Sponsored by

Carcinomas of the Hypopharynx, Larynx and Trachea Histopathology Reporting Guide

Family/Last name

Given name(s)

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are CORE. Elements in **grey text** are NON-CORE.

☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (Note 1)

- ◯ Information not provided
- ◯ Information provided (select all that apply)
  - ☐ Previous therapy
    - ☐ Surgery
    - ☐ Chemotherapy
    - ☐ Radiotherapy
    - ☐ Targeted therapy, *specify if available*
    - ☐ Immunotherapy, *specify if available*
  - ☐ Clinical staging, *specify*
  - ☐ Other clinical information, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)

- ◯ Not specified
- ◯ Biopsy (excisional, incisional, core needle), *specify*
- ☐ Resection
  - ◯ Cordectomy
  - ◯ Supraglottic laryngectomy
  - ◯ Hemilaryngectomy, *specify side*
  - ◯ Partial laryngectomy, *specify type*
  - ◯ Total laryngectomy
- ☐ Neck (lymph node) dissection,[a] *specify*
- ☐ Other, *specify*

[a] *If a neck (lymph node) dissection is submitted, then a separate dataset is used to record the information.*

SPECIMEN(S) SUBMITTED (select all that apply) (Note 3)

- ◯ Not specified
- ☐ Larynx
  - ☐ Endolaryngeal excision
  - ☐ Transoral laser excision
  - ☐ Supraglottic laryngectomy
  - ☐ Supracricoid laryngectomy
  - ☐ Vertical hemilaryngectomy, *specify side*
  - ☐ Partial laryngectomy, *specify type*
  - ☐ Total laryngectomy
  - ☐ Other, *specify*
- ☐ Hypopharynx
  - ☐ Laryngopharyngectomy
  - ☐ Other, *specify*
- ☐ Trachea
- ☐ Neck (lymph node) dissection,[a] *specify*
- ☐ Other, *specify*

TUMOUR SITE (select all that apply) (Note 4)

- ◯ Not specified
- ☐ Larynx, supraglottis
  - ☐ Epiglottis
    - ☐ Lingual aspect
    - ☐ Laryngeal aspect
  - ☐ Aryepiglottic fold
  - ☐ Arytenoid
  - ☐ False vocal cord/fold
  - ☐ Ventricle

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TUMOUR SITE (select all that apply) (Note 4) **continued**

- ☐ Larynx, glottis
  - ☐ True vocal cord/fold
  - ☐ Anterior commissure
  - ☐ Posterior commissure
- ☐ Larynx, subglottis
- ☐ Hypopharynx
  - ☐ Piriform sinus
  - ☐ Postcricoid
  - ☐ Pharyngeal wall (posterior and/or lateral)
  - ☐ Other, *specify*
- ☐ Trachea
- ☐ Other, *specify*

TUMOUR LATERALITY (select all that apply) (Note 4)

- ◯ Not specified
- ☐ Left
- ☐ Right
- ☐ Midline

TUMOUR FOCALITY (Note 5)

- ◯ Unifocal
- ◯ Bilateral
- ◯ Multifocal
  - Specify number of tumours
- ◯ Cannot be assessed, *specify*

TUMOUR DIMENSIONS (Note 6)

Maximum tumour dimension (largest tumour)[b] (pathology and/or imaging determination)

mm

Additional dimensions (largest tumour)

mm x mm

- ◯ Cannot be assessed, *specify*

[b] *Non-core for larynx.*

BLOCK IDENTIFICATION KEY (Note 7)

(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 8)

(Value list based on the World Health Organization Classification of Head and Neck Tumours (2024))

- ☐ Squamous cell carcinoma, conventional type
- ☐ Squamous cell carcinoma, subtypes
  - ◯ Verrucous squamous cell carcinoma
  - ◯ Basaloid squamous cell carcinoma
  - ◯ Papillary squamous cell carcinoma
  - ◯ Spindle cell squamous cell carcinoma
  - ◯ Adenosquamous carcinoma
  - ◯ Lymphoepithelial carcinoma
- ☐ Salivary gland-type carcinoma,[c] *specify type*
- ☐ Neuroendocrine neoplasm
  - ◯ Neuroendocrine tumour, grade 1
  - ◯ Neuroendocrine tumour, grade 2
  - ◯ Neuroendocrine tumour, grade 3
  - ◯ Small cell neuroendocrine carcinoma
  - ◯ Large cell neuroendocrine carcinoma
  - ◯ Mixed neuroendocrine and non-neuroendocrine, *specify type*
- ☐ Other, *specify*

[c] *For histological type of salivary gland-type carcinomas, refer to the Carcinomas of the major salivary glands dataset.*

HISTOLOGICAL TUMOUR GRADE[d] (Note 9)

(Applicable to conventional squamous cell carcinoma and minor salivary gland tumours only)

- ◯ Grade 1, well differentiated, low grade
- ◯ Grade 2, moderately differentiated, intermediate grade
- ◯ Grade 3, poorly differentiated, high grade
- ◯ Undifferentiated
- ◯ High grade transformation

Grading system used, *specify*

- ◯ Cannot be assessed, *specify*

[d] *Neuroendocrine neoplasms are graded as part of the tumour classification (see Histological Tumour Type).*

PATTERN OF INVASIVE FRONT (Note 10)

(Applicable to resection specimens only)

- ◯ Cohesive
- ◯ Non-cohesive

Tumour budding

Number of buds per 0.785 mm^2

- ◯ <5 buds
- ◯ ≥5 buds

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EXTENT OF INVASION (Note 11)

Larynx

- ◯ Not identified
- ◯ Present (select all that apply)
  - ☐ Clinical observation and/or imaging
  - ☐ Histologic

  ↓
  - ☐ Mucosa involvement
  - ☐ Paraglottic space involvement
  - ☐ Pre-epiglottic space involvement
  - ☐ Inner cortex of cartilage
  - ☐ Full thickness invasion of cartilage
  - ☐ Soft tissues of neck, thyroid, prevertebral space, carotid artery or mediastinal structures involvement
  - ☐ Other, *specify*
  - ◯ Cannot be assessed, *specify*

Hypopharynx

- ◯ Not identified
- ◯ Present (select all that apply)
  - ☐ Clinical observation and/or imaging
  - ☐ Histologic

  ↓
  - ☐ Limited to wall of hypopharynx
  - ☐ Extends outside wall of hypopharynx
  - ☐ Other, *specify*
  - ◯ Cannot be assessed, *specify*

LYMPHOVASCULAR INVASION (Note 12)

- ◯ Not identified
- ◯ Present
- ◯ Indeterminate, *specify reason*

PERINEURAL INVASION (Note 13)

- ◯ Not identified
- ◯ Present
- ◯ Indeterminate, *specify reason*

MARGIN STATUS (Note 14)

Invasive carcinoma

- ◯ Not involved
  - Distance of tumour from closest margin: ____ mm
  - ◯ Distance not assessable
  - Specify closest margin(s), if possible
- ◯ Involved
  - Specify margin(s), if possible
- ◯ Cannot be assessed, *specify*

Carcinoma in situ/high grade dysplasia[e]

- ◯ Not applicable
- ◯ Not involved
  - Distance of carcinoma in situ/high grade dysplasia from closest margin: ____ mm
  - ◯ Distance not assessable
  - Specify closest margin(s), if possible
- ◯ Involved
  - Specify margin(s), if possible
- ◯ Cannot be assessed, *specify*

[e] *High grade dysplasia is synonymous with moderate/severe dysplasia.*

COEXISTENT PATHOLOGY (select all that apply) (Note 15)

- ◯ None identified
- ☐ Necrotising sialometaplasia
- ☐ Infection, *specify*
- ☐ Dysplasia, *specify*
- ☐ Hyperplasia, *specify*
- ☐ Other, *specify*

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ANCILLARY STUDIES (Note 16)

- ◯ Not performed
- ◯ Performed
  - **Neuroendocrine neoplasms** (select all that apply)
    - ◯ Not applicable
    - ☐ Neuroendocrine markers, *specify*
    - ☐ Cytokeratin(s), *specify*
    - ☐ Ki-67 proliferation index %
    - ☐ Rb
      - ☐ Retained
      - ☐ Deficient
    - ☐ p53
      - ◯ Abnormal, *specify*
    - ☐ Other, *record test(s), methodology and results*

Squamous cell carcinoma and subtypes
Record test(s), methodology and results

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

PATHOLOGICAL STAGING (UICC TNM 8th edition)[f] (Note 17)

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

- ☐ m - multiple primary tumours
- ☐ r - recurrent
- ☐ y - during or following multimodality therapy

Primary tumour: Supraglottis[g]

- ◯ T1 Tumour limited to one subsite of supraglottis with normal vocal cord mobility
- ◯ T2 Tumour 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 piriform sinus) without fixation of the larynx
- ◯ T3 Tumour limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
- ◯ T4a Tumour invades through the thyroid cartilage and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, or oesophagus
- ◯ T4b Tumour invades prevertebral space, encases carotid artery, or mediastinal structures

Primary tumour: Glottis[g]

- ◯ T1 Tumour limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
  - ◯ T1a Tumour limited to one vocal cord
  - ◯ T1b Tumour involves both vocal cords
- ◯ T2 Tumour extends to supraglottis and/or subglottis and/or with impaired vocal cord mobility
- ◯ T3 Tumour limited to the larynx with vocal cord fixation and/or invades paraglottic space, and/or inner cortex of the thyroid cartilage
- ◯ T4a Tumour invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid, oesophagus
- ◯ T4b Tumour invades prevertebral space, encases carotid artery, or mediastinal structures

Primary tumour: Subglottis[g]

- ◯ T1 Tumour limited to subglottis
- ◯ T2 Tumour extends to vocal cord(s) with normal or impaired mobility
- ◯ T3 Tumour limited to larynx with vocal cord fixation
- ◯ T4a Tumour invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), strap muscles, thyroid, oesophagus
- ◯ T4b Tumour invades prevertebral space, encases carotid artery, or mediastinal structures

Primary tumour: Hypopharynx[g]

- ◯ T1 Tumour limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
- ◯ T2 Tumour invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension, without fixation of hemilarynx
- ◯ T3 Tumour more than 4cm in greatest dimension, or with fixation of hemilarynx or extension to oesophageal mucosa
- ◯ T4a Tumour invades any of the following: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment soft tissue[h]
- ◯ T4b Tumour invades prevertebral fascia, encases carotid artery, or invades mediastinal structures

[f] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 12th July 2024).*

[g] *Note that the results of neck (lymph node) dissection are derived from a separate dataset.*

[h] *Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.*

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Definitions

CORE elements

CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence[1]). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element.

Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.

The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.

NON-CORE elements

NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.

Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of the DAC.

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Scope

The dataset has been developed for the reporting of resection and biopsy specimens of invasive epithelial malignancies of the larynx, hypopharynx and trachea. Salivary-type malignancies arising from minor mucoserous glands of the hypopharynx and larynx should be recorded in this dataset; the paucity of prognostic or predictive data suggest that tumour type and grade (as described in the ICCR Carcinomas of the major salivary glands dataset[2]), size and margin status should be recorded. Neuroendocrine neoplasms, as newly defined, include paraganglioma, neuroendocrine tumours (NET), and neuroendocrine carcinomas (NEC). NETs are separated into grades (1, 2, and 3) based on mitotic rate and Ki-67 proliferation index, but these criteria are not yet fully developed for each of the anatomic sites in the head and neck. At present, the site, tumour category, and grade should be reported, with additional advances in this field incorporated when validated further.

Mucosal melanoma is presented in a separate ICCR dataset.[3] Lymphomas and sarcomas are not included. Malignancies arising at other sites in the head and neck region, and neck dissections and nodal excisions are dealt with in separate ICCR datasets which may be used, as appropriate, in conjunction with this dataset.[4]

Where more than one anatomically or histologically distinct primary tumour occur, a separate dataset should be completed for each tumour (see **NOTE 5 – TUMOUR FOCALITY**).

This dataset is intended for use for primary cancer resections. For resections of recurrent disease, the reporting guide may be used pragmatically but some data items may be not applicable or not assessable.

The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Head and Neck Tumours, 5th edition, 2024.[5]

Tracheal carcinomas

Tracheal malignancies are rare and represented in the literature as single case reports and small case series. Most reports describe squamous cell carcinomas (SCC) and carcinomas of salivary type arising from mucosal glands.[6-15] Too few cases are reported to analyse prognostic or predictive data and there is no TNM classification for tracheal malignancies under either the Union for International Cancer Control (UICC) or American Joint Committee on Cancer (AJCC) systems. Thus, staging criteria for tracheal carcinomas are not yet performed, although recording core elements as available, may aid in further development.[15]

A list of changes in this dataset edition can be accessed here.

The authors of this dataset can be accessed here.

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Note 1 – Clinical information (Core and Non-core)

Clinical information about previous surgery or the use of neoadjuvant therapy will help the pathologist correctly interpret the histologic findings. While the extent of tumour necrosis or post-therapy fibrosis are not currently used as an important guide to management, it is good practice to document the effects of previous treatment within the 'other' free text box, pragmatically, estimating the percentage tumour volume affected by necrosis or fibrosis.

In the case of prior treatment, the initial stage of the disease or at least information about the mobility of the larynx are helpful guides to staging.

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Note 2 – Operative procedure (Core)

The nature of the operative procedure will influence the required level of detail in the pathological report. Diagnostic/incisional biopsies will usually generate a limited set of data items compared to excision/ resection specimens. As an example, the status of resection margins does not require detailed consideration for diagnostic biopsies except for very small carcinomas where the entire cancer may be present in the diagnostic specimen. When a lymph node biopsy or neck dissection is included, a separate dataset is used to record the elements.

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Note 3 – Specimen(s) submitted (Core)

The pathologist needs to be informed about the nature of surgery (type of specimen) so that their description and dissection are focused on selecting appropriate tissues to guide accurate cancer staging.[16,17]

The following commentary is intended to assist pathologists in understanding the complex anatomy of the larynx and related structures. Anatomical sites and tissue compartments of the larynx are shown in Figures 1 and 2.

The **supraglottis** includes the epiglottis, aryepiglottic fold (laryngeal aspect), arytenoid, ventricular bands (false cords) and laryngeal ventricles.

The **glottis** extends from the ventricle to approximately 10 millimetres (mm) below the free level of the true vocal cord and includes the vocal cords, anterior commissure and posterior commissure.

The **subglottis** extends from approximately 10 mm below the level of the true vocal cord to the inferior rim of the cricoid cartilage.

Note that transglottic carcinomas cross the ventricles in a vertical direction to involve both true and false vocal cords.

The **hypopharynx** is the part of the pharynx extending from the plane of the superior border of the hyoid bone (or floor of the vallecula) to the plane corresponding to the lower border of the cricoid cartilage. The contents of the hypopharynx include:

- left and right pyriform sinuses which expand bilaterally and forward around the sides of the larynx and lie between the larynx and the thyroid cartilage;
- lateral and posterior hypopharyngeal walls; and
- postcricoid region extending from the level of the arytenoid cartilages to the inferior border of the cricoid cartilage.

The **paraglottic space** is a potential space antero-lateral and deep to the ventricles and saccules and filled with adipose tissue and connective tissue (Figure 1). It is bounded by the conus elasticus inferiorly, the thyroid cartilage laterally, the quadrangular membrane medially, and the pyriform sinus posteriorly.

The **pre-epiglottic space** is anterior to the base of the epiglottis and filled with adipose tissue and connective tissue (Figure 2); it is triangular and is bounded by the thyroid cartilage and thyrohyoid membrane anteriorly, the epiglottis and thyroepiglottic ligament posteriorly, and the hyoepiglottic ligament at its base (Figures 1 and 2).

Additionally, involvement of the adjacent soft tissues of the neck or thyroid gland (including the infrahyoid muscles (strap muscles), extrinsic muscle of the tongue, oesophagus, and/or trachea) are noted when more advanced disease is present, with significantly advanced disease identified when the tumour involves the prevertebral space, encases the carotid artery or invades any of the mediastinal structures.

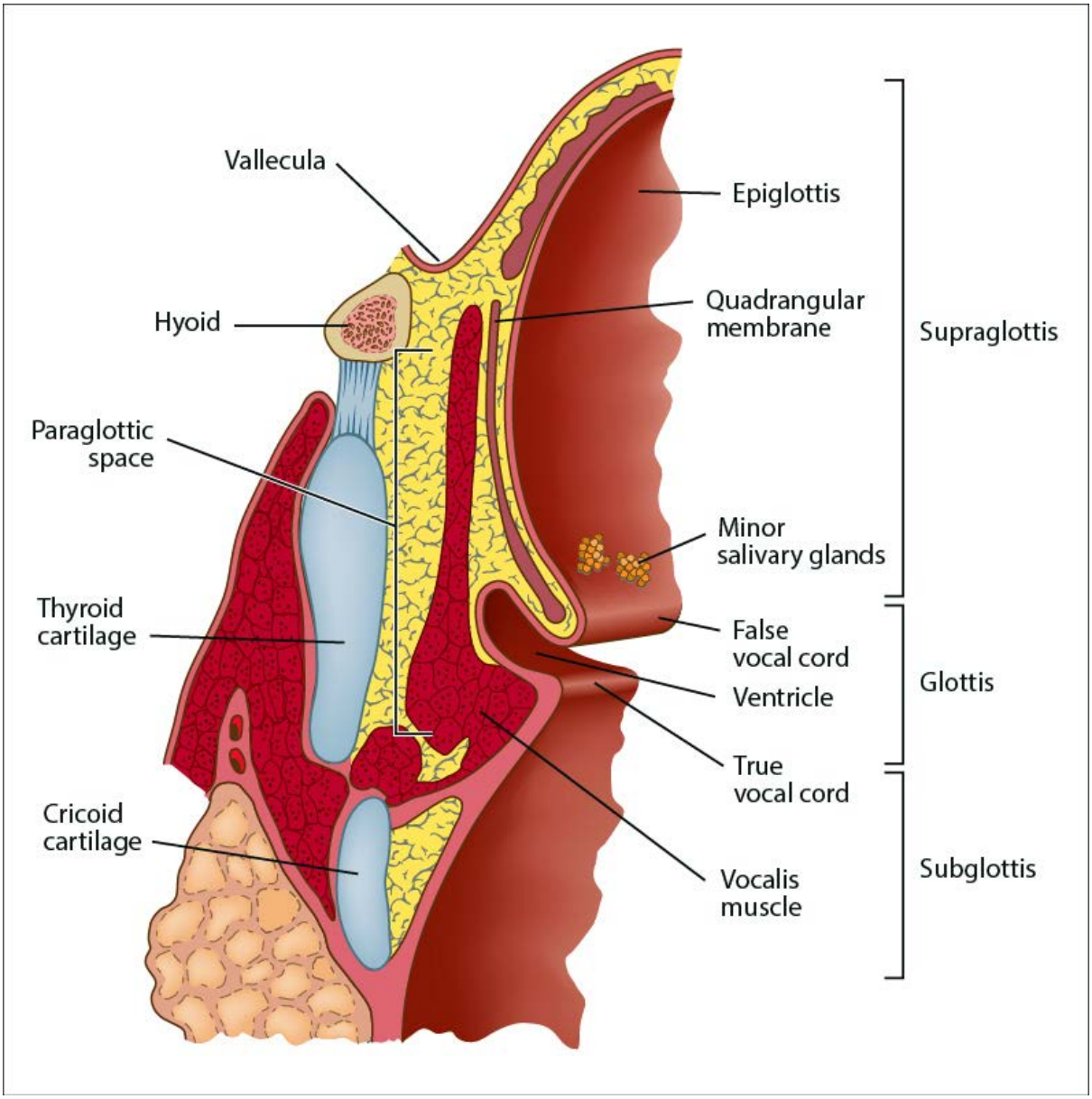

Figure 1: Coronal section through the larynx to show the main structures and paraglottic space.

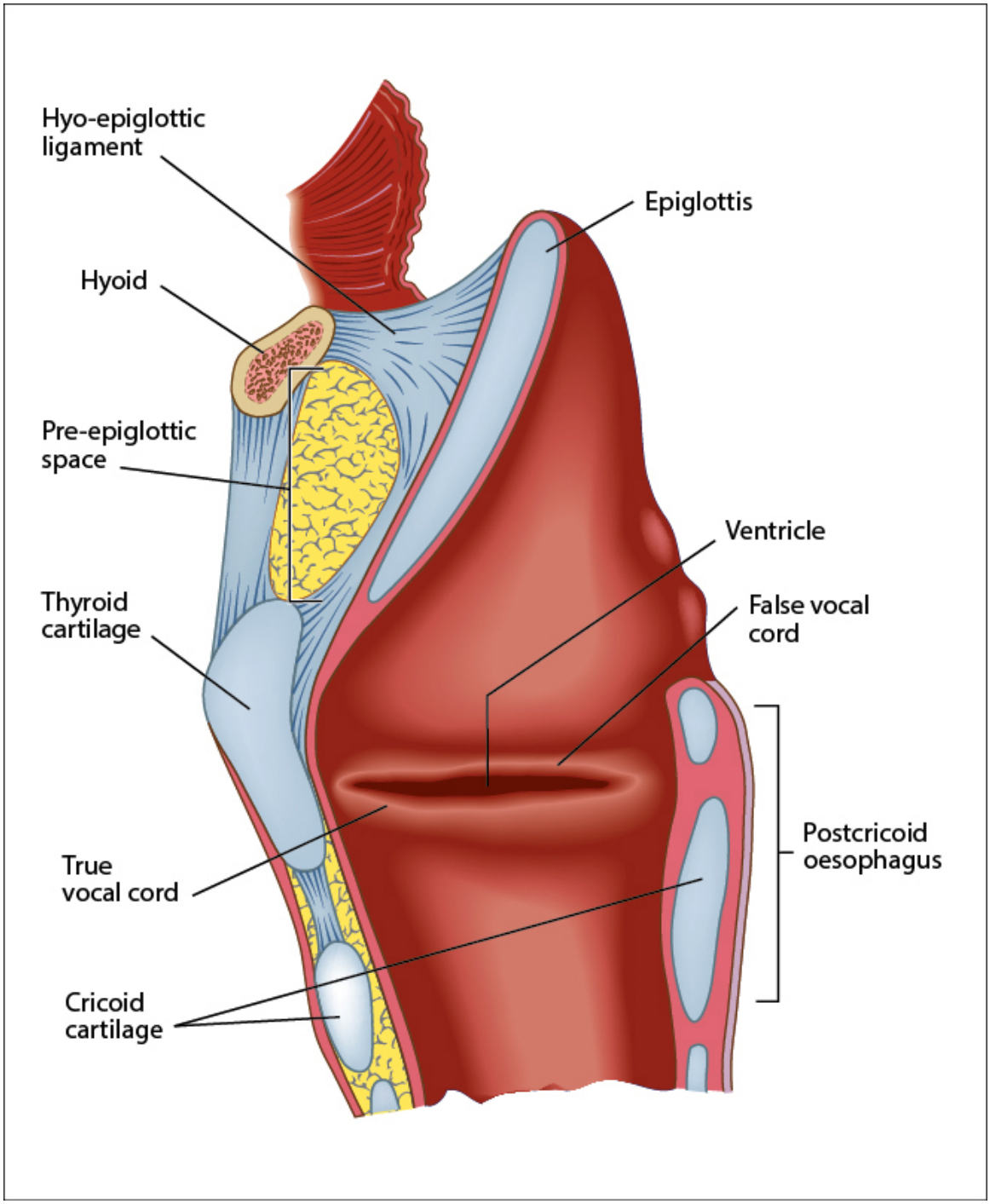

Figure 2: Sagittal section through the larynx to show main structures and the pre-epiglottic space.

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Note 4 – Tumour site (Core) and Tumour laterality (Core)

Accurate documentation of the laterality and site of the specimen and tumour avoids errors in the delivery of therapy. The site of the primary tumour is a key determinant in clinicopathological staging systems for hypopharynx and larynx.

For carcinomas that involve more than one site, the principal site of involvement should be recorded and coded; this may not be the site of origin. If required, the involvement of associated sites can be noted to help in further data analysis. Sites and subsites should be recorded according to the UICC nomenclature.[5,18]

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Note 5 – Tumour focality (Core)

The presence of multiple or multifocal tumours is an important clue to a cancerization or field-effect phenomenon, potentiated by radiotherapy, alcohol, and various forms of tobacco use.[19-23] Multifocality is defined as separate foci of tumour in the same organ, while multicentricity is defined as multiple tumours in separate organs/sites (e.g., hypopharynx, larynx, oral cavity).[24] These designations apply to primary tumours, not metastases, and require histologic confirmation that tumour is present. In some cases, it may not be possible to determine whether there is direct extension or a new primary (hypopharynx and supraglottis). Similarly, it may not be possible to determine whether a fragmented specimen may contain multifocal tumours. At present, there is no defining distance of intervening, normal, uninvolved mucosa between tumour sites. By inference, using 10 mm of uninvolved mucosa between invasive tumours may be a useful guide to suggest multifocality when there is more than one tumour present. Specimens should be carefully examined both macroscopically and microscopically to determine whether multiple tumours are present, as patients with multiple tumours tend to have a worse overall long-term prognosis.[25,26]

Where more than one anatomically or histologically distinct primary tumours occur, a separate dataset should be completed for each tumour.

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Note 6 – Tumour dimensions (Core and Non-core)

Tumour dimension is an important component in pathologic staging of the tumours of hypopharynx (core element). The macroscopic diameter (in millimetres) should be used unless the histological extent is greater than macroscopically apparent, in which case the microscopic dimension is used. As for other tissues, measurements are made pragmatically, acknowledging distortion of tissues by fixation and processing.[18,27]

Tumour dimension is not important in pathologic staging of the tumours of larynx (non-core).[18,27]

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Note 7 – Block identification key (Non-core)

The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important when further internal or external review arises. The reviewer needs to have unequivocal description of the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It is highly encouraged to have a digital image (photograph) of the specimen and record of the key of the tumour blocks.

Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.

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Note 8 – Histological tumour type (Core)

All tumours of the hypopharynx, larynx and trachea should be given a type based on the most recent edition of the WHO Classification of Head and Neck Tumours, 5th edition, 2024 (Table 1).[5]

Histopathological type is important for cancer registration and prognosis, with strength of evidence varying for different types. Verrucous and papillary carcinomas tend to have a good prognosis while, adenosquamous carcinomas have a worse prognosis than conventional and spindle cell carcinomas. For most of the subtypes of SCC, surgery with adequate margins is the main treatment. In some malignancies, such as large cell NECs, a combination of irradiation and chemotherapy is indicated.[5,28-30]

Epithelial neuroendocrine neoplasms are classified as NETs, NECs and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN).

Neuroendocrine tumours (NET) are separated into grades (1, 2, and 3) based on mitotic rate and Ki-67 proliferation index, but these criteria are not yet fully developed for each of the anatomic sites in the head and neck. At present, the general cutoffs are: grade 1: <2 mitoses/2 mm^2 and <2% Ki-67 proliferation index; grade 2: ≥2-10 mitoses/2 mm^2 and 2-20% Ki-67 proliferation index; and grade 3: >10 mitoses/2mm^2 and >20% Ki-67 proliferation index.[31,32]

Further, NECs are separated into small cell NEC and large cell NEC, showing tumour necrosis, >10 mitoses/ 2 mm^2 and >20% Ki-67 proliferation index,[31,33-35] with universal Rb1 loss and common p53 overexpression.[36]

Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) usually consist of a poorly differentiated NEC component and a SCC or adenocarcinoma component. Immunohistochemically confirmed and morphologically distinct tumour components should be recognised and reported irrespective of their extent.

For salivary-type tumour arising from mucosal glands, please refer to the ICCR Carcinomas of the major salivary glands dataset for descriptors and ICD-O codes.[2]

Table 1: World Health Organization classification of tumours of the hypopharynx, larynx and trachea.[5]

Descriptor	ICD-O codes[a]
Malignant surface epithelial tumours	
Conventional squamous cell carcinoma	8070/3
Verrucous squamous cell carcinoma	8051/3
Basaloid squamous cell carcinoma	8083/3
Papillary squamous cell carcinoma	8052/3
Spindle cell squamous carcinoma	8074/3
Adenosquamous carcinoma	8560/3
Lymphoepithelial carcinoma	8082/3
Epithelial neuroendocrine neoplasms	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Carcinoma mixed with small cell neuroendocrine carcinoma[b]	8045/3
Carcinoma mixed with large cell neuroendocrine carcinoma[b]	8013/3

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).[37] Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

[b] This terminology is synonymous with the ICD-O terminology of combined small/large cell neuroendocrine carcinomas.

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Note 9 – Histological tumour grade (Core)

Although human papillomavirus (HPV)-associated carcinomas arising in the oropharynx are not graded (see ICCR Carcinomas of the oropharynx and nasopharynx dataset[38]), there is insufficient evidence to justify this approach in the hypopharynx and larynx. The recommendation is that HPV assessment should not be performed except for basaloid, lymphoepithelial, and papillary carcinomas. The conventional grading system for classical SCCs should be used for all tumours at these sites.[5,39-44]

Grading is based on the degree of resemblance of the carcinoma to the normal epithelium and follows the descriptions in the WHO Classification.[5] The most aggressive area is graded as well, moderately, or poorly differentiated. This system is widely used and prognostically useful, even though it suffers from inter-observer variability and sampling problems. While most SCCs will be well or moderately differentiated, it is important for prognostication to separate tumours based on differentiation. Where a tumour has a varied appearance, then the highest grade (poorest differentiation) is recorded as a core data item, while the predominant pattern may be recorded as non-core data.

Squamous cell carcinoma (SCC) subtypes (such as verrucous, basaloid, adenosquamous and spindle cell) are considered to have intrinsic biological potential and are not graded.

Still, several grading systems for each tumour type are available, with differing merits, and as such, recording which system has been applied is more clinically meaningfully (use 'specify' to state the system used), with the ICCR deferring to the WHO Classification current edition for grading guidance and preference.[5]

For the grading of salivary-type tumour arising from mucosal glands, please refer to the ICCR Carcinomas of the major salivary glands dataset for descriptors.[2]

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Note 10 – Pattern of invasive front (Non-core)

The pattern of invasion at the invasive tumour front is of proven prognostic value for oral and oropharyngeal carcinomas, and there is evidence that a similar approach may be of value to predict nodal metastasis for hypopharyngeal and laryngeal carcinomas too.[39,45-47] The invasive tumour front may show cohesive or non-cohesive patterns. Cohesive invasion pattern consists of broad sheets of tumour cells or nests with >15 tumour cells. Non-cohesive invasion pattern is characterised by narrow strands and small groups of ≤15 tumour cells and single tumour cells.

Additionally, tumour budding has emerged as a promising biomarker in various carcinomas, with early evidence suggesting that it is an independent adverse prognostic factor in carcinoma of the larynx and hypopharynx.[48-54]

Tumour budding is defined as single tumour cells or clusters of up to four tumour cells at the invasive tumour front. There is no consensus yet how it should be assessed and graded in laryngeal and hypopharyngeal carcinomas. It has been recommended to count the number of buds on hematoxylin and eosin (H&E) slides in areas showing maximal budding, in a single x20 high power field (HPF).[48,49,54] Depending on the eyepiece field diameter of the microscope, the number of buds may need to be normalised to represent the number for a field of 0.785 mm^2 (objective lens 20x with eyepiece diameter of 20 mm). For risk stratification in SCC of the head and neck, a cutoff point of 5 buds (low risk <5 buds versus high risk ≥5 buds) has been used in the majority of the published studies.[49,54]

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Note 11 – Extent of invasion (Core)

In the larynx, the invasion of tissue compartments deep to the mucosa is important for staging. The important tissues for staging purposes are the paraglottic space, the pre-epiglottic space and the thyroid and cricoid cartilages. One of the points of distinction between T3 and T4a carcinomas is whether cartilage invasion involves the inner cortex (partial) or outer cortex (full thickness). Further, involvement of the adjacent soft tissues, oesophagus, trachea, encasement of the carotid artery, and/or involvement of the mediastinum, are seen in advanced disease and are prognostically significant.[5,18,27,55]

In the hypopharnyx, the extent of invasion is important, too. The involvement oesophagus, thyroid/cricoid cartilage, hyoid bone, thyroid gland, central compartment soft tissue (prelaryngeal strap muscle, subcutanous fat), prevertebral fascia, carotid structures and mediastinal structures are important for staging and prognostically significant.[5]

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Note 12 – Lymphovascular invasion (Core)

Reports on the prognostic value of lymphovascular invasion in laryngeal and hypopharyngeal carcinomas are variable, but some studies suggest that it is an independent indicator of poor outcome.[56-60] The consensus of the DAC was that lymphovascular invasion should be a core element.

Lymphovascular invasion is recognised by the presence of tumour cells within an endothelial-lined space and should be distinguished from retraction artefact.

Small vessel invasion includes invasion of the lymphatics, capillaries or post-capillary venules. As it is often difficult to distinguish among the types of small vessels, their invasion by tumour cells is reported as lymphovascular invasion.

Recognition of lymphovascular invasion may be difficult and subjective and can be improved by using immunohistochemistry (e.g., D2-40, CD61) and histochemical stains (e.g., elastic staining to identify venous elastic lamina) but this is not recommended in routine work. Specifically, CD61 is a marker of activation of the fibrinogen cascade, and its presence in a linear fashion on platelets in a space confirms fibrin is present, and thus genuine vascular/endothelial destruction.[61]

Cases that are still equivocal after taking additional steps may be reported as 'indeterminate' for lymphovascular invasion, but this designation should be sparingly used and it is useful to provide the reason in a comment in the report.

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Note 13 – Perineural invasion (Core)

The presence or absence of perineural invasion should be recorded, regardless of the size of the nerve. Invasion of the perineural plane is a predictor of local recurrence and nodal metastasis and may prompt consideration of adjuvant chemoradiotherapy.[44,45,58,62-68]

The perineural plane is a potential space between the bundles of axons and the perineurium; the presence of carcinoma around a nerve (external to the perineurium) is not regarded as perineural invasion. There is currently insufficient evidence to separate it into extratumoural and intratumoural invasion though some studies suggest that extratumoural perineural invasion is more important.[63] For this dataset, either intratumoural or extratumoural invasion is regarded as a positive finding.

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Note 14 – Margin status (Core)

A positive margin is usually defined by the presence of an invasive carcinoma or carcinoma in situ at margins. It is recommended that the distance from in situ or invasive carcinoma to the closest margin is measured and reported in mm, if assessable. Margin status is a predictor of local recurrence and may require consideration of adjuvant therapy.[69-75]

The definition of a 'close margin' varies between published series, typically being regarded as between 3 and 5 mm.[76] For laser resections of glottic carcinomas even 1 mm may be adequate due to the thermal damage and shrinkage of tissue at the margin.[69,76-79]

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Note 15 – Coexistent pathology (Non-core)

This is a non-core element to provide the pathologist with the flexibility to record any other diseases that have potential impact on clinical management, such as infections, necrotising sialometaplasia, dysplasia, hyperplasia.

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Note 16 – Ancillary studies (Core and Non-core)

For neuroendocrine neoplasms core elements are neuroendocrine markers, epithelial markers, and Ki-67 proliferation index. The diagnosis of neuroendocrine neoplasms (specifically NETs and NECs) must be confirmed immunohistochemically, with positive reaction for neuroendocrine markers (synaptophysin, chromogranin, INSM1) and for epithelial markers (pancytokeratin, cytokeratin). Furthermore, a proliferation index as determined by Ki-67 immunohistochemical analysis is recommended for grading all NETs, helping to confirm NECs, and p53 and Rb1 may be helpful in the distinction between NET and NEC, especially G3 NET from NEC.[32,80,36]

The majority of SCCs are diagnosed on the basis of morphology. Immunohistochemistry must be used only in case of poorly differentiated SCC to confirm the diagnosis (e.g., p40, CK 5/6, p63). If necessary, other malignant tumours such as melanoma and lymphomas must be excluded by the use of the appropriate immunohistochemistry. Special stains for mucin and FISH for *MAML2* rearrangement may help to diagnose mucoepidermoid carcinoma.

The literature recognises that a very few HPV-associated carcinomas may occur in the hypopharynx and larynx, but prognostic relevance is uncertain.[81] There is some evidence suggesting that HPV-associated hypopharyngeal and laryngeal carcinoma may have a better prognosis.[82-84] HPV testing may be performed, particularly in cases with basaloid, papillary, lymphoepithelial or warty morphology.[5,82,85] p16INK4a immunohistochemistry as a surrogate marker for HPV-associated carcinoma may be less reliable in the larynx than in the oropharynx.[86]

Programmed cell death-ligand 1 (PD-L1) expression has been used as predictive biomarker for checkpoint inhibitor therapy since the anti-programmed cell death-1 receptor (PD-1) antibodies, nivolumab and pembrolizumab, have been approved for the treatment of patients with recurrent and/or unresectable metastatic head and neck SCC.[87,88] It is currently advised to use antibody 22C3 and to calculate a combined positive score (CPS), defined as the number of PD-L1-positive cells (tumour cells, lymphocytes, and macrophages) divided by the total number of tumour cells × 100. PD-L1 expression is associated with an increased objective response rates in patients with CPS ≥1, with a better response with CPS ≥20.[89,90] However, the lack of response in some PD-L1 positive patients clearly indicates that other factors are involved in the resistance to treatment with check-point inhibitors.[91]

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Note 17 – Pathological staging (Core)

By UICC/AJCC convention,[18,27] the designation 'T' refers to a primary tumour that has not been previously treated. The symbol 'p' refers to the pathologic classification of the stage, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumour 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. There is no pathologic M0 category as this designation requires clinical evaluation and imaging. Clinical classification (cTNM) is usually carried out by the evaluating clinician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathological staging is usually performed after surgical resection of the primary tumour and depends on documentation of the anatomic extent of disease, whether or not the primary tumour has been completely removed. If a biopsied tumour 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 tumour can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied even though total removal of the primary cancer was not performed.

UICC TNM 8[18]

Primary Tumour: Subglottis

Note that the UICC and AJCC staging differs for T3/T4a subglottic carcinomas.[18,27] In the AJCC system, T3 carcinomas include those limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage.[27]

Larynx

Normal (T1) or impaired (T2) vocal cord mobility and vocal cord fixation (T3) may only be determined clinically.

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 tumours 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 categorises the extent of tumour actually present at the time of that examination. The 'y' categorisation is not an estimate of tumour prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy).

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

For the pN classification of regional lymph nodes, see ICCR Nodal excisions and neck dissection specimens dataset.[92]

Reporting of pathological staging categories (pT, pN, pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM8 and AJCC TNM8,[18,27] the final stage grouping

of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

Pathological staging should not be reported if the submitted specimen is insufficient for definitive staging, especially with biopsy samples (core needle, incisional or excisional). Staging is based on the submitted resection, and even if there is grossly residual disease or there is tumour at the margin, pT staging should only be reported on findings in the resection specimen and/or at operation.[18,27]

The reference document TNM Supplement: A commentary on uniform use, 5th Edition (C Wittekind et al. editors) may be of assistance when staging.[93]

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