COLLEGE of AMERICAN PATHOLOGISTS

# Protocol for the Examination of Specimens from Patients with Cancers of the Oral Cavity

**Version:** 4.3.0.0
**Protocol Posting Date:** April 2026

**CAP Laboratory Accreditation Program Protocol Required Use Date:** January 2027
The changes included in this current protocol version affect accreditation requirements. The new deadline for implementing this protocol version is reflected in the above accreditation date.

**For accreditation purposes, this protocol should be used for the following procedures AND tumor types:**

| Procedure | Description |
|---|---|
| Resection | Includes specimens designated wet (mucosal) lip and tongue |
| **Tumor Type** | **Description** |
| Carcinoma | Includes squamous cell carcinoma and neuroendocrine carcinoma |

**This protocol is NOT required for accreditation purposes for the following:**

| Procedure |
|---|
| Biopsy |
| Primary resection specimen with no residual cancer (e.g., following neoadjuvant therapy) |
| Cytologic specimens |
| Squamous cell carcinoma in situ (Tis) |

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

| Tumor Type |
|---|
| Sarcoma (consider the Bone or Soft Tissue protocol) |
| Carcinomas of dry vermillion lip (consider Cutaneous Head and Neck Squamous Cell Carcinoma protocol) |
| Hematologic malignancies (consider the Precursor and Mature Lymphoid Malignancies, Myeloid and Mixed / Ambiguous Lineage Neoplasms, and Plasma Cell Malignancies protocols) |
| Mucosal melanoma (consider the Head and Neck Mucosal Melanoma protocol) |
| Salivary glands (consider the Salivary Gland Cancer protocol) |

## Version Contributors

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## Glossary:

**Author:** Expert who is designated by the chair of the Cancer Committee.
**Expert Panel Contributors:** Includes members of other CAP committees or external subject matter experts who contribute to the current version of the protocol.

**Accreditation Requirements**
Synoptic reporting with core and conditional data elements for designated specimen types* is required for accreditation.

- Data elements designated as core must be reported.
- Data elements designated as conditional only need to be reported if applicable.
- Data elements designated as optional are identified with "+". Although not required for accreditation, they may be considered for reporting.

This protocol is not required for recurrent or metastatic tumors resected at a different time than the primary tumor. This protocol is also not required for pathology reviews performed at a second institution (i.e., second opinion and referrals to another institution).

Full accreditation requirements can be found on the CAP website under Accreditation Checklists.
A list of core and conditional data elements can be found in the Summary of Required Elements under Resources on the CAP Cancer Protocols website.
**Includes definitive primary cancer resection and pediatric biopsy tumor types.*

**Synoptic Reporting**
All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired Data element: Response format is NOT considered synoptic.
- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including "Cannot be determined" if appropriate.
- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable
- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location
- Organizations and pathologists may choose to list the required elements in any order, use additional methods in order to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

**Summary of Changes**

**v 4.3.0.0**

- Updates to cover page, content, and explanatory notes reflecting the separation of select Head and Neck protocols
- Tumor Site and Histologic Type question updates
- Removal of Grade / Intrinsic Biologic Potential question, ADDITIONAL FINDINGS section, and optional elements for reporting special studies
- Separation of “Intraparotid” and “Periparotid” terms to Nodal Site(s) with Tumor question
- Laterality of Lymph Nodes(s) with Tumor, Size of Largest Nodal Metastatic Deposit, Extranodal Extension (ENE) questions changed from conditionally required to required (core)
- Clarification of Tumor Bed margin Status for Non-invasive Tumor to include new parenthetical statement (High-grade Dysplasia / Carcinoma In Situ)
- Modification to pTNM Classification pT, pN, and pM categories to remove mucosal melanoma staging and make minor typographical updates

## Reporting Template

**Protocol Posting Date:** April 2026
**Select a single response unless otherwise indicated.**
**CASE SUMMARY: (ORAL CAVITY)**
**Standard(s)**: AJCC 8

**SPECIMEN**

**Procedure (select all that apply)**
___ Excision
___ Glossectomy (specify): _____
___ Buccal mucosal resection (specify): _____
___ Mandibulectomy (specify): _____
___ Maxillectomy (specify): _____
___ Palatectomy
___ Neck (lymph node) dissection (specify): _____
___ Other (specify): _____
___ Not specified

**TUMOR**

**Multiple Primary Sites (e.g., lower gingiva and floor of mouth) (required only if applicable)#**
*# Please complete a separate checklist for each primary site*
___ Not applicable (no additional primary site(s) present)
___ Present: _____

**Tumor Focality**
___ Unifocal
___ Multifocal: _____
___ Cannot be determined (explain): _____

**Tumor Site(s) (Note A) (select all that apply)**
___ Wet mucosa of upper lip
___ Wet mucosa of lower lip
___ Wet mucosa of lip, NOS
___ Lateral border of tongue
___ Ventral surface of tongue
___ Dorsal surface of tongue
___ Anterior two-thirds of tongue
___ Tongue, NOS
___ Upper gingiva
___ Lower gingiva
___ Gingiva, NOS
___ Anterior floor of mouth
___ Lateral floor of mouth
___ Hard palate

___ Buccal mucosa
___ Vestibule of mouth, maxillary
___ Vestibule of mouth, mandibular
___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not specified

**Tumor Laterality (select all that apply)**
___ Right
___ Left
___ Midline
___ Not specified

**Tumor Size (Note B)**
___ Greatest dimension in Centimeters (cm): _____ cm
___ Cannot be determined (explain): _____

**Histologic Type (Note C)**
*Squamous Cell Carcinoma and Subtypes*
___ Squamous cell carcinoma and subtypes
*Select all that apply*
___ Squamous cell carcinoma, conventional [keratinizing]
___ Squamous cell carcinoma, non-keratinizing
___ Adenosquamous carcinoma
___ Basaloid squamous cell carcinoma
___ Acantholytic squamous cell carcinoma
___ Papillary squamous cell carcinoma
___ Spindle cell [sarcomatoid] squamous carcinoma
___ Verrucous carcinoma
___ Carcinoma cuniculatum
___ Lymphoepithelial carcinoma [non-nasopharyngeal]
*Neuroendocrine*
___ Neuroendocrine tumor, grade 1
___ Neuroendocrine tumor, grade 2
___ Neuroendocrine tumor, grade 3
___ Neuroendocrine carcinoma, small cell type
___ Neuroendocrine carcinoma, large cell type
___ Combined (or composite) neuroendocrine carcinoma
**Type of Combined Histology# (select all that apply)**
*# Please note that the user must select at least one neuroendocrine type and at least one carcinoma type from the list below.*
___ Squamous cell carcinoma: _____
___ Adenocarcinoma: _____
___ Neuroendocrine carcinoma, small cell type
___ Neuroendocrine carcinoma, large cell type
___ Other (specify): _____
*Other*
___ Other histologic type not listed (specify): _____

___ Carcinoma, type cannot be determined: _____

**+Histologic Type Comment: _____**

**Histologic Grade (required only if applicable)# (Note D)**
*# Required only for squamous cell carcinoma and subtypes*
___ Not applicable
___ G1, well-differentiated
___ G2, moderately differentiated
___ G3, poorly differentiated
___ Other (specify): _____
___ GX, cannot be assessed: _____

**Tumor Depth of Invasion (DOI) (Note B)**
___ Specify depth in Millimeters (mm): _____ mm
___ At least in Millimeters (mm): _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined (explain): _____

**Tumor Extent (specify other structures involved) (required only if pT defined elements are applicable): _____**

**Lymphatic and / or Vascular Invasion**
___ Not identified
___ Present: _____
___ Cannot be determined (explain): _____

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

**+Worst Pattern of Invasion (WPOI) (Note F)**
___ WPOI 5
___ WPOI 1-4

**+Tumor Comment: _____**

**MARGINS (Note G)**

**Specimen Margin Status for Invasive Tumor**

___ All specimen margins negative for invasive tumor

**Distance from Invasive Tumor to Closest Specimen Margin**

*Specify in Millimeters (mm)*

___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined (explain): _____

**Closest Specimen Margin(s) to Invasive Tumor**

___ Specify location(s) of closest specimen margin(s): _____
___ Cannot be determined (explain): _____

**+Other Close Specimen Margin(s) to Invasive Tumor**

___ Specify location(s) and distance(s) of other close specimen margin(s): _____
___ Cannot be determined: _____

___ Invasive tumor present at specimen margin(s)

**Specimen Margin(s) Involved by Invasive Tumor (per orientation)**

___ Specify involved specimen margin(s): _____
___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____
___ Not applicable

**Specimen Margin Status for Non-invasive Tumor (High-grade Dysplasia / Carcinoma In Situ) (required only if applicable)#**

*# Specimen margin status for non-invasive tumor is required only for squamous cell carcinoma when closer than invasive tumor.*

___ Not applicable
___ All specimen margins negative for non-invasive tumor

**+Distance from Non-invasive Tumor to Closest Specimen Margin**

*Specify in Millimeters (mm)*

___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____

**+Closest Specimen Margin(s) to Non-invasive Tumor (use orientation when provided)**

___ Specify closest specimen margin(s): _____
___ Cannot be determined: _____

___ High-grade dysplasia / in situ disease present at specimen margin

**Specimen Margin(s) Involved by Non-invasive Tumor (per orientation)**

___ Specify involved specimen margin(s): _____
___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

**Tumor Bed Margin Status (separately submitted) (required only if applicable)#**
*# Applicable only to squamous cell carcinoma and its histologic subtypes.*
___ Not applicable
___ Tumor bed margins assessed

**Tumor Bed Margin Orientation**
___ Oriented to true margin surface
___ Unoriented to true margin surface
___ Cannot be determined (explain): _____

**Tumor Bed Margin Status for Invasive Tumor**
___ All tumor bed margins negative for invasive tumor
**+Distance from Invasive Tumor to True Margin Surface (pertinent to oriented specimens which are sectioned perpendicularly)**
*Specify in Millimeters (mm)*
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
___ Invasive tumor present at tumor bed margin(s)
**Tumor Bed Margin(s) Involved by Invasive Tumor (per part labeling)**
___ Specify involved tumor bed margin(s): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

**Tumor Bed Margin Status for Non-invasive Tumor (High-grade Dysplasia / Carcinoma In Situ) (required only if applicable)#**
*# Margin status for non-invasive tumor is required only for squamous cell carcinoma when closer than invasive tumor*
___ Not applicable
___ All tumor bed margins negative for high-grade dysplasia / in situ disease
**+Distance from Non-invasive Tumor to True Margin Surface (pertinent to oriented specimens which are sectioned perpendicularly)**
*Specify in Millimeters (mm)*
___ Exact distance: _____ mm
___ Greater than: _____ mm
___ Less than 1 mm
___ Other (specify): _____
___ Cannot be determined: _____
___ High-grade dysplasia / in situ disease present at tumor bed margins
**Tumor Bed Margin(s) Involved by Non-invasive Tumor (per orientation)**
___ Specify involved tumor bed margin(s): _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

___ Other (specify): _____
___ Cannot be determined (explain): _____

**+Margin Comment: _____**

**REGIONAL LYMPH NODES (Note H)**

**Regional Lymph Node Status**
___ Not applicable (no regional lymph nodes submitted or found)
___ Regional lymph nodes present
___ All regional lymph nodes negative for tumor
___ Tumor present in regional lymph node(s)

**Number of Lymph Nodes with Tumor**
___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

**Laterality of Lymph Node(s) with Tumor**
___ Ipsilateral (including midline): _____
___ Contralateral: _____
___ Bilateral: _____
___ Cannot be determined (explain): _____

**+Nodal Site(s) with Tumor (select all that apply)**
___ Intraparotid: _____
___ Periparotid: _____
___ Level I: _____
___ Level II: _____
___ Level III: _____
___ Level IV: _____
___ Level V: _____
___ Other (specify): _____
___ Cannot be determined: _____

**Size of Largest Nodal Metastatic Deposit**
*Specify in Centimeters (cm)*
___ Exact size: _____ cm
___ At least (specify): _____ cm
___ Greater than: _____ cm
___ Less than: _____ cm
___ Other (specify): _____
___ Cannot be determined (explain): _____

**Extranodal Extension (ENE) (Note H)**
___ Not identified
___ Present

**+Distance of ENE from Lymph Node Capsule**
*Specify in Millimeters (mm)*
___ Exact distance: _____ mm

___ Greater than 2 mm (major ENE)
___ Less than or equal to 2 mm (minor ENE)
___ Less than 1 mm (minor ENE)
___ Other (specify): _____
___ Cannot be determined: _____
___ Cannot be determined (explain): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

**Number of Lymph Nodes Examined**

___ Exact number (specify): _____
___ At least (specify): _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

**+Regional Lymph Node Comment: _____**

**DISTANT METASTASIS**

**Distant Site(s) Involved, if applicable (select all that apply)**

___ Not applicable
___ Lung: _____
___ Bone: _____
___ Brain: _____
___ Liver: _____
___ Other (specify): _____
___ Cannot be determined (explain): _____

**pTNM CLASSIFICATION (AJCC 8th Edition) (Note I)**

*Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.*

**Modified Classification (required only if applicable) (select all that apply)**

___ Not applicable
___ y (post-neoadjuvant therapy)
___ r (recurrence)

**pT Category**

*DOI is depth of invasion and not tumor thickness*

___ pT not assigned (cannot be determined based on available pathological information)
___ pTis: Carcinoma in situ
___ pT1: Tumor less than or equal to 2 cm with depth of invasion (DOI) less than or equal to 5 mm
___ pT2: Tumor less than or equal to 2 cm with DOI greater than 5 mm or tumor greater than 2 cm and less than or equal to 4 cm with DOI less than or equal to 10 mm
___ pT3: Tumor greater than 2 cm and less than or equal to 4 cm with DOI greater than 10 mm or tumor greater than 4 cm with DOI less than or equal to 10 mm

*pT4: Moderately advanced or very advanced local disease*

*# Superficial erosion of bone / tooth socket (alone) by gingival primary is not sufficient to classify a tumor as T4*

___ pT4a: Moderately advanced local disease. Tumor greater than 4 cm with DOI greater than 10 mm or tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face)#

___ pT4b: Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base, and / or encases internal carotid artery

___ pT4 (subgroup cannot be determined)

**T Suffix (required only if applicable)**

___ Not applicable

___ (m) multiple primary synchronous tumors in a single organ

**pN Category# (Note H)**

*# Midline nodes are considered ipsilateral nodes*
*Pathological ENE should be recorded as ENE(−) or ENE(+)*
*Measurement of the metastatic focus in the lymph nodes is based on the largest metastatic deposit size, which may include matted or fused lymph nodes*

___ pN not assigned (no nodes submitted or found)

___ pN not assigned (cannot be determined based on available pathological information)

___ pN0: No regional lymph node metastasis

___ pN1: Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)

*pN2: Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); OR larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); OR metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); OR in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)*

___ pN2a: Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); OR a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)

___ pN2b: Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)

___ pN2c: Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-)

___ pN2 (subgroup cannot be determined)

*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 multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); OR a single contralateral node of any size and ENE(+)*

___ pN3a: Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-)

___ pN3b: Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); OR multiple ipsilateral, contralateral or bilateral nodes any with ENE(+); OR a single contralateral node of any size and ENE(+)

___ pN3 (subgroup cannot be determined)

**pM Category (required only if confirmed pathologically)**

___ Not applicable - pM cannot be determined from the submitted specimen(s)

___ pM1: Microscopic confirmation of distant metastasis

**SPECIAL STUDIES**

*For reporting molecular testing and other cancer biomarker testing results, the CAP Head and Neck Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.*

**COMMENTS**

**Comment(s): _____**

## Explanatory Notes

**A. Anatomic Tumor Site(s)**

**Anatomic Tumor Site(s) for Oral Cavity**[1]

- Mucosa of wet upper and lower lips
- Buccal mucosa
  - Cheek mucosa
  - Retromolar areas
- Upper alveolus and gingiva (upper gum)
- Lower alveolus and gingiva (lower gum)
- Hard palate
- Tongue
  - Dorsal surface and lateral borders anterior to circumvallate papillae (anterior two-thirds)
  - Inferior (ventral) surface
- Floor of mouth

The protocol applies to all carcinomas arising at these sites.

**Mucosal Lip**. The mucosal lip begins at the junction of the wet and dry mucosa of the lip (the anterior border of the portion of the lip that comes into contact with the opposed lip) and extends posteriorly into the oral cavity to the attached gingiva of the alveolar ridge. For staging purposes, tumors of the dry vermilion lip and vermilion border are now grouped with cutaneous sites given their shared pathogenesis and similar embryologic origin of these subsites to skin; only mucosal sites are covered by this protocol.

**Buccal Mucosa (Inner Cheek)**. This includes all the membrane lining of the inner surface of the cheeks and lips from the line of contact of the opposing lips to the line of attachment of mucosa of the alveolar ridge (upper and lower) and pterygomandibular raphe.

**Lower Alveolar Ridge**. This refers to the mucosa overlying the alveolar process of the mandible, which extends from the line of attachment of mucosa in the buccal gutter to the line of free mucosa of the floor of the mouth. Posteriorly it extends to the ascending ramus of the mandible.

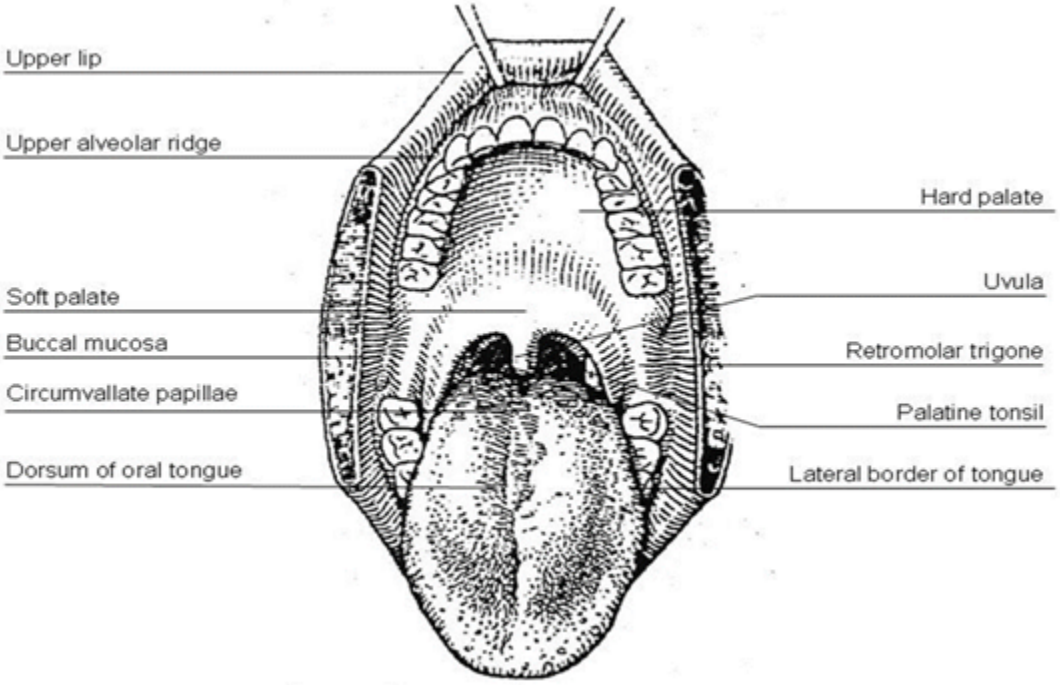
**Upper Alveolar Ridge**. This refers to the mucosa overlying the alveolar process of the maxilla, which extends from the line of attachment of mucosa in the upper gingival buccal gutter to the junction of the hard palate. Its posterior margin is the upper end of the pterygopalatine arch.

**Retromolar Gingiva (Retromolar Trigone).** This is the attached mucosa overlying the ascending ramus of the mandible from the level of the posterior surface of the last molar tooth and the apex superiorly, adjacent to the tuberosity of the maxilla.

**Floor of the Mouth.** This is a semilunar space over the myelohyoid and hypoglossus muscles, extending from the inner surface of the lower alveolar ridge to the undersurface of the tongue. Its posterior boundary is the base of the anterior pillar of the tonsil. It is divided into 2 sides of the submaxillary and sublingual salivary glands.

**Hard Palate.** This is the semilunar area between the upper alveolar ridge and the mucous membrane covering the palatine process of the maxillary palatine bones. It extends from the inner surface of the superior alveolar ridge to the posterior edge of the palatine bone.

**Anterior Two-Thirds of the Tongue (Oral Tongue).** This is the freely mobile portion of the tongue that extends anteriorly from the line of circumvallate papillae to the undersurface of the tongue at the junction of the floor of the mouth. It is composed of 4 areas: the tip, the lateral borders, the dorsum, and the undersurface (non-villous ventral surface of the tongue).



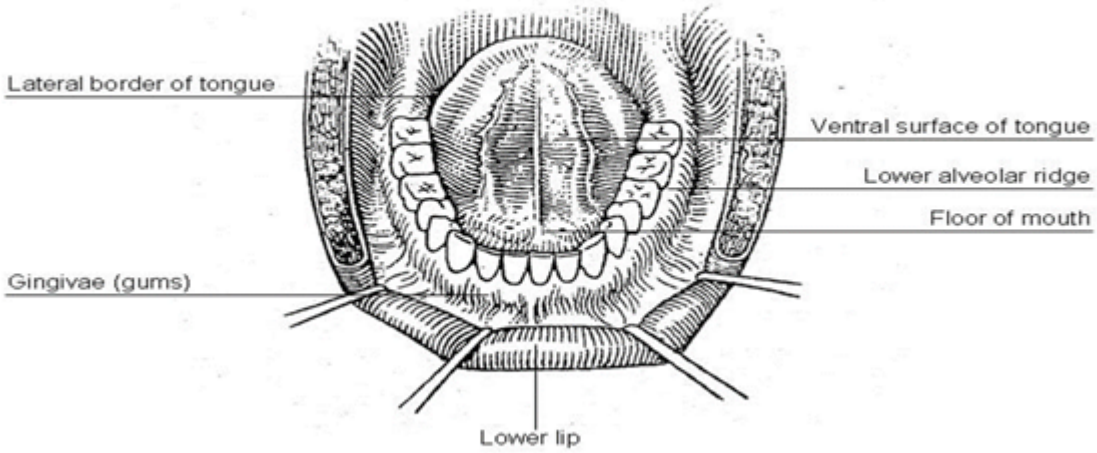



**Figure 1.** Diagrams illustrating the oral cavity anatomic subsites. Figure courtesy of Beth Israel Medical Center, St. Luke's and Roosevelt Hospitals, New York.

References

1. Ridge JA, Lydiatt WM, Patel SG, et al. Oral Cavity. In: Amin MB, ed. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017.

**B. Tumor Thickness/Depth of Invasion**

The microscopic measurement of tumor thickness or depth of invasion (DOI) has long been considered a valuable parameter for predicting regional nodal involvement and survival in oral cavity squamous cell carcinoma.[1,2] Proper gross techniques (avoidance of tangential cuts and serial sectioning of the lesion at 2-3 mm intervals) will facilitate subsequent microscopic assessment. Thickness and DOI have slight differences,[2] though from a practical standpoint T category discordance based on thickness vs DOI occurs in only 5-6% of cases.[3,4,5] Thus, if DOI is not possible on a given specimen, thickness is a reasonable surrogate. Thickness is usually measured from the mucosal surface of the tumor to the deepest point of tissue invasion in a perpendicular fashion with an optical micrometer or transparent ruler overlaid on the slide, while DOI is measured from the basement membrane of adjacent normal to the deepest point of invasion of the tumor. AJCC 8th edition now uses DOI for T classification[6] and a basic approach is outlined in Figures 2, A and B. Given the uneven contour of the surface of many oral cancers, a more nuanced methodology utilizing an 'arcuate plumb line' methodology to account for this is now advocated.[3,4] Prior biopsy may alter assessment of DOI as well, particularly for T1 tumors. Thus, when available, biopsy findings may be integrated with the final DOI determination on resection.[3] It is recognized that exophytic tumors are not particularly amenable to DOI determination, and doing so may result in a 'negative DOI'. However, there is no data-driven solution to this problem currently. In such cases, selecting 'less than 1 millimeter' is appropriate.

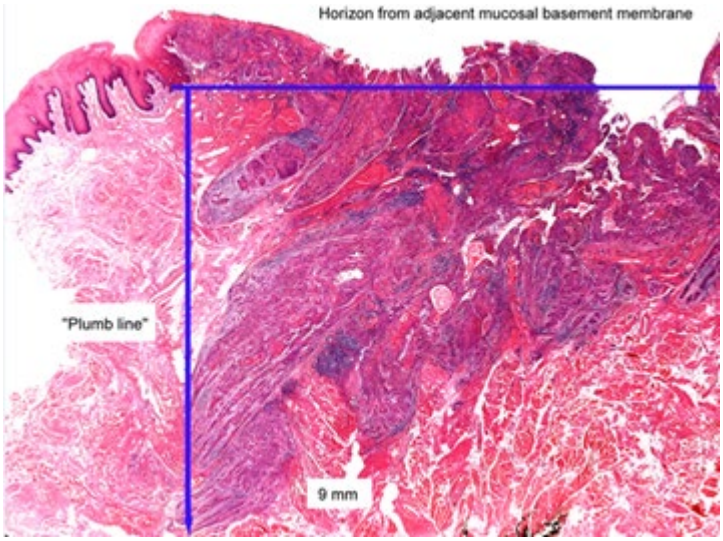



**Figure 2, A.** Depth of invasion (DOI). The horizon is established at the level of the basement membrane relative to the closest intact squamous mucosa. The greatest DOI is measured by dropping a "plumb line" from the horizon. From *AJCC Cancer Staging Manual.* 8th ed. New York: Springer; 2017. © American Joint Committee on Cancer. Reproduced with permission.

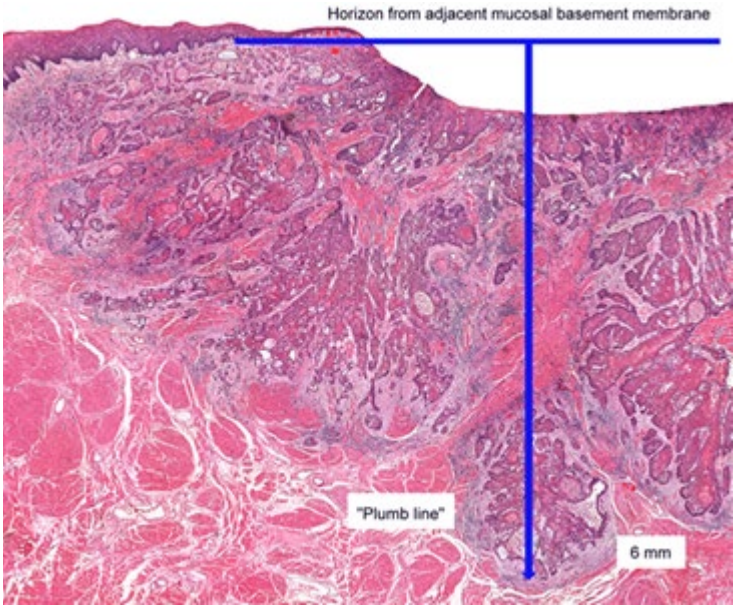



**Figure 2, B.** Depth of invasion (DOI) in an ulcerated carcinoma. Notice how "tumor thickness" would be deceptively thinner than DOI. From *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017. © American Joint Committee on Cancer. Reproduced with permission.

References

1. Pentenero M, Navone R, Motta F, et al. Clinical features of microinvasive stage I oral carcinoma. *Oral Dis*. 2011;17(3):298-303.
2. Ebrahimi A, Gil Z, Amit M. International Consortium for Outcome Research (ICOR) in Head and Neck Cancer. Primary tumor staging for oral cancer and a proposed modification incorporating depth of invasion: an international multicenter retrospective study. *JAMA Otolaryngol Head Neck Surg.* 2014;140(12):1138-1148.
3. Berdugo J, Thompson LDR, Purgina B, et al.Measuring Depth of Invasion in Early Squamous Cell Carcinoma of the Oral Tongue: Positive Deep Margin, Extratumoral Perineural Invasion, and Other Challenges. *Head Neck Pathol.* 2019 Jun;13(2):154-161.
4. Salama AM, Valero C, Katabi N, et al. Depth of invasion versus tumour thickness in early oral tongue squamous cell carcinoma: which measurement is the most practical and predictive of outcome? *Histopathology*. 2021 Sep;79(3):325-337.
5. Dirven R, Ebrahimi A, Moeckelmann N, et al. Tumor thickness versus depth of invasion - Analysis of the 8th edition American Joint Committee on Cancer Staging for oral cancer. *Oral Oncol.* 2017 Nov; 74:30-33.
6. Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In: Amin MB, ed. *AJCC Cancer Staging Manual.* 8th ed. New York, NY: Springer; 2017.

**C. Histologic Type**

A modification of the WHO classification of carcinomas of the oral cavity, including the lip, is shown below.[1] This list may not be complete. This protocol applies only to carcinomas but does not apply to melanomas, lymphomas, or sarcomas.

**Squamous Cell Carcinoma**

- Squamous cell carcinoma, conventional (keratinizing)
- Squamous cell carcinoma, non-keratinizing
- Adenosquamous carcinoma
- Basaloid squamous cell carcinoma
- Papillary squamous cell carcinoma
- Spindle cell squamous carcinoma
- Verrucous carcinoma
- Carcinoma cuniculatum
- Lymphoepithelial carcinoma (non-nasopharyngeal)

**Neuroendocrine Carcinoma**

The recommended histologic classification for neuroendocrine neoplasms has been standardized across all head and neck sites.[1] The entities relevant to this protocol are listed below:

- Neuroendocrine tumor, grade 1-3
- Neuroendocrine carcinoma, small cell type
- Neuroendocrine carcinoma, large cell type

Additionally, composite tumors with non-neuroendocrine CA components exist throughout the upper aerodigestive tract. The carcinoma component can then be captured in this protocol accordingly.

References

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**D. Histologic Grade**

For histologic types of carcinomas that are amenable to grading, 3 histologic grades are suggested, as shown below. For conventional squamous cell carcinoma, histologic grading as a whole does not perform well as a prognosticator.[1,2] Nonetheless, it should be recorded when applicable, as it is a basic tumor characteristic. Selecting either the most prevalent grade or the highest grade for this synoptic protocol is acceptable. Subtypes of squamous cell carcinoma (i.e., verrucous, basaloid, etc.) have an intrinsic biologic potential.

| | | | |
|---|---|---|---|
| Grade | 1 | | Well-differentiated |
| Grade | 2 | Moderately | differentiated |
| Grade | 3 | Poorly | differentiated |
| Grade | X | Cannot be | assessed |

The WHO 5th edition has standardized the terminology for head and neck neuroendocrine neoplasms across all subsites.[3] Tumors previously designated as carcinoid and well-differentiated neuroendocrine carcinoma would now be considered grade 1 neuroendocrine tumors, while atypical carcinoids/moderately-differentiated neuroendocrine carcinomas are now considered grade 2 neuroendocrine tumors. Grade 3

neuroendocrine tumor is a provisional category with no historical analogue. *It must be emphasized that this category in head and neck sites is provisional, with no current evidence to support its use in head and neck sites.* Practically speaking, tumors that exceed the mitotic rate for grade 2 neuroendocrine tumors are usually more in keeping with neuroendocrine carcinomas (see below). Grading of neuroendocrine tumors is summarized in Table 1. Ki-67 proliferation indices are recommended for neuroendocrine tumors of the head and neck, but are not required elements, and delineation of grades 1 and 2 at this site by proliferation index is not yet established.

**Table 1: WHO Classification of Head and Neck Neuroendocrine Tumors**

| Neuroendocrine Tumor Grade | Mitoses per two $mm^2$ | Necrosis |
|---|---|---|
| 1 | Less than 2 | Absent |
| 2 | 2-10 | Present |
| 3 | *Undefined* | |

Neuroendocrine carcinoma, small cell types and large cell types, on the other hand, have not changed much in terms of their designation and reflect poorly differentiated neuroendocrine malignancies that were previously labeled small cell and large cell neuroendocrine carcinomas, respectively. These characteristically show necrosis and have mitotic counts that exceed 10 per two $mm^2$. While neuroendocrine tumors and carcinomas are defined by neuroendocrine marker expression (synaptophysin, chromogranin, and/or INSM-1), other tumor types at each head and neck subsite may express these. Morphologic, other immunophenotypic, and molecular features would then supersede this neuroendocrine marker expression for classification.

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**E. Perineural Invasion**

Traditionally, the presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.[1] The presence of perineural invasion (neurotropism) in the primary cancer is associated with poor local disease control and regional control, as well as being associated with metastasis to regional lymph nodes.[1] Further, perineural invasion is associated with decrease in disease-specific survival and overall survival.[1] There is conflicting data relative to an association between the presence of perineural invasion and the development of distant metastasis, with some studies showing an increased association with distant metastasis, while other studies showing no correlation with distant metastasis.[1] The relationship between perineural invasion and prognosis is independent of nerve diameter.[2] Additionally, emerging evidence suggests that extratumoral perineural

invasion may be more prognostically relevant.[3] Although perineural invasion of small, unnamed nerves may not produce clinical symptoms, the reporting of perineural invasion includes nerves of all sizes, including small peripheral nerves (i.e., less than 1 mm in diameter). Aside from the impact on prognosis, the presence of perineural invasion also guides therapy. Concurrent adjuvant chemoradiation therapy has been shown to improve outcomes in patients with perineural invasion (as well as in patients with extranodal extension and bone invasion).[4,5] Given the significance relative to prognosis and treatment, perineural invasion is a required data element in the reporting of head and neck cancers. Extent of perineural invasion is an emerging element, and features such as extratumoral extent are suggested for reporting.

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**F. Worst Pattern of Invasion (WPOI)**

Worst pattern of invasion (WPOI) has been validated as a prognosticator for oral cavity squamous carcinomas.[1,2,3] While there are 5 patterns noted, distinction between WPOI-5 and other patterns is what is most relevant. WPOI-5 is defined by tumor dispersion ≥1 mm between tumor satellites. Examples of pattern 5 are shown in Figure 3. WPOI has been validated on multivariate analysis in oral tumors, also specifically in low stage tumors. However, WPOI can be viewed as redundant and only optional for reporting purposes as extratumoral perineural invasion (PNI), and angiolymphatic invasion also count as WPOI-5.[4]

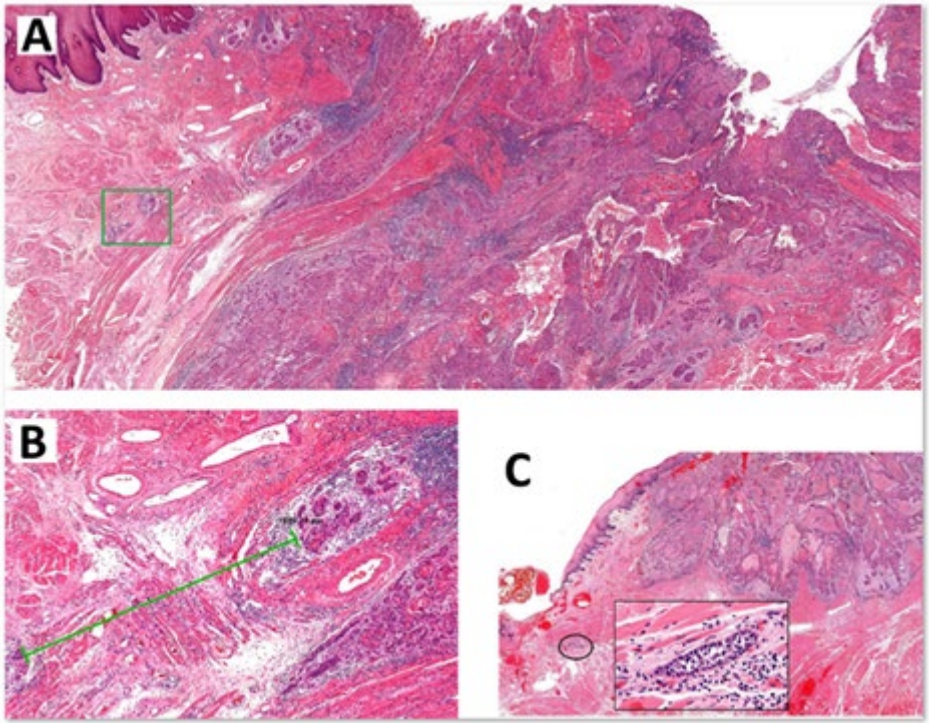


**Figure 3.** A. Low-power overview demonstrating generalized tumor dispersion, which is measured at the advancing tumor edge. Carcinoma satellites in the green box are shown in B., lower edge. The green line denotes spread of almost 2 mm, fulfilling criteria for WPOI-5. C. This carcinoma reveals rare, dispersed satellites fulfilling this criteria, likely due to extratumoral lymphovascular emboli. From *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017. © American Joint Committee on Cancer. Reproduced with permission.

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**G. Margins and Orientation**

The definition of a positive margin is somewhat controversial given the varied results from prior studies.[1,2] However, overall, several studies support the definition of a positive margin to be invasive carcinoma or carcinoma in situ/high-grade dysplasia present at margins (microscopic cut-through of tumor).[3] Furthermore, reporting of surgical margins should also include information regarding the distance of

invasive carcinoma, carcinoma in situ, or high-grade dysplasia from the surgical margin. Tumors with "close" margins also carry an increased risk for local recurrence.[2,3] The definition of a "close" margin is not standardized as the effective cut-off varies between studies and between anatomic subsites. Commonly used cut points to define close margins are 5 mm in general. However, values ranging from 3 mm to 7 mm have been used with success.[2,4] In oral cavity, the subjectivity and preconceived nature of these statements has been recently diminished by a multi-institutional review of 494 patients in which each mm of clearance of a pT1-2N0 oral SCC diminished the risk of local recurrence by 33% up until ~5 mm where the risk flattens, validating this as the breakpoint for adequacy of resection. Main specimen margin status and perineural invasion in fact outperformed pTNM in this group of patients for predicting local and locoregional recurrence. Thus, distance of tumor from the nearest margin should be recorded.

Regarding what actually represents the relevant margin status, it now clear that margins obtained from the main resection specimen have more reliable prognostic value.[5,6,7,8,9] The clinical value of tumor bed margins (i.e., margins taken separately) is often undermined by their uncertain origin with respect to the main resection,[10] infrequent orientation as to the new margin surface, and fragmentation. Biopsies of tumor bed (or tumor bed margins) have low sensitivity for detecting a positive margin from the actual resection specimen and, by definition, cannot identify "close" resection specimen margins. It is then justifiable to report the specimen margin status separately from the tumor bed margin status (see below). Of note, these findings have also been reported in other anatomic sites.[7,11,12,13]

Nonetheless, tumor bed margin status is still utilized in various practice settings for patient management.[14,15] However, the challenge for pathologists is to arrive at a "final" margin status, integrating both tumor bed and specimen margin status. As it is in multi-part resections, the pathologist's ability to confidently establish the relationship between the main resected specimen and additional, separately submitted parts and to assess the adequacy of excision is compromised.

To optimize reporting, both specimen margin and tumor bed margin status should thus be reported separately. The "final" margin status then becomes a multidisciplinary integration of these findings. For instance, in cases with differing margin statuses (i.e., resection specimen margin positive, corresponding tumor bed margin negative), the small size and lack of orientation of the tumor bed margin may preclude a reliable conversion to final negative margin. Conversely, in some cases the tumor bed specimen (e.g., revision of margin) may be a reliable indicator of a true final margin. This is a judgment call that requires close interaction between the surgeon and pathologist, but, generally, the following basic requirements are met: (1) tumor bed margins are quite large (i.e., thick enough to be readily processed as radial margins and large enough to match the corresponding aspect of the main specimen margin); (2) are oriented as to the new true margin surface (by ink or stitch); (3) the physical relationship between the main resection specimen and additional tumor bed margins is confirmed by pathologist and surgeon (usually through unequivocal labeling, and even fitting the tumor bed margin to the main specimen). In such a case, the tumor bed margin could be considered a final margin.

Complex specimens should be examined and oriented with the assistance of the operating surgeon(s). 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 or photograph of the resected specimen showing the extent of the tumor and its relation to the anatomic structures of the region. The lines and extent of the resection can be depicted on preprinted adhesive labels and attached to the surgical pathology request forms.

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**H. Regional Lymph Nodes**

**Direct Extension of Tumor to Lymph Node**

While data are essentially nonexistent for defining N status for lymph nodes involved by tumor via direct extension for head and neck cancers, the general convention based on other organ sites is to consider these positive for N categorization and counting purposes. It is recommended however to denote in the report the number of lymph nodes involved in this manner as it may influence more nuanced management decisions.

**Measurement of Tumor Metastasis**

The cross-sectional diameter of the largest lymph node metastasis (not the lymph node itself) is measured in the gross specimen at the time of macroscopic examination or, if necessary, on the histologic slide at the time of microscopic examination.[1,2]

**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. The generic recommendation is that lymph nodes with ITCs found by either histologic examination, immunohistochemistry, or non-morphologic techniques (e.g., flow cytometry, DNA analysis, PCR amplification of a specific tumor marker) should be classified as N0 or M0, respectively.[3] Evidence for the validity of this practice in head and neck squamous cell carcinoma and other histologic subtypes is however lacking even on systematic review.[4,5] In fact, rare studies relevant to head and neck sites indicate that isolated tumor cells may actually be a poor prognosticator in terms of local control.[6]

**Lymph Node Number**

For assessment of pN, a selective neck dissection will ordinarily include 10 or more lymph nodes, and a comprehensive neck dissection (radical or modified radical neck dissection) will ordinarily include 15 or more lymph nodes. In oral cavity, a minimal adequate dissection of 18 lymph nodes[7] has been popularized. While lymph node yield does seem to have prognostic value on systematic review, studies show heterogeneity in terms of quality and actual cutoffs (ranging from 12-26).[8] Examination of fewer tumor-free nodes still mandates a pN0 designation.

**Classification of Neck Dissection**

1. Radical neck dissection
2. Modified radical neck dissection, internal jugular vein and/or sternocleidomastoid muscle spared
3. Selective neck dissection (SND), as specified by the surgeon (Figure 4), defined by dissection of less than the 5 traditional levels of a radical and modified radical neck dissection. The following dissections are now under this category:[2,9,10]
    a. Supraomohyoid neck dissection
    b. Posterolateral neck dissection
    c. Lateral neck dissection
    d. Central compartment neck dissection
4. Superselective neck dissection (SSND), a relatively new term defined by dissection of the fibrofatty elements of 2 or less levels[11]
5. Extended radical neck dissection, as specified by the surgeon

For purposes of pathologic evaluation, lymph nodes are organized by levels as shown in Figure 4.

**Figure 4**. The 6 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 on 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 stylohyoid muscle.

**Level III. Middle Jugular Group**
Lymph nodes located around the middle third of the internal jugular vein extending from the carotid bifurcation superiorly to the omohyoid muscle (surgical landmark), or cricothyroid notch (clinical landmark) inferiorly. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the sternohyoid muscle.

**Level IV. Lower Jugular Group**
Lymph nodes located around the lower third of the internal jugular vein extending from the omohyoid muscle superiorly to the clavicle inferiorly. The posterior boundary is the posterior border of the sternocleidomastoid muscle, and the anterior boundary is the lateral border of the sternohyoid muscle.

**Level V. Posterior Triangle Group (Sublevels VA and VB)**
This group comprises predominantly the lymph nodes located along the lower half of the spinal accessory nerve and the transverse cervical artery. The supraclavicular nodes are also included in this group. The posterior boundary of the posterior triangle is the anterior border of the trapezius muscle, the anterior boundary of the posterior triangle is the posterior border of the sternocleidomastoid muscle, and the inferior boundary of the posterior triangle is the clavicle.

**Level VI. Anterior (Central) Compartment**
Lymph nodes in this compartment include the pre- and paratracheal nodes, precricoid (Delphian) node, and the perithyroidal nodes, including the lymph nodes along the recurrent laryngeal nerve. The superior boundary is the hyoid bone, the inferior boundary is the suprasternal notch, the lateral boundaries are the common carotid arteries, and the posterior boundary by the prevertebral fascia.

**Level VII. Superior Mediastinal Lymph Nodes**
Metastases at level VII are considered regional lymph node metastases; all other mediastinal lymph node metastases are considered distant metastases.

Lymph node groups removed from areas not included in the above levels, e.g., scalene, suboccipital, and retropharyngeal, should be identified and reported from all levels separately. Midline nodes are considered ipsilateral nodes.

**Extranodal Extension**
The status of cervical lymph nodes is the single most important prognostic factor in aerodigestive cancer. All macroscopically negative or equivocal lymph nodes should be submitted in toto. For oral cancers, reporting of lymph nodes containing metastasis should include whether there is presence or absence of extranodal extension (ENE),[12] which is part of N classification for these tumor types.

Extranodal extension criteria and gross submission guidelines have been recently outlined by international consensus groups, HNCIG, and HN-CLEAR.[13,14] Sampling should optimize surface area/perimeter examined, and to optimize this, serial sectioning is recommended for all lymph nodes above 5 mm. Grossly

negative lymph nodes should be submitted entirely while grossly positive lymph nodes can be representatively submitted. However, focus on sampling of the nodal periphery is recommended to enrich for extranodal extension.[14]

Only definitive ENE as per HNCIG, HN-CLEAR[13,14] criteria should be recorded as positive. New terminology for microscopic expression includes[14]:

- 'Matted' where tumor crosses from one lymph node to another adjacent lymph node. This is considered ENE positive
- 'Fused, adherent, confluent, and conglomerate' lymph nodes refer to lymph nodes that are adherent based on inflammation and stromal reaction and show no transgression of tumor across capsules. These are considered ENE negative

Additionally, soft tissue deposits are considered ENE positive, while extranodal lymphatic/vascular invasion and perineural invasion are considered ENE negative but count towards lymphatic/vascular invasion and perineural invasion even if the primary tumor does not show this locally.

**Other Elements**
Anatomic compartment location of positive lymph nodes is now a non-core element.

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**I. pTNM Classification**

The protocol recommends the TNM staging system of the American Joint Committee on Cancer.[1] The 2 key significant alterations in the 8th edition for oral cavity are the incorporation of depth of invasion (DOI) into T classification and extranodal extension (ENE) into N classification.[1] Table 2 summarizes T classification by size and depth of invasion.

**Table 2: T Classification by Size and Depth of Invasion**

| Size | Depth ≤ 5 mm | Depth >5 mm but ≤ 10mm | Depth >10 mm |
|---|---|---|---|
| **≤ 2 cm** | pT1 | pT2 | pT2 |
| **> 2 cm but ≤ 4 cm** | pT2 | pT2 | pT3 |
| **> 4 cm** | pT3 | pT3 | pT4a |

Pathologic ENE(+) will increase the nodal category by 1.

By AJCC/UICC convention, the designation “T” refers to a primary tumor that has not been previously treated. The symbol “p” refers to the pathologic classification of the TNM, as opposed to the clinical classification, and based on clinical stage information supplemented/modified by operative findings and gross and microscopic evaluation of the resected specimens.[2] pT entails a resection of the primary tumor or biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

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

**TNM Descriptors**

For identification of special cases of TNM or pTNM classifications, the “m” suffix and “y”, “r”, and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis. Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. As per the AJCC (Chapter 1, 8th Ed.) it is the managing

physician's responsibility to establish the final pathologic stage based upon all pertinent information, including but potentially not limited to this pathology report.

The "m" suffix indicates the presence of multiple primary tumors in a single site and is recorded in parentheses: pT(m)NM.

The "y" prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a "y" prefix. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "y" categorization is not an estimate of tumor prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy).

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

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

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