridization (FISH) analysis, which 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). The expression of androgen receptor and estrogen receptor-beta may potentially guide treatment with targeted multiagent chemotherapies.

Mucoepidermoid Carcinoma, the most common malignant salivary gland carcinoma, may contain the translocation *CRTC1-MAML2* (40-80%) or *CRTC3-MAML2* (5%). *MAML2* rearrangement testing is currently more helpful in differentiating mucoepidermoid carcinoma variants from aggressive salivary gland carcinomas rather than as prognostic value.

In adenoid cystic carcinoma, *MYB* overexpression has been linked to pathogenesis of the lesion and can be used diagnostically on biopsies.

Hyalinizing clear cell carcinoma and mammary analogue secretory carcinoma are generally low-grade lesions in which translocation analysis will aid to differentiate them from higher grade, more aggressive lesions. In Hyalinizing clear cell carcinoma, *EWSR1-ATF1* translocation helps in differentiating this cancer from clear cell mucoepidermoid carcinoma and squamous cell carcinoma with clear cell change.

Mammary analogue secretory carcinoma resembles secretory breast cancer, sharing the *ETV6-NTRK3* translocation. This will help distinguish the lesion from zymogen-poor acinic cell carcinoma, low-grade cribriform cystadenocarcinoma, and mucoepidermoid carcinoma.

Although a very common benign tumor, a pleomorphic adenoma may undergo malignant change as carcinoma ex pleomorphic adenoma. The genes involved, *HMGA2* and *PLAG1*, are identified though FISH.

Unlike other cancers of the head and neck, HPV testing is not indicated due to inconsistent, irreproducible and even controversial results. While earlier research indicated links between salivary gland cancers and high-risk HPV 16 and 18 by evidence of positive immunohistochemical staining of p16 protein, it has not been shown to reveal detection of HPV DNA on PCR. Therefore, the overexpression of p16, a tumor suppressor, may be evidence of another mechanism besides HPV infection and does not represent an HPV infection-induced cancer. Until a more definitive link between high risk HPV infection and oncogenic transformation in salivary gland tumors is elucidated, HPV testing remains investigative.

These tests can be performed on formalin fixed paraffin embedded tissue sections. The macroscopic description should provide the fixative used. 10% neutral buffered formalin is the preferred fixative. It is recommended that the duration of fixation be provided as well.

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol:**

  - Excision
  - Parotidectomy, superficial
  - Parotidectomy, deep
  - Parotidectomy, total
  - Resection, submandibular gland
  - Resection, sublingual gland
  - Neck (Lymph node) dissection (specify)

- **Specimen Size and Extent of Resection:**

  - Specify laterality
  - Three dimensions (when oriented, specimen dimensions should be specified (e.g., anterior to posterior, medial to lateral, superior to inferior))
  - Parotid gland
    - Superficial lobe only
    - Deep lobe only
    - Total parotid
  - Submandibular gland
  - Sublingual gland
  - List adjacent structures (ear canal, mandible or maxilla, nerve tissue, skin)

- **Specimen Integrity and Adequacy:**

  - Provide an assessment of the specimen integrity.
  - Identify and describe any defects or disruptions. *

  **Statements should include completeness of resection, as complete surgical removal is a primary therapeutic modality. Disruptions of margins should be differentially inked, and their anatomic locations must also be noted. Surgical disruptions should be differentiated from tumor breach by consultation with the surgeon and pathologist. Describe the relationship of any defects or disruptions to the tumor, especially if they serve to hinder assessment of the final surgical margin. Specifically, macroscopic extraparenchymal extension constitutes a pT3 lesion.*

TUMOR ("T" of TNM)

- **Tumor Size:**

  - Provide three dimensions in cm (when oriented, specimen dimensions should be specified [e.g., anterior to posterior, medial to lateral, superior to inferior]).
  - If multiple tumors are present, provide dimensions of all tumors identified and distances between tumors in cm.

- **Tumor Site(s):** *(Figure 1)*

  - Parotid gland
    - Superficial lobe
    - Deep lobe
    - Entire parotid gland
  - Submandibular gland
  - Sublingual gland
  - Other (specify)

  Note: Tumors arising from minor salivary glands (mucus-secreting glands in the lining membrane of the upper aerodigestive tract) are staged according to their regional structures (oral cavity, pharynx, etc.).

- **Tumor Focality:**

  - Specify if tumor is unifocal or multifocal.

- **Sectioning Recommendations:**

  At least one section per centimeter of tumor is recommended for most major salivary gland neoplasms. Adequate sampling is necessary for high grade transformation assessment. High grade transformation does not change the TNM category but can significantly alter the adjuvant therapy and/or patient follow up. In addition, while low grade salivary gland cancers are rare to metastasize, high grade lesions have a significantly increased risk.

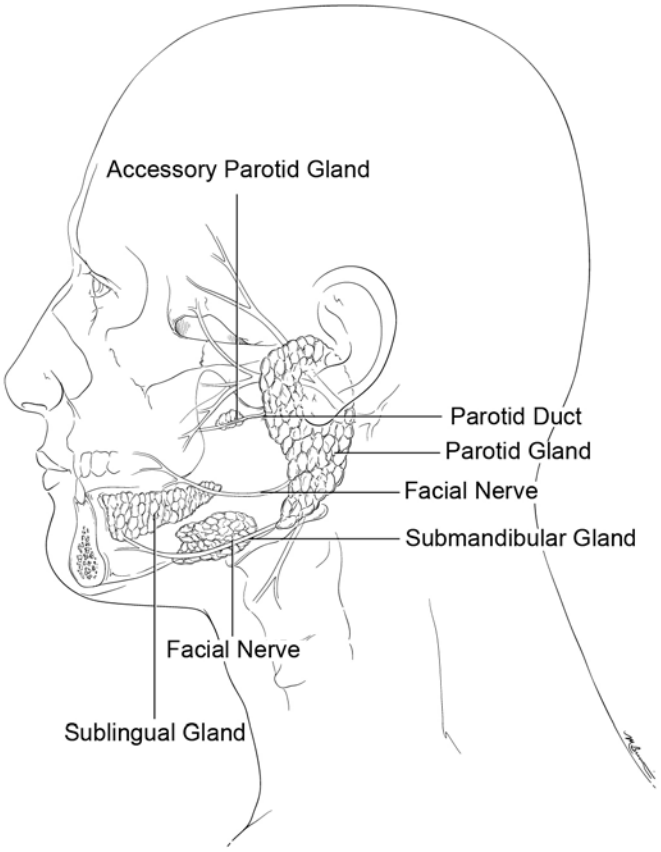

Figure 1: Major Salivary Glands - General Anatomy

- **Tumor Depth of Invasion and Relationship to Attached Organs / Structures:**

Definition or Primary Tumor (pT)

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pTis	Carcinoma *in situ*
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 disease. Tumor invades skin, mandible, ear canal, or facial nerve
pT4b	Very advanced disease. Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

*Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes.

A definitive statement should be provided regarding the presence or absence of macroscopic extraparenchymal extension.

TNM Definitions:

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.

Residual Tumor (R) Category

The absence or presence of residual tumor at the primary tumor site after treatment is denoted by the symbol R. The R categories for the primary tumor site are as follows:

R	R Definition
RX	Presence of residual tumor cannot be assessed
R0	No residual tumor
R1	Microscopic residual tumor
R2	Macroscopic residual tumor at the primary cancer site or regional nodal sites

- **Margins: ***

  Assess the distance and location(s) to all soft tissue margins, vascular margins and nerve margins in mm, providing sections for each. Re-excision is indicated for macroscopically positive margins.

  **It is recommended to take radial (perpendicular) margins whenever possible, even when margins are distant from the tumor. With this technique, the distance to occult tumor or dysplasia, if present, can still be measured. Bone margins may be taken en face, and if applicable, the gingival margin close to bone/tooth must be scraped or shaved off and then can only be submitted en face.*

- **Explanatory Notes:**

  The presence of facial nerve dysfunction and perineural involvement is an indicator for neck dissection, radiation therapy and poor survival. Perineural invasion of the facial nerve is a predictor for lower survival rates, tumor recurrence and could indicate occult metastasis.

LYMPH NODES ("N" of TNM)

- **Lymph Nodes:** (if applicable)

  - The status of cervical lymph nodes is the single most significant predictor of poor prognosis in head and neck cancer of virtually all sites.

  - Reporting of lymph nodes containing metastasis should include whether there is presence or absence of extranodal extension (ENE) which is now part of N staging.

    Extranodal extension is defined as 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.

  - In general, the intraparenchymal and periglandular lymph nodes (especially in the parotid) should be assessed; however cervical neck lymph nodes represent the regional nodes for major salivary gland tumors. Size of positive lymph nodes is a clinically significant factor.

  - Regional dissemination tends to progress from intraglandular to adjacent (periparotid, submandibular) nodes, then to upper and midjugular nodes, apex of the posterior triangle (level VA), and occasionally to retropharyngeal nodes. Bilateral lymphatic spread is rare.

Definition of Regional Lymph Node (N)
Pathological N (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in a single ipsilateral positive lymph node, 3 cm or smaller in greatest dimension and ENE(-)
pN2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); *or* in bilateral or contralateral lymph 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 node(s), 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(-)
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(+)

Notes:

- A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
- Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+).

Lymph Node Examination:

- Specify laterality of lymph nodes
  - Ipsilateral (including midline)
  - Contralateral
  - Bilateral
- Count and give size range in three dimensions.
- Submit all lymph nodes resulting from complete lymph node dissection.
- Note anatomic location if known.
- Submit smaller lymph nodes in toto.
- Bivalve or serially section larger macroscopically negative lymph nodes and submit entirely.
- Representative sectioning of macroscopically positive nodes is acceptable.
  - Specify the largest metastatic deposit in cm. *
- If possible, submit lymph node sections so that the long axis of the lymph node is demonstrated.
- Take steps to ensure that an accurate lymph node count can be rendered.

* Measurement of a metastatic focus in lymph nodes is based on the largest metastatic deposit size, which may include matted or fused lymph nodes. 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.

- Additional sections should be submitted to assess for extranodal extension.
  - If extranodal extension is macroscopically identified, measure the distance from lymph node capsule in mm.

- **Explanatory Notes:**

- Extranodal extension, a predictor of regional relapse and a criterion for postoperative radiotherapy, is indicated by lymph node matting. Lymph nodes over 3 cm in greatest dimension may represent a confluence of lymph nodes which already display tumor extension into surrounding tissue. Consequently, extra sampling of macroscopically positive lymph nodes may be necessary to rule out extranodal extension, even if not macroscopically evident.

- Mucoepidermoid carcinoma, the most common major salivary gland malignancy, predominately affects the parotid gland and spreads to adjacent preauricular lymph nodes before proceeding to minor salivary gland sites such as the submandibular region. Regional lymphatic spread (especially bilaterally) of salivary gland cancers is rare in low grade tumors but is considerably higher in high grade tumors. Lymphatic spread is usually clinically apparent and tends to be orderly depending on the primary site, beginning from the periparotid region to the upper jugular nodes and down to the apex of the posterior triangle.

Classification of Neck Dissection: *(Figure 2)*

- Radical neck dissection
- Modified radical neck dissection, internal jugular vein and/or sternocleidomastoid muscle spared
- Selective neck dissection (SND), as specified by surgeon
  - Supraomohyoid neck dissection: above the hyoid bone, which includes lymph nodes of levels IA, IB, IIA and IIB
  - Posterolateral neck dissection: bordered anteriorly by the stylohyoid muscle and posteriorly by the sternocleidomastoid, it includes level III lymph nodes above the hyoid and level IV below the hyoid
  - Lateral neck dissection: anteriorly bordered by the sternocleidomastoid muscle, it includes level VA, VB and supraclavicular lymph nodes
  - Central compartment neck dissection: includes the pre- and paratracheal, Delphian and perithyroid lymph nodes of level VI
- Superselective neck dissection, as specified by the surgeon – “SSND” with levels and sublevels designated
  - Fibrofatty soft tissue contents of two (or less) contiguous neck levels are removed both electively for patients with no nodal metastasis (N0) or persistent lymph node disease following chemoradiotherapy (N+).
- Extended radical neck dissections, as specified by surgeon

Note: Superior mediastinal lymph nodes are considered regional lymph nodes (level VII). All midline lymph nodes are considered ipsilateral.

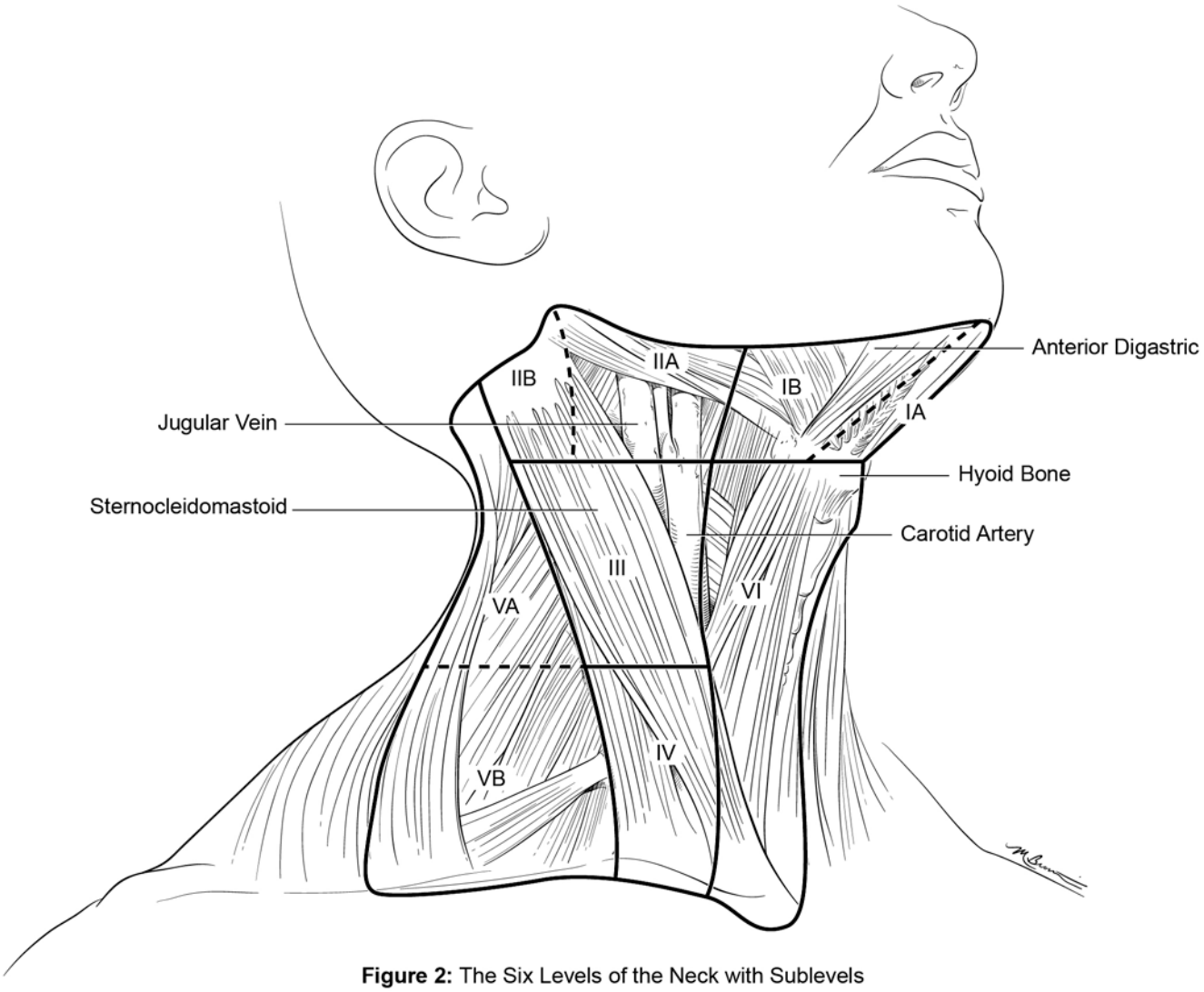

Figure 2: The Six Levels of the Neck with Sublevels

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 III: Middle jugular group
Level IV: Lower jugular group
Level VA: Spinal accessory nodes
Level VB: Supraclavicular and transverse cervical nodes
Level VI: Anterior (central) compartment

METASTASIS ("M" of TNM)

- **Metastasis:**

Definition of Distant Metastasis (M) (required only if confirmed pathologically)

pM Category	pM Criteria
M0	No distant metastasis
pM1	Distant metastasis

Specify metastatic site, if known.

Distant metastases are most frequently found in the lungs.

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