Protocol for the Examination of Specimens from Patients with Cancers of the Larynx

Protocol applies to all invasive carcinomas of the larynx, including supraglottis, glottis and subglottis. Mucosal melanoma is included. Hypopharyngeal squamous cell carcinoma, lymphoma, and sarcoma are not included in this protocol.

Based on:

AJCC/UICC TNM, 8th edition
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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 Larynx 4.0.0.1.

Procedures Covered in this Protocol:

- Excisional biopsy
- Resection:
  - Endolaryngeal excision
  - Transoral laser excision (TLE) /Transoral laser microsurgery (TLM)
  - Supraglottic laryngectomy
  - Supracricoid laryngectomy
  - Vertical hemilaryngectomy
  - Partial laryngectomy
  - Total laryngectomy
- Neck dissection
  - Radical neck dissection (RND)
  - Modified radical neck dissection (MRND)
  - Selective neck dissection (SND)
  - Extended radical neck dissection (ERND)

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The purpose of the Protocols is to support Laboratory Personnel engaged in the macroscopic examination of cancer resection specimens. The Protocols are based on specified relevant source documents, drafted by pathologists' assistant experts, and supported by information provided by the College of American Pathologists (CAP) and the American Joint Committee on Cancer (AJCC). These Protocols are intended to serve patients by ensuring that the macroscopic examination of cancer resection specimens is compliant with CAP Cancer Protocols, the AJCC Cancer Staging Manual, and provide optimization of the pre-analytic steps necessary to promote appropriate molecular studies.

The AAPA cautions that the use of the Protocols in practice may require the use of additional considerations that are beyond the scope of the Protocols. The AAPA does not offer medical advice or diagnoses, or engage in the practice of medicine. The information provided in the Protocols is not intended or implied to be a substitute for the Laboratory Personnel's own training, professional medical opinion, diagnosis, or treatment advice. All content, including text, graphics, images and information contained in the Protocols are for the above stated purposes only. Laboratory Personnel are encouraged to confirm any information provided in these Protocols with other sources. The inclusion of a product name, organization, or service in an AAPA publication, including without limitation the Protocols, should not be construed as an endorsement of such product, organization, or service, nor is failure to include the name of a product, organization or service to be construed as disapproval.

Molecular and Immunohistochemistry Considerations:

TP53 mutations are early genetic alterations in head and neck squamous cell carcinoma (HNSCC) that are already present in (dysplastic) precursor lesions and residual cancer cells. Because a mutation in the TP53 gene often causes protein overexpression, immunohistochemistry can be utilized to identify the source of the mutated DNA (cancer cells or precursor lesions) in the surgical margins.

Epidermal growth factor receptor (EGFR) is frequently overexpressed in laryngeal squamous cell carcinoma (LSCC), mainly by a post-translational mechanism. EGFR expression retains a strong predictive value independent of treatment (surgery, chemotherapy and radiation) and adversely influences overall recurrence rate and metastasis-free survival in LSCC. At present, EGFR is the most reliable biological marker for molecular characterization, aggressiveness, and invasiveness of LSCC.

Although rare, mucosal melanoma may occur in the larynx with immunohistochemical stains including S-100, HMB-45, Melan-A, MITF and PNL-2 helping to confirm the diagnosis.

To date, there are no data linking HPV with laryngeal carcinoma, and the utility of testing for the presence of HPV in laryngeal carcinomas is unproven.

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

PROCEDURES AND GENERAL ANATOMIC CONSIDERATIONS:

- **Procedures Covered by this Protocol:**

  - Excisional biopsy
  - Resection:
    - Endolaryngeal excision*
    - Transoral laser excision (TLE) or transoral laser microsurgery (TLM)
    - Supraglottic laryngectomy
    - Supracricoid laryngectomy
    - Vertical hemilaryngectomy (specify side)
    - Partial laryngectomy
    - Total laryngectomy
  - Neck dissection (specify)
    - Radical neck dissection (RND)
    - Modified radical neck dissection (MRND)
    - Selective neck dissection (SND)
    - Extended radical neck dissection (ERND)

  *In the last two decades, increased use of nonsurgical, organ-sparing methods has been a growing practice for early and advanced laryngeal cancer. Endoscopic / microsurgery (TLM) is increasingly used and includes: subepithelial cordectomy; subligamental cordectomy; transmuscular cordectomy; total cordectomy; extended cordectomy - contralateral vocal fold and anterior commissure; extended cordectomy - arytenoid; extended cordectomy - which encompasses the subglottis; extended cordectomy - ventricle; anterior commissurectomy with bilateral anterior cordectomy.

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

  - Specify the type of specimen received:
    - Total laryngectomy
    - Partial laryngectomy
      - Hemilaryngectomy
      - Supraglottic laryngectomy
      - Supracricoid laryngectomy
      - Vertical hemilaryngectomy

  - Provide measurement of larynx in three dimensions (superior to inferior; anterior to posterior; right to left lateral) with specific subsite, (i.e., epiglottis to tracheal ring, indicating composition of the specimen).

  - Provide identification and dimensions (if appropriate) of attached structures such as tongue, thyroid gland, skin, strap muscles, neck dissection, pharynx, pyriform sinus, esophagus, nerve, internal jugular vein.
    - One random section through each available thyroid lobe and isthmus should be taken with targeting of any visible lesion.

  - Specify orientation. **

**Complex specimens should be examined and oriented with the assistance of the surgeon. Direct communication between the surgeon and pathologist is an essential component in specimen orientation and proper sectioning. A drawing or photograph of the resected specimen demonstrating the extent of the tumor and its relation to the regional anatomic structures is recommended.

- **Specimen Integrity and Adequacy:**

  - Provide an assessment of the specimen integrity.
    - Specify if the specimen is intact, disrupted, or fragmented.
    - If fragmented, provide an aggregate measurement of tissue fragments.
    - Specify if the laryngectomy specimen is open or unopened.

  - Identify and describe any defects or disruptions. *

    ** Statements should include the location of any defects in relation to surrounding anatomical structures and the tumor. Disruptions of margins must also be noted. Surgical disruptions should be differentiated from tumor breach by consultation with the surgeon and pathologist. The defect may need to be specifically identified and inked. It may be critical to determine the breach of a particular margin, especially if such a margin constitutes an increase in staging.*

TUMOR ("T" of TNM)

- **Tumor Focality, Size, and Descriptors:**

  - State if unifocal or multifocal.
  - Provide three dimensions for each tumor in cm.
  - Use descriptors for tumor (e.g., polypoid, exophytic, endophytic, sessile, ulcerated).

- **Tumor Site(s):** (*Figures 1A and 1B*)

  - Specify laterality
    - Right
    - Left
    - Midline

  - For indicating tumor location, laryngeal cancer is divided into four subtypes: supraglottic, glottic, subglottic, and transglottic.

    - Larynx, supraglottic:
      - Suprahyoid epiglottis, including tip, lingual aspect and laryngeal aspect
      - Aryepiglottic folds (specify laterality)
      - Arytenoid(s) (specify laterality)
      - Infrahyoid epiglottis
      - False vocal cords (specify laterality)
      - Ventricle

    - Larynx, glottis:
      - True vocal cord
      - Anterior commissure
      - Posterior commissure
      - With subglottic extension

    - Larynx, subglottis:
      - Extends approximately 1 cm below the level of the true vocal cord to the lower border of the cricoid cartilage

    - Larynx, transglottic
      - Represents a carcinoma that crosses the ventricles in a vertical direction arising in either the glottis or supraglottic larynx

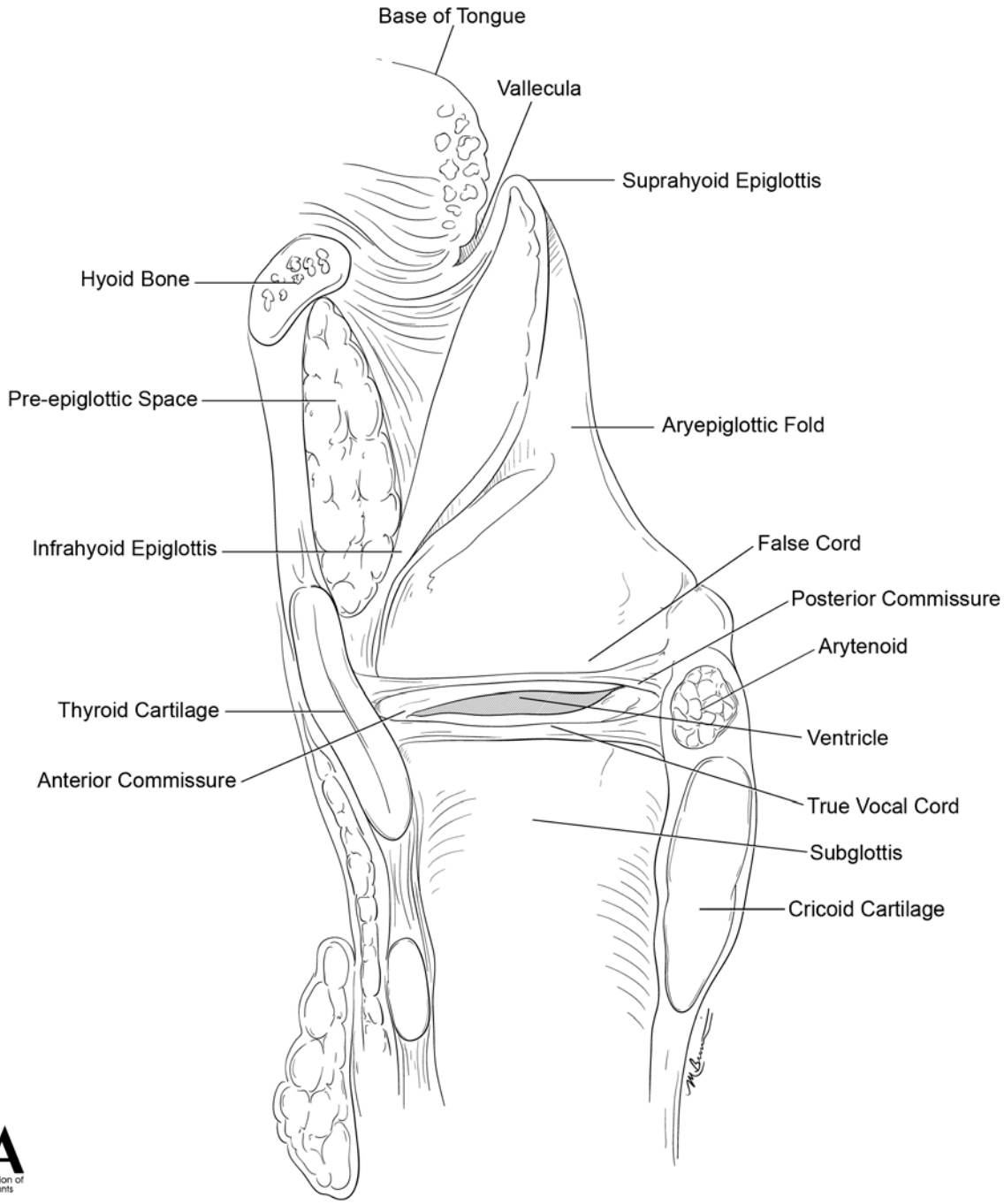


Figure 1A: Larynx Anatomy

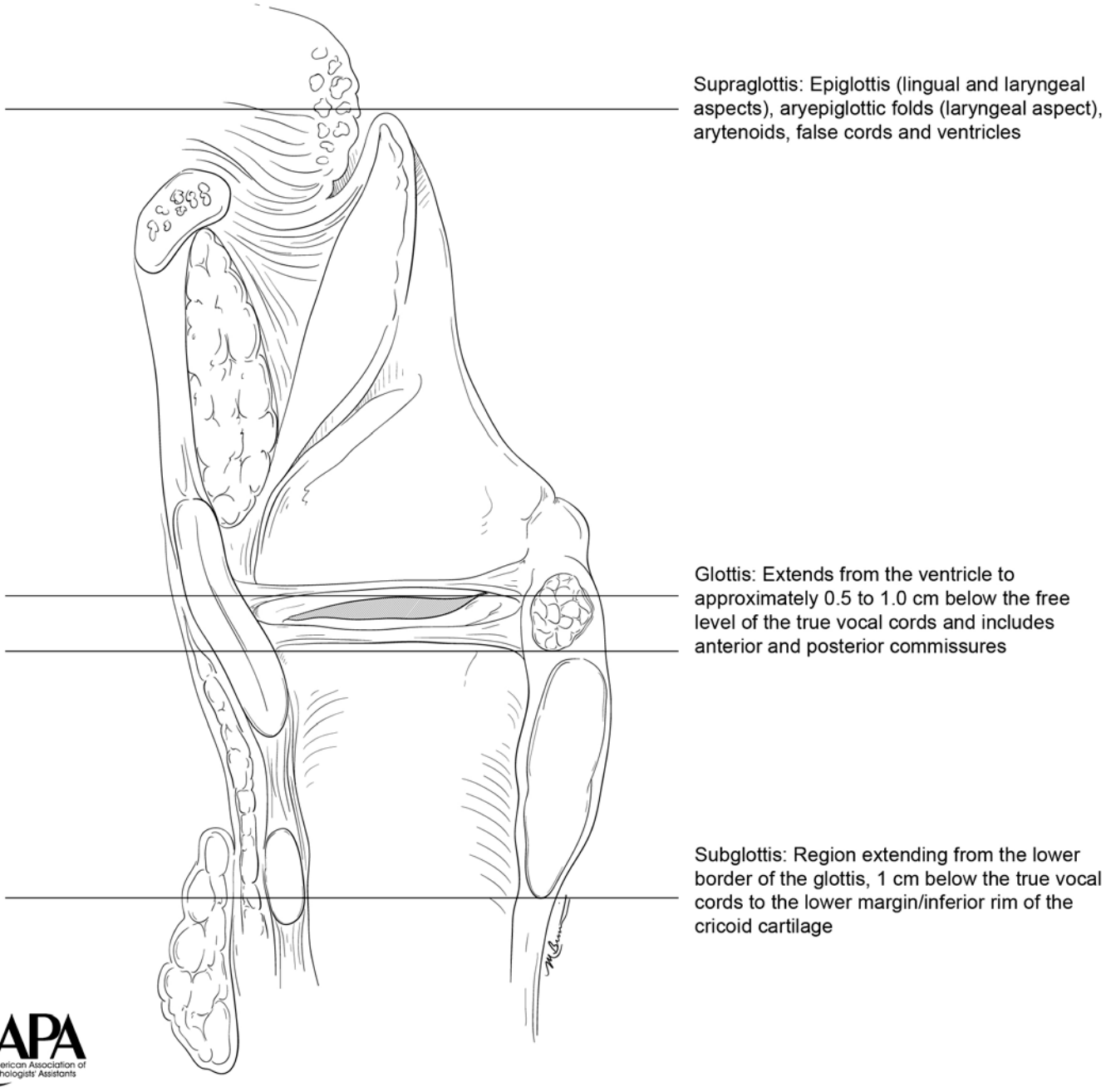


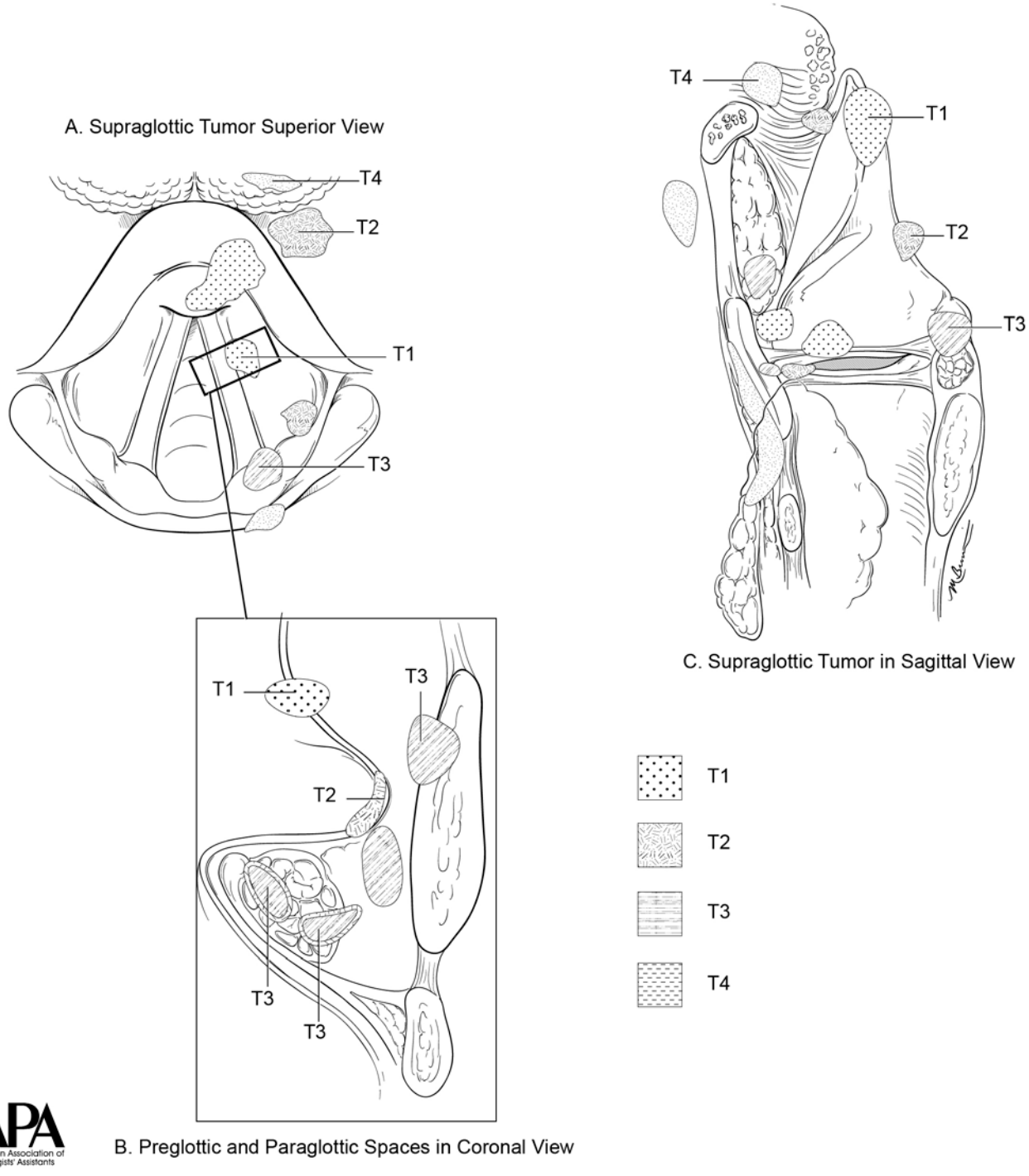
Figure 1B: Supraglottis, Glottis, Subglottis

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

  - For staging purposes, laryngeal cancer is divided into three anatomic sites: supraglottic, glottic, and subglottic.
  - For indicating tumor location, laryngeal carcinoma is divided into four subtypes: supraglottic, glottic, subglottic, and transglottic.
  - Transglottic carcinoma represents a carcinoma that crosses the ventricles in a vertical direction arising in either the glottis or supraglottic larynx.
  - Tumor invasion occurs along the lines of least resistance in potential spaces.

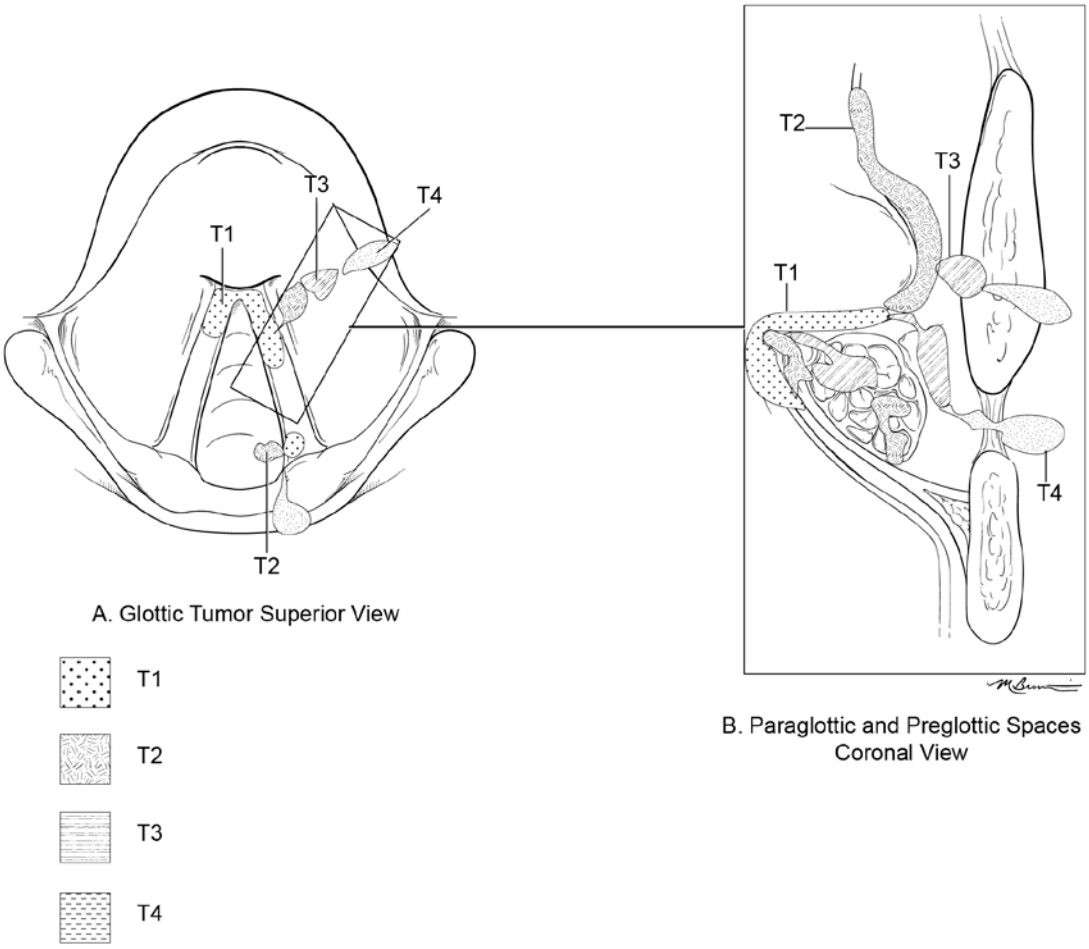
  ❖ Supraglottic cancer: (*Figures 2A, 2B, 2C)*

    - Usually remain localized.
    - Involves the structures of the supraglottic larynx, including the epiglottis, aryepiglottic folds, arytenoids, false vocal cords, and ventricles.
    - Tumor behavior is influenced by exophytic or ulcerative growth.
    - Pushing margins are generally better differentiated, exophytic, and less invasive.
      - Exophytic tumors tend to remain above the ventricle and have less mucosal spread.
    - Ulcerative tumors tend to extend inferiorly to the ventricle and thyroid cartilage.
    - Suprahyoid epiglottic tumors tend to spread to the vallecula and base of tongue.
    - Infrahyoid epiglottic tumors tend to invade the pre-epiglottic space through lacunae and anterior glottis.
    - False cord tumors usually spread upward to the epiglottis, aryepiglottic fold, and arytenoid.
    - Ventricle tumors often appear transglottic at presentation with pre-epiglottic space invasion.
    - Arytenoid and aryepiglottic fold lesions usually extend to the pyriform sinus and posterior cricoid cartilage.
    - Thyroid cartilage involvement occurs via pre-epiglottic space and paraglottic space.
    - Lymph node metastases occur in level II, III, IV.



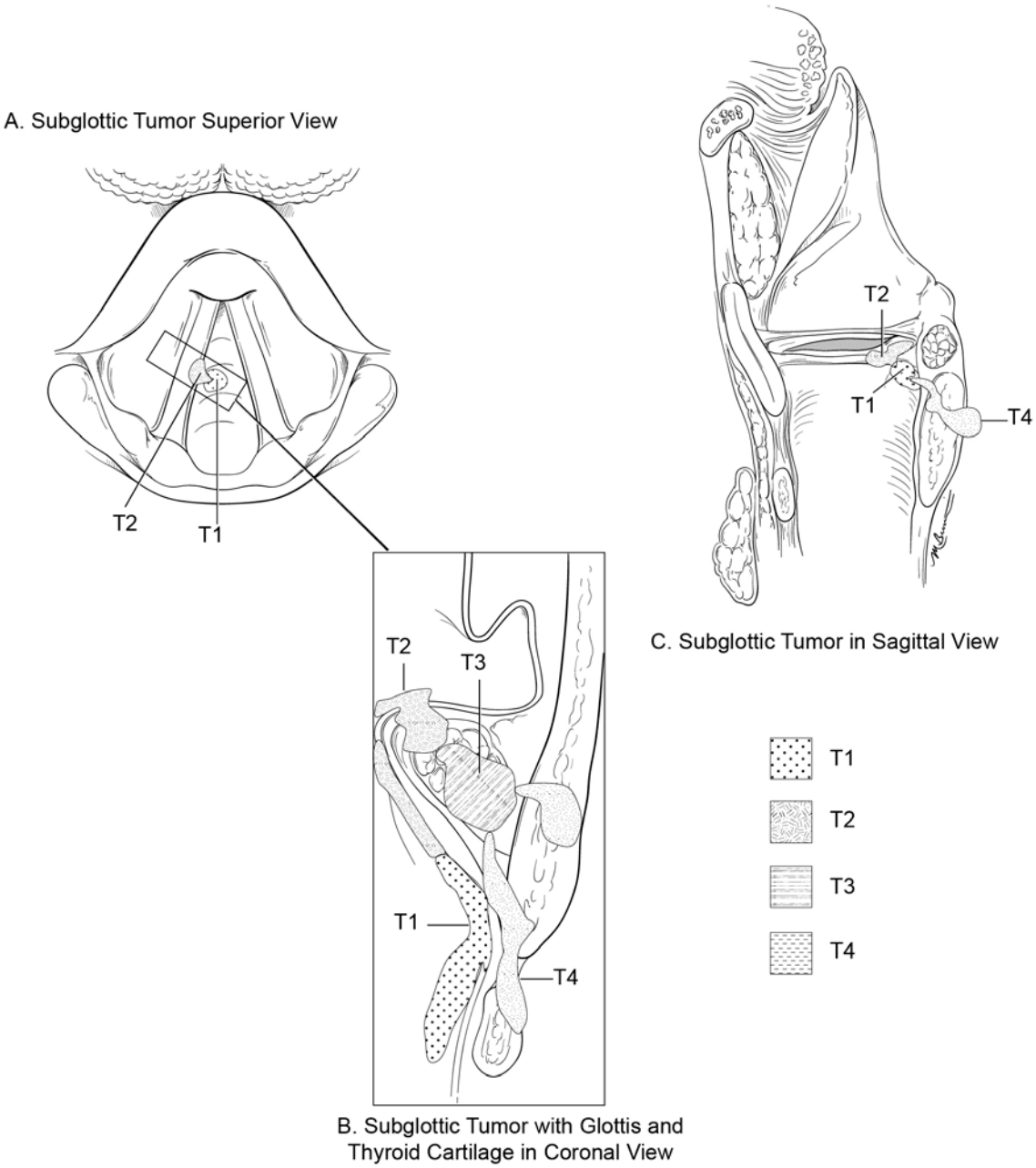
Figures 2A, 2B, 2C: Supraglottic Tumor - T1-T4 Criteria in Superior, Coronal, and Sagittal Views

- Glottic cancer: (*Figures 3A and 3B*)
  - Involves structures of the glottis, including the true vocal cords, and the anterior and posterior commissures.
  - Glottic lesion with mobile cord indicates the lesion is superficial to conus elasticus.
  - Glottic lesion with fixed cord indicates thyroarytenoidus involvement (most common), vocal process of arytenoid involvement, subglottic extension, and potential perineural spread.
  - Thyroid cartilage invasion is common in ossified parts.
  - Extralaryngeal spread occurs:
    - Anterior midline – through thyroid cartilage invasion and cricothyroid membrane.
    - Laterally – through cricothyroid space.
  - Anterior commissure lesions invade cartilage through Broyles ligament, superiorly to petiole of epiglottis, inferiorly to subglottis and cricothyroid membrane with extra-laryngeal spread
  - Nodal metastasis occurs in level II, III, IV, and Delphian (pre-tracheal node).



Figures 3A and 3B: Glottic Tumor - T1-T4 Criteria in Superior and Coronal Views

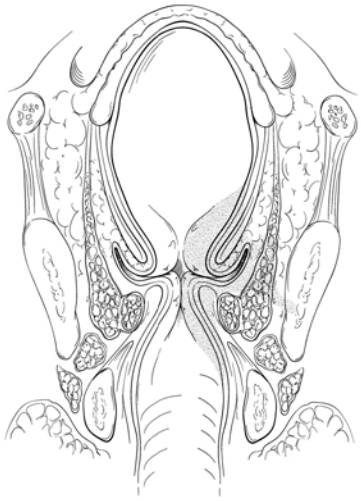
- Subglottic cancer: (*Figures 4A, 4B, 4C*)
    - Involves the subglottis beginning 1 cm below the apex of the ventricle to its inferior border represented by the rim of the cricoid cartilage.
    - Primary tumor spreads circumferentially, and commonly involves the glottis.
        - Subglottic extension of glottic cancer is more common.
    - Vocal Cord lesions extending 1 cm or more below vocal cord level have more tendency for cartilage invasion, extra-laryngeal spread, and poor prognosis.
    - Thyroid gland and pre-tracheal node involvement.



Figures 4A, 4B, 4C: Subglottic Tumor - T1-T4 Criteria in Superior, Coronal, and Sagittal Views

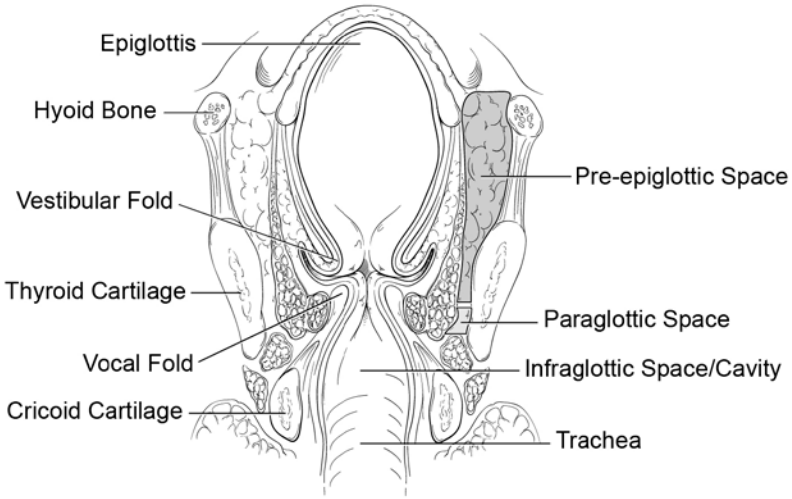
- Transglottic cancer: (*Figures 5A and 5B*)
  - Ventricular lesions that spread vertically to involve the supraglottis and the glottis.
  - Lesion invades paraglottic space, lateral part of thyroid ala, and cricothyroid membrane with extra-laryngeal invasion.
  - Often little mucosal involvement.

Figure 5A: Transglottic Cancer



Transglottic cancers cross the ventricles in a vertical direction arising in either the glottic or supraglottic larynx and spread within the paraglottic space.

Figure 5B: Pre-epiglottic Space and Paraglottic Space Relationship



- The pre-epiglottic space (PES) exists not only anterior, but also posteriolateral and inferiolateral to the epiglottis. Its posterior end is located in the anterioposterior midpoint of the thyroid lamina.
- The PES contains fat with blood vessels, lymphatics and nerve. The supraglottic tumor often spreads to neck nodes via the PES.
- The paraglottic space (PGS) is located on each side of the glottis bounded laterally by the thyroid cartilage and posteriorly by the pyriform sinus. Anteriorly, it extends into the PES. It is an important route of transglottic cancer and extralaryngeal spread.

Figures 5A and 5B

Definition of Primary Tumor (pT)

Supraglottis

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pTis	Carcinoma *in situ*
pT1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
pT2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
pT3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
pT4	Moderately advanced or very advanced
pT4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissue beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
pT4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pTis	Carcinoma *in situ*
pT1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
pT1a	Tumor limited to one vocal cord
pT1b	Tumor involves both vocal cords
pT2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
pT3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of thyroid cartilage
pT4	Moderately advanced or very advanced
pT4a	Moderately advanced local disease. Tumor invades through outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, cricoid cartilage, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
pT4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottis

pT Category	pT Criteria
pTX	Primary tumor cannot be assessed
pTis	Carcinoma *in situ*
pT1	Tumor limited to subglottis
pT2	Tumor extends to vocal cord(s) with normal or impaired mobility
pT3	Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
pT4	Moderately advanced or very advanced
pT4a	Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
pT4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Pathologic staging requires the use of all information obtained in clinical staging and in histologic study of the surgically resected specimen. Vocal cord mobility / fixation (immobility) of the larynx may only be determined clinically

TNM Classification for Mucosal Melanoma:

Mucosal melanoma is an aggressive neoplasm that calls for separate consideration. Approximately two-thirds of these lesions arise in the nasal cavity and paranasal sinuses; one quarter are found in the oral cavity and the remainder occur only sporadically in other mucosal sites of the head and neck. Even small cancers behave aggressively with advanced initial presentation, high rates of recurrence and death. To reflect this aggressive behavior, primary cancers limited to the mucosa are considered T3 lesions.

Definition of Primary Tumor (pT)

pT Category	pT Criteria
pT3	Tumor limited to the mucosa and immediately underlying soft tissue, regardless of thickness or greatest dimension; for example, polypoid nasal disease, pigmented or nonpigmented lesions of the oral cavity, pharynx, or larynx
pT4	Moderately advanced or very advanced disease
pT4a	Moderately advanced disease. Tumor involving deep soft tissue, cartilage, bone, or overlying skin
pT4b	Very advanced disease. Tumor involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures

TNM and Stage Groupings:

Of note in the 7th edition of AJCC staging of head and neck cancer is the division of T4 lesions into T4a (moderately advanced local disease) and T4b (very advanced local disease), leading to the stratification of stage IV into stage IVA (moderately advanced local/regional disease), stage IVB (very advanced local/regional disease), and stage IVC (distant metastatic disease).

Relative to supraglottic and glottic cancers, the determination between a T3 cancer with "minor thyroid cartilage erosion" versus a T4a cancer with "invasion through thyroid cartilage" can be problematic as there is no specific definition whether "invasion through thyroid cartilage" means complete infiltration through and through the cartilage or whether tumors invading short of completely through the thyroid cartilage (e.g., half way through, other) qualify as a pT4a cancer.

When confronted with this issue, review of the operative report and imaging studies, as well as direct communication with the surgeon may provide insight or consensus of opinion. Generally, if the tumor invades at least into the center of the cartilage but not "through," most authorities would stage such a lesion as a T4a cancer.

There are no significant alterations in the 8th edition of the AJCC Cancer Staging Manual to T stage of the larynx. This includes mucosal melanomas.

***TNM Descriptors**:*

For identification of special cases of TNM or pTNM classifications, the "m" suffix and "y" and "r" 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).

rTNM: The "r" prefix indicates a recurrent tumor when staged after a documented disease-free interval.

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

Residual Tumor (R) Category

The absence or presence or 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:**

  - Apply ink to the soft tissue margins and evaluate mucosal and soft tissue margins followed by sectioning of the tumor relative to cartilage/bone and soft tissue margins.

    - Transoral laser excision (TLE) or Transoral laser microsurgery (TLM) and Endolaryngeal excision:
      - If the specimen is received oriented, maintain the orientation by differentially inking the margins.
      - Measure, describe, and entirely submit, utilizing plane of sectioning and ink pattern to ensure orientation is maintained throughout processing.

    - Laryngectomies:
      - Circumferential inferior tracheal ring – en face (parallel) section.
      - Mucosal margins – en face or radial (perpendicular) sections as discussed with the pathologist.
      - If tumor is less than or equal to 5 mm from the margin, submit radial (perpendicular) margins.
      - If tumor is more than 5 mm from the margin, submit en face (parallel) margins or radial (perpendicular) sections. *
      - Mucosal margins include:
        - Right and left arytenoid area, at posterior cricoid cartilage
        - Right and left aryepiglottic fold or pyriform sinus, at lateral edge
        - Right and left anterior epiglottis, at vallecula
      - Submit soft tissue margins radially (perpendicular).

    **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.*

  - If margins are macroscopically uninvolved by tumor:
    - Specify the distance from the closest margin in mm.
    - Specify the location of the closest margin, per orientation, if possible.
    - Specify the location and distance of other close margins.

  - If margins are macroscopically involved by tumor (see note on premalignant lesions below for assistance in determining involvement of the margin by carcinoma in situ):
    - Specify the margin(s), per orientation, if possible.

Explanatory Notes:

The definition of a positive margin is somewhat controversial. Many studies support the definition of a positive margin to be invasive carcinoma or carcinoma in situ/high-grade dysplasia present at the margins. Tumors with “close” margins also carry an increased risk for local recurrence. Commonly used cut points to define close margins are 5 mm in general and 2 mm with respect to glottis larynx. Values ranging from 3 mm to 7 mm have been used with success, and for glottic tumors, as low as 1 mm.

Premalignant Lesions:

The clinical appearance of premalignant or “incipient” lesions of the mucosal surface of the upper aerodigestive tract include leukoplakia, erythroplakia, or speckled leukoplakia reflecting the presence of a white, red, or white / red lesion, respectively. Among these clinical changes, erythroplakic lesions are commonly associated with ominous histopathologic alterations, including severe dysplasia, CIS or invasive carcino-

ma. Although the risk of developing a malignancy in a leukoplakic lesion is low, there is still a risk (approximately 10-12%) of malignant transformation. Speckled leukoplakia should be viewed as a variant of erythroplakia.

LYMPH NODES ("N" of TNM)

- **Lymph Nodes:**

The status of cervical lymph nodes is the single most important factor in aerodigestive cancer. The supraglottis has a rich and bilaterally interconnected lymphatic network, and tumor commonly spreads to the deep cervical regional nodes (level IIA and III). The advanced glottic tumor may extend to level VI lymph nodes and supraglottic or subglottic regional nodes. The subglottic drainage is to the lower deep cervical nodes (level III-IV), partially via peri and paralaryngeal / tracheal nodes, and precricoid (Delphian) lymph nodes (level VI). *

* Primary laryngeal cancers have different treatment approaches based on the tumor origin site.

Definition of Regional Lymph Nodes (pN)

Pathological N (pN)

pN Category	**pN Criteria**
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph nodes 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* metastasis in a single ipsilateral lymph node, 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* metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)
pN2a	Metastasis in a single ipsilateral node, 3 cm or smaller in greatest dimension and ENE(+); *or* metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
pN2b	Metastases in multiple ipsilateral lymph 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(-)
pN3	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(-); *or* metastasis in a single ipsilateral node, larger than 3 cm in greatest dimension and ENE(+); *or* metastases in multiple ipsilateral, contralateral, or bilateral lymph nodes and 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* metastases in multiple ipsilateral, contralateral, or bilateral lymph nodes and any with ENE(+); *or* a single contralateral node of any size and ENE(+)

Note: 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 in lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(-) or ENE(+).

Note: Metastases at level VII are considered regional lymph node metastases. Midline nodes are considered ipsilateral nodes.

Definition of Regional Lymph Node for Mucosal Melanoma (pN)

pN Category	pN Criteria
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastases
pN1	Regional lymph node metastases present

Regional Lymph Nodes Submission:

Macroscopically positive:

- Count and submit representative sections of all macroscopically positive lymph nodes.
- Specify the location of the lymph node (if known).
- Measure the lymph nodes in three dimensions.
- Section the lymph node along the long axis.
- Take steps to ensure that an accurate lymph node count can be rendered.
- Additional sections should be submitted to assess for extranodal extension. *
- 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.

**Extranodal extension is metastatic tumor present within the confines of the lymph node that extends through the lymph node capsule into the surrounding connective tissue. The 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.*

Macroscopically negative:

- Count and submit macroscopically negative or equivocal smaller nodes in toto and larger nodes entirely.
- Specify the location of lymph node (if known).
- Measure the lymph nodes in three dimensions.
- Section the lymph nodes along the long axis.
- Take steps to ensure that an accurate lymph node count can be rendered.

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

Non-regional lymph nodes:

Lymph node groups removed from areas such as scalene, suboccipital, and

retropharyngeal should be identified. The above procedure may be employed for more distant level lymph nodes.

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.

The presence of matting is an indication of extranodal extension and correspondingly increases the N stage and carries a poor prognosis. If a single mass of less than 3 cm positive lymph nodes consists of several matted nodes, the N stage is considered pN2b and not pN1. A 6 cm mass consisting of multiple matted nodes is considered pN2b and not pN3.

If matted lymph nodes invade the strap muscle, nerve, or internal jugular vessel, provide distances of tumor with involved structures and resection margins.

In a previously treated patient, lymph nodes appearing macroscopically positive may be fibrotic or cystic without gross tumor. A generous sampling is recommended to detect microscopic metastasis.

Regional Lymph Node (pN0): Isolated Tumor Cells

Isolated tumor cells (ITCs) are single cells or small clusters of cells ≤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. Evidence for the validity of this practice in head and neck squamous cell carcinoma and other histologic subtypes is lacking. Only rare studies relevant to head and neck sites indicate that isolated tumor cells, may be a poor prognostic indicator in terms of local control.

Classification of Neck Dissection:

- Radical neck dissection
  Includes 22 or more lymph nodes
- Modified radical neck dissection, internal jugular vein and/or sternocleidomastoid muscle spared
  Includes 15 or more lymph nodes
- Selective neck dissection (SND), as specified by surgeon, defined by dissection of less than the 5 traditional levels of a radical and modified radical neck dissection
  Includes 15 or more lymph nodes
  - Supraomohyoid neck dissection
  - Posterolateral neck dissection
  - Lateral neck dissection
  - Central compartment neck dissection
- Superselective neck dissection (SSND), defined by dissection of the fibrofatty elements of 2 levels or less
- Extended radical neck dissection, as specified by the surgeon

For purposes of pathologic evaluation, lymph nodes are organized by levels. *(Figure 6)*

Deep cervical lymph node groups, boundaries & primary tumor sites:

Level I. Submental Group (Sublevel IA)
Lymph nodes within the triangular boundary of the anterior belly of the digastric muscles and the hyoid bone. Harboring metastasis of mouth, anterior tongue, anterior mandible alveolar ridge, and lower lip.

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. Metastases from the oral cavity, anterior nasal cavity, skin, and soft tissue structures of the mid face and submandibular area.

Level II. Upper Jugular Groups (Sublevels IIA and IIB)
Lymph nodes located around the upper third of the internal jugular vein and adjacent spinal accessory nerve extending from the level of the carotid bifurcation (surgical landmark) or hyoid bone (clinical landmark) to the skull base. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the stylohyoid muscle. The spinal accessory nerve traveling obliquely across this area and subdivides this group into IIA and IIB: IIA- superior-posterior to the nerve; IIB- inferior- anterior to the nerve. This group has greater risk of harboring metastatic nodes from primary tumors of oral cavity, nasal cavity, nasopharynx, oropharynx and hypopharynx, larynx, and parotid gland.

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. This group has greater risk of harboring metastatic nodes from the oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, and larynx.

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. This group most commonly harbors metastasis arising from cancers of the hypopharynx, thyroid, cervical esophagus, and larynx.

Level V. Posterior triangle (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. This level is also subdivided by a plane defined by the inferior border of cricoid cartilage into level VA superiorly and level VB inferiorly. This group has greater risk of harboring metastatic nodes from cancers that originate from the nasopharynx, oropharynx, and posterior scalp and neck.

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. Lymph nodes in the

central compartment are not routinely excised in radical neck dissections; however, they are removed for thyroid, laryngeal, and hypopharyngeal cancer.

Level VII. Superior Mediastinal Lymph Nodes
Lymph nodes between the carotid arteries from the suprasternal notch superiorly to the innominate vein inferiorly. It includes pre-tracheal, para-tracheal, and esophageal groove lymph nodes. This group has greater risk of harboring metastatic nodes from cancers that originate in the thyroid and esophagus.

Metastases at level VII are considered regional lymph node metastases; all other mediastinal lymph node metastases are considered distant metastases.

Other Lymph Nodes
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. When staging lymph node involvement by metastases from nasopharyngeal carcinoma, the supraclavicular fossa refers to a triangular region, the base of which is the superior margin of the clavicle between its sternal and lateral ends, and the apex of which is the point where the neck meets the shoulder. This includes caudal portions of Levels IV and V.

Note:
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*

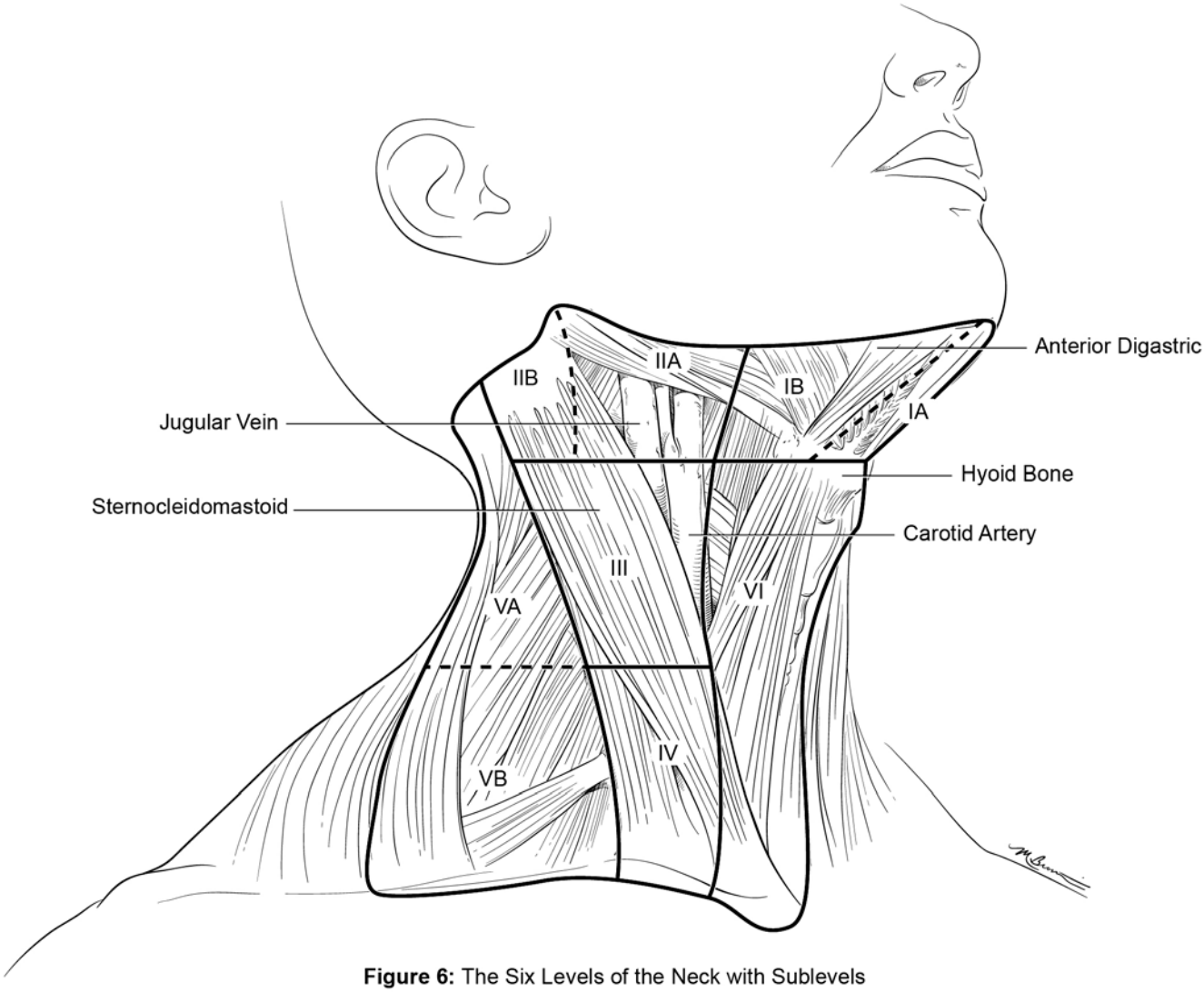


Figure 6: The Six Levels of the Neck with Sublevels

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 (pM) (required only if confirmed pathologically)

pM Category	pM Criteria
M0	No distant metastasis
pM1	Distant metastasis

- Specify site of distant metastasis if known.
- Distant spread is common for patients who have bulky regional lymphadenopathy.
- Mediastinal lymph node metastases are considered distant metastases except level VII lymph nodes (anterior superior mediastinum, cephalad to the innominate artery).
- When distant metastases occur, spread to the lungs is most common; skeletal or hepatic metastases occur less often.

Mucosal Melanoma:

pM Category	pM Criteria
M0	No distant metastasis
pM1	Distant metastasis present

- Specify site of distant metastasis if known.

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