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# Carcinomas of the Oropharynx and Nasopharynx 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*
  - ☐ Other clinical information, *specify*

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

- ◯ Not specified
- ◯ Biopsy (excisional, incisional, core needle), *specify*
- ☐ Resection
  - ◯ Transoral laser microsurgical resection
  - ◯ Transoral robotic surgical resection
  - ◯ Other, *specify*
- ☐ 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
- ☐ Oropharynx
  - ☐ Palatine tonsil
  - ☐ Base of tongue (lingual tonsil)
  - ☐ Soft palate
  - ☐ Uvula
  - ☐ Pharyngeal wall (posterior)
  - ☐ Pharyngeal wall (lateral)
  - ☐ Other, *specify*
- ☐ Nasopharynx, *specify*
- ☐ Neck (lymph node) dissection,[a] *specify*
- ☐ Other, *specify*

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

- ◯ Not specified
- ☐ Oropharynx
  - ☐ Palatine tonsil
  - ☐ Base of tongue (lingual tonsil)
  - ☐ Soft palate
  - ☐ Uvula
  - ☐ Pharyngeal wall (posterior)
  - ☐ Pharyngeal wall (lateral)
  - ☐ Other, *specify*
  - ◯ Cannot be determined
- ☐ Nasopharynx
  - ☐ Nasopharyngeal tonsils (adenoids)
  - ☐ Fossa of Rosenmüller
  - ☐ Pharyngeal wall (lateral)
  - ☐ Pharyngeal wall (posterior)
  - ☐ Other, *specify*
  - ◯ Cannot be determined
- ☐ Other, *specify*



Version 2.0 Published July 2024 ISBN: 978-1-922324-47-4

**TUMOUR LATERALITY** (select all that apply)

◯ Not specified ☐ Midline
☐ Left ☐ Right

**TUMOUR DIMENSIONS** (Note 5)

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

mm

Additional dimensions (largest tumour)

mm x mm

◯ Cannot be assessed, *specify*

**BLOCK IDENTIFICATION KEY** (Note 6)

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

**HISTOLOGICAL TUMOUR TYPE** (select all that apply) (Note 7)

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

**Carcinomas of the oropharynx**

☐ Squamous cell carcinoma
- ◯ Squamous cell carcinoma, HPV-associated
- ◯ Squamous cell carcinoma, HPV-independent

**Carcinomas of the nasopharynx**

☐ Low grade nasopharyngeal papillary adenocarcinoma
☐ Keratinising squamous cell carcinoma
☐ Non-keratinising squamous cell carcinoma
☐ Basaloid squamous cell carcinoma

**Salivary gland-type carcinoma,[b] *specify type***

**Neuroendocrine neoplasm, *specify type***

**Other, *specify***

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

**HISTOLOGICAL TUMOUR GRADE[c]** (Note 8)

*(Applicable to conventional HPV- or EBV-independent tumours, salivary gland tumours or neuroendocrine 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*

[c] *Grading of neuroendocrine tumours is non-core. Use only Grade 1, 2 and 3 for neuroendocrine tumours; neuroendocrine carcinomas are considered high grade by definition and are therefore not graded.*

**EXTENT OF INVASION** (Note 9)

◯ Not identified
◯ Present, *specify*

☐ Clinical observation and/or imaging ☐ Histologic

◯ Cannot be assessed, *specify*

**LYMPHOVASCULAR INVASION** (Note 10)

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

**PERINEURAL INVASION[d]** (Note 11)

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

[d] *Non-core for nasopharyngeal carcinomas.*

**MARGIN STATUS** (Note 12)

**Invasive carcinoma[e]**

◯ 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[f,g]**

◯ 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] *There is no clear morphologic distinction between invasive and in situ carcinoma for HPV-associated oropharyngeal and EBV-associated nasopharyngeal carcinomas, so all carcinoma at margin should be included in evaluation simply as 'involved by carcinoma'.*

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

[g] *Only applicable for HPV-independent oropharyngeal and EBV-independent nasopharyngeal tumours and for tonsillar surface disease.*



ISBN: 978-1-922324-47-4

**COEXISTENT PATHOLOGY** (Note 13)

- ◯ None identified
- ◯ Present, *specify*

**ANCILLARY STUDIES** (Note 14)

**Viral testing/Viral tumour markers**

- ◯ Not performed/Not known
- ◯ Performed (select all that apply)
  - ☐ p16 immunohistochemistry[h]
    - ◯ Positive
      - ◯ >70% block-like, nuclear and cytoplasmic staining of at least moderate to strong intensity
      - ◯ Other criterion used, *specify*
    - ◯ Negative
      - Criteria used to determine results, *specify*
  - ☐ EBV (EBER) in situ hybridization[i]
    - ◯ Positive
    - ◯ Negative
  - ☐ High risk HPV specific testing[h]
    - DNA PCR: ◯ Not identified ◯ Present
    - DNA in situ hybridization: ◯ Not identified ◯ Present
    - E6/E7 mRNA in situ: ◯ Not identified ◯ Present
    - E6/E7 mRNA RTPCR: ◯ Not identified ◯ Present

**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***

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

[h] *Only recommended for oropharynx.*

[i] *Only recommended for nasopharynx.*

**PATHOLOGICAL STAGING (UICC TNM 8th edition)[j]** (Note 15)

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

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

**Primary tumour (pT)[k]**

p16 POSITIVE OROPHARYNX (HPV-ASSOCIATED)

- ◯ T0 No evidence of primary tumour, but p16 positive cervical node(s) involved
- ◯ T1 Tumour 2 cm or less in greatest dimension
- ◯ T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension
- ◯ T3 Tumour more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
- ◯ T4 Tumour invades any of the following: larynx,[l] deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, mandible,[l] lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery

p16 NEGATIVE OROPHARYNX (HPV-INDEPENDENT)

- ◯ Tis Carcinoma in situ
- ◯ T1 Tumour 2 cm or less in greatest dimension
- ◯ T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension
- ◯ T3 Tumour more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
- ◯ T4a Moderately advanced local disease
  Tumour invades any of the following: larynx,[l] deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, or mandible
- ◯ T4b Very advanced local disease
  Tumour invades any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery

NASOPHARYNX

- ◯ T0 No evidence of primary tumour, but EBV-positive (EBV-associated) cervical node(s) involved
- ◯ T1 Tumour confined to the nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal involvement
- ◯ T2 Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles
- ◯ T3 Tumour invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses
- ◯ T4 Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or infiltration beyond the lateral surface of the lateral pterygoid muscle

[j] *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).*

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

[l] *Mucosal extension to lingual surface of epiglottis from primary tumours of the base of the tongue and vallecula does not constitute invasion of the larynx.*

# 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 DAC.

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# Scope

The dataset has been developed for the reporting of resection and biopsy specimens of the oropharynx and nasopharynx. For resections of recurrent disease, the reporting guide may be used pragmatically although some data elements may be not applicable nor assessable. The protocol applies to all primary carcinomas (including of minor salivary glands) of the nasopharynx and oropharynx, the latter including the base of tongue, tonsils, tonsillar fossa, tonsillar pillars, soft palate, posterior and lateral walls, and uvula. Although rare, neuroendocrine tumours (NET) and neuroendocrine carcinomas (NEC) are also included. It does not apply to recurrent disease but may be used for residual disease after prior therapy (see below). Lymphomas, sarcomas, and mucosal melanomas 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 datasets which may be used, as appropriate, in conjunction with this dataset.[2]

When a biopsy specimen is the only specimen ever received, elements specific to the biopsy should be reported, recognising elements applicable to surgically resected tumours cannot be reliably completed. Although multiple synchronous and metachronous primary oropharyngeal squamous cell carcinomas (SCC) are uncommon and are usually of the same high risk human papillomavirus (HPV) type, there is no data to suggest that they are not simply separate primary tumours.[3] Thus, for oropharyngeal carcinomas, each distinct focus should be considered a separate primary tumour, and should receive its own separate dataset. However, for nasopharyngeal tumours, even if the tumour appears to be multifocal clinically and pathologically, these are regarded and treated as a single primary.[4-6]

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.[7]

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)

Treatment with primary chemoradiation is the most common approach for patients with carcinomas of the nasopharynx and oropharynx as a first line therapy. However, for oropharynx cancer patients, primary surgery can be used with or without adjuvant therapy after surgery based on the staging, particularly for small primary tumours and clinically early-stage patients. Neoadjuvant therapy prior to surgery is typically administered in the context of a clinical trial. Patients should be clinically staged based on the features at primary presentation, irrespective of the subsequent treatment undertaken. Salvage surgery may be performed and prior treatment can have a profound impact on the tumour, including its stage. For this reason, it should be clearly stated if the patient has received prior therapy (definitive or neoadjuvant), whether chemotherapy, targeted therapies, immunotherapies, radiation or multimodality.

Unlike other anatomic sites where pathologic treatment response quantification/characterisation is prognostic and may determine additional treatments, in oropharyngeal carcinomas, this has not been clearly established as clinically significant. However, some data suggests that complete pathologic treatment response may be prognostically favourable, particularly in post-treatment neck dissection specimens.[8]

For nasopharyngeal carcinomas, primary surgical resection is rare. Most patients will receive primary chemotherapy and radiation (usually as concurrent treatment, but as induction chemotherapy for T4 or N2/N3 disease) with post-treatment endoscopy and imaging between 6 to 12 weeks later, with the simple binary presence of viable tumour or not dictating need for additional therapy.[9-11] The degree of treatment response, at least on pathologic grounds, has not been determined to be significant.

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## Note 2 – Operative procedure (Core)

**Oropharynx**

Many oropharyngeal carcinomas are treated non-surgically so that guidance relating to small biopsies is most appropriate for these tumours.[12]

Transoral surgical approaches such as transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) have shown promising oncologic outcomes and are also utilised, particularly for small, early carcinomas, both HPV-associated and HPV-independent.[13-15] Open surgical resection is uncommon. Resection specimens of carcinomas from this area should be carefully oriented by the surgeon so that surgically important resection margins can be appropriately sampled and reported.

**Nasopharynx**

The vast majority of nasopharyngeal carcinomas are treated non-surgically so that guidance relating to small biopsies is most appropriate for these tumours.[16,17] The rare primary resection specimens of carcinomas from this area and salvage nasopharyngectomy specimens should be carefully oriented by the surgeon so that surgically important resection margins can be appropriately sampled and reported.

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## Note 3 – Specimen(s) submitted (Core)

**Oropharynx (Figures 1 and 2)**

The oropharynx is the portion of the continuity of the pharynx extending from the plane of the superior surface of the soft palate to the plane of the superior surface of the hyoid bone or floor of the vallecula.[18,19] The contents of the oropharynx include:

- soft palate
- palatine tonsils
- anterior and posterior tonsillar pillars
- tonsillar fossa
- uvula
- base of tongue (lingual tonsil)
- vallecula
- posterior oropharyngeal wall
- lateral oropharyngeal wall.

**Nasopharynx (Figure 1)**

The nasopharynx is the superior portion of the pharynx and is situated behind the nasal cavity and above the soft palate; it begins anteriorly at the posterior choana and extends along the plane of the airway to the level of the free border of the soft palate.[18,19] The inferior portion of the soft palate is oropharyngeal and the superior portion nasopharyngeal. Superiorly, the nasopharynx extends to the skull base. The contents of the nasopharynx include:

- nasopharyngeal tonsils (adenoids) which lie along the posterior and lateral aspect of the nasopharynx
- orifices of the Eustachian tubes which lie along the lateral aspects of the nasopharyngeal wall anterior to the fossa of Rosenmüller

- torus tubarius which is an elevation of mucosa that separates the Eustachian tube from the fossa of Rosenmüller
- fossa of Rosenmüller (lateral pharyngeal recess)
- posterior nasopharyngeal wall.

**Waldeyer's ring**

Waldeyer's ring is formed by a ring or group of extranodal lymphoid tissues at the upper end of the pharynx and consists of the:

- palatine tonsils
- nasopharyngeal tonsils (adenoids)
- base of tongue (lingual tonsil)
- adjacent submucosal lymphatic tissues.

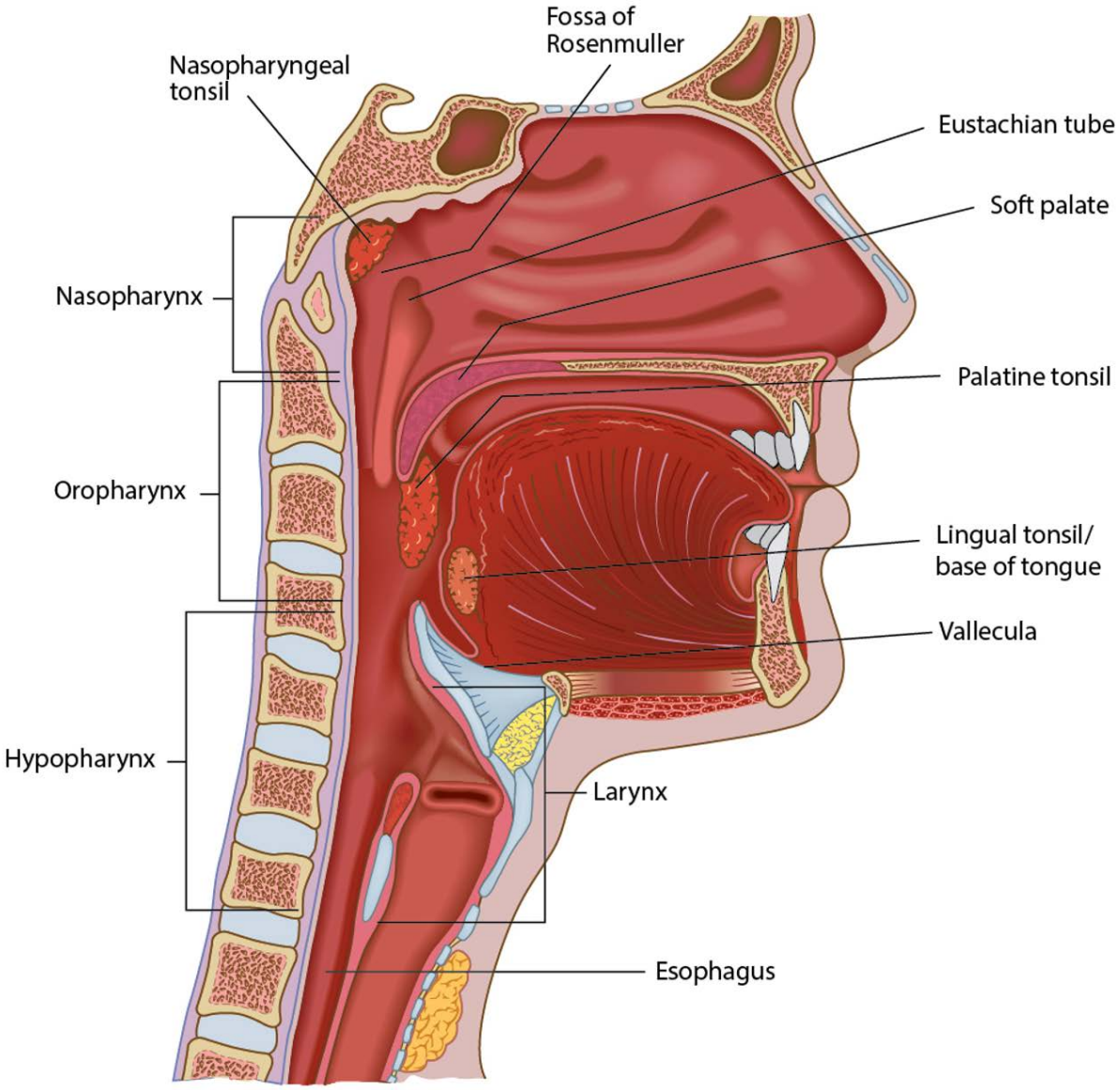


**Figure 1: Normal anatomy of the pharynx.**

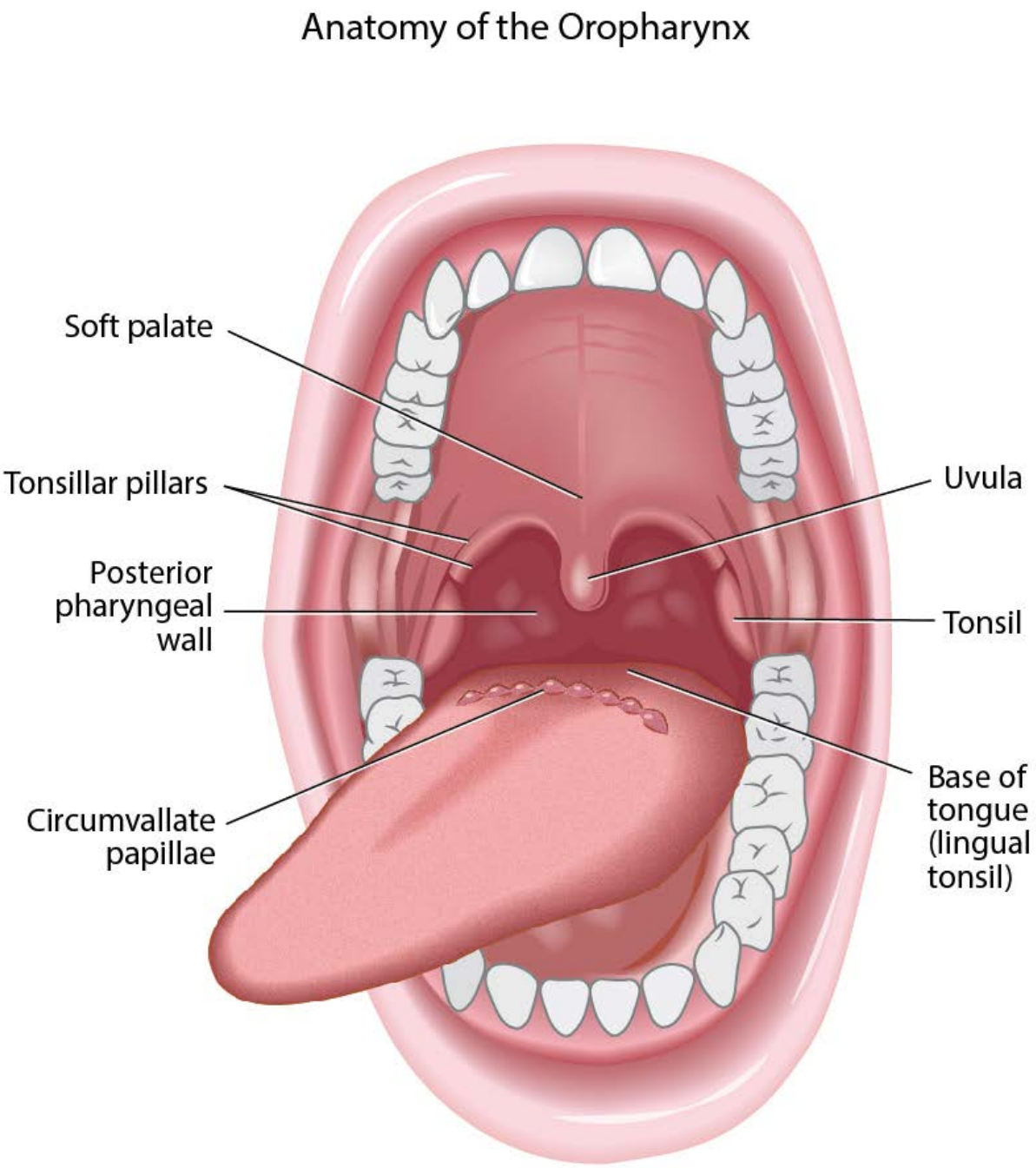


**Figure 2: Normal anatomy of the oropharynx.**



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## Note 4 – Tumour site (Core)

Tumour site is important for understanding the locations within the pharynx in pathology specimens that are affected by tumour and provides information beyond T-classification that may be useful for the management of patients, such as for precisely targeted radiation therapy and for surgical resection or re-resection.[18,19] Furthermore, the majority of HPV-associated cancers arise in the palatine tonsils or base of tongue. Tumour location may provide important information about the likelihood of HPV association, if HPV testing cannot be performed.

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## Note 5 – Tumour dimensions (Core and Non-core)

Tumour dimensions are used for T-classification of oropharyngeal carcinomas, at least for early stage tumours.[18,19] In addition, tumour size may be helpful clinically in making decisions about the details of therapy or extent of disease in post-treatment recurrence specimens. At least the greatest tumour dimension should be reported (core); preferably all three dimensions should be evaluated (non-core).

The macroscopic diameter (in millimetres) should be used unless the histological extent measured on the glass slides is greater than what is macroscopically apparent, in which case the microscopic dimension is used. As for other tissues, measurements are made pragmatically, acknowledging distortion of tissues by cautery, processing, and other possible artefacts. For cases where the exact size of the tumour cannot be precisely assessed pathologically, such as transoral resection specimens received fragmented, an estimate should be provided that will allow for provision of one of the T-classifiers that are based on size.[20] Tumour size is also important in salvage nasopharyngectomy specimens as a correlate to prognosis after surgery.[21-24]

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## Note 6 – 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 should the need for internal or external review arise. The reviewer needs to be clear about 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 may be useful to have a digital image of the specimen and record of the origin of the tumour blocks in some cases.

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

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## Note 7 – Histological tumour type (Core)

All tumours of the oropharynx and nasopharynx should be classified based on the most recent edition of the WHO Classification of Head and Neck Tumours, 5th edition, 2024 (Tables 1 and 2).[7]

The latest WHO Classification of carcinomas of the oropharynx[7] has simplified the nomenclature of oropharyngeal SCC to HPV-associated (p16 positivity is an acceptable surrogate marker) and HPV-independent (p16 negativity is an acceptable surrogate marker), removing further histologic typing. Specifically, HPV-associated is the term applied even if only p16 is performed. This is because for HPV-associated SCCs, histologic subtype (non-keratinising, basaloid, papillary, etc.) does not appear to further segregate outcomes in any meaningful or reproducible way. However, even if the HPV status is known, the histologic type can still be useful for pathology practice (comparison to possible new primaries, for frozen sections, and for comparison with possible metastases that may subsequently occur). In this ICCR dataset we recommend recording histological type and viral status as separate data items.

For nasopharyngeal carcinomas, the WHO Classification[7] still refers to them by histologic type. However, Epstein-Barr virus (EBV) status (generally by EBER in situ hybridisation) should be assessed and reported as well, if possible.

Salivary gland carcinomas are classified based on 5th edition WHO Classification, and matching the ICCR Carcinomas of the major salivary glands dataset.[7,25,26] Histologic type essentially defines biologic behaviour amongst salivary gland carcinomas and thus influences prognosis, patterns of recurrence, and thus clinical management.[27-29] Refer to the ICCR Carcinomas of the major salivary glands dataset for more details.[25] The ICCR Carcinomas of the oropharynx and nasopharynx dataset applies only to minor salivary carcinomas arising at these specific sites.

For neuroendocrine neoplasms, there is a paucity of data regarding stage variables and outcome in the oropharynx and nasopharynx, but histologic typing (see **SCOPE**) provides strong and useful information for treatment and prognosis.[30,31] A subset of oropharyngeal NECs are HPV-associated, however, HPV status does not appear to affect prognosis.[32]

**Table 1: World Health Organization classification of tumours of the oropharynx.[7]**

| Descriptor | ICD-O codes[a] |
|---|---|
| **Squamous cell carcinoma** | |
| Squamous cell carcinoma, HPV-associated | 8085/3 |
| Squamous cell carcinoma, HPV-independent | 8086/3 |

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).[33] 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.

**Table 2: World Health Organization classification of tumours of the nasopharynx.**[7]

| Descriptor | ICD-O codes[a] |
|---|---|
| **Nasopharyngeal carcinoma** | |
| Non-keratinising squamous cell carcinoma | 8072/3 |
| Keratinising squamous cell carcinoma | 8071/3 |
| Basaloid squamous cell carcinoma | 8083/3 |
| Low grade nasopharyngeal papillary adenocarcinoma | 8260/3 |

[a] These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).[33] 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.



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## Note 8 – Histological tumour grade (Core)

Histological tumour grade is only applicable for conventional, EBV-negative nasopharyngeal carcinomas and for HPV-independent oropharyngeal and nasopharyngeal carcinomas and for carcinomas where the viral status cannot be determined. If the tumour is post-treatment, grading is not applicable since there are no studies establishing its significance. The 'other' category should be selected for salivary carcinomas and neuroendocrine neoplasms. Salivary carcinomas should be graded according to grading systems for individual tumour types, when applicable (refer to the ICCR Carcinomas of the major salivary glands dataset for details[25]). Neuroendocrine neoplasms should be graded as per the ICCR Carcinomas of the hypopharynx, larynx and trachea dataset.[34]

For virus-associated oropharyngeal and nasopharyngeal SCCs, formal grading is not applicable.[35] HPV-associated oropharyngeal carcinomas and EBV-positive nasopharyngeal carcinomas are prognostically favourable relative to the virus negative ones, yet appear poorly-differentiated morphologically due to their lymphoepithelial or non-keratinising morphology.[36,37-39]

For the virus negative SCCs ('conventional' tumours) in both the oropharynx and nasopharynx, grading is based on the degree of resemblance to the normal epithelium and follows the descriptions in the WHO Classification.[7] This is identical to conventional SCCs at other head and neck anatomic subsites. Specific variants of SCC, such as spindle cell, verrucous, basaloid, papillary, and adenosquamous, have intrinsic biological behaviours and currently do not require grading.

Neuroendocrine neoplasms, as newly defined,[7] include paraganglioma/pheochromocytoma, NETs, and NECs. NETs are separated into grades (1, 2, and 3) based on mitotic rate: grade 1: <2 mitoses/2 millimetres $(mm)^2$; grade 2: ≥2-10 mitoses/2 $mm^2$; grade 3: ≥11 mitoses/2 $mm^2$. Ki-67 proliferation indices should be reported, but criteria for grading based on Ki-67 are not yet fully developed for each of the anatomic sites in the head and neck. Grade 1 tumours generally have a Ki-67 proliferation index of < 2%, grade 2 of 2-20% and grade 3 >20%.[31,40] NECs are separated into small cell and large cell categories, showing tumour necrosis, >10 mitoses/2 $mm^2$ and >20% Ki-67 proliferation index,[31,41-43] with universal Rb1 loss and common p53 overexpression.[44] At present, the site, tumour category, and grade should be reported, with additional advances in this field incorporated when validated further.

Salivary gland neoplasms in minor sites are sufficiently uncommon as to make prognostication challenging. As such, reporting of the histologic tumour type and grade based on the ICCR Carcinomas of the major salivary glands dataset is recommended,[25] while still reporting the additional findings based on anatomic location of the tumour.

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## Note 9 – Extent of invasion (Core)

Extent of tumour invasion is a key parameter used to assign appropriate T category for both oropharyngeal and nasopharyngeal carcinomas.[18,19] T category provides important prognostic information and, therefore, must be documented for resection specimens.[45-50] Because nasopharyngectomies are uncommon and performed as a salvage treatment option, there is limited prognostic data but pathologic T category appears to correlate with outcomes even in this setting.[24,51] It should be noted that the Tis (carcinoma in situ) category does not apply to either HPV-associated oropharyngeal or EBV-associated nasopharyngeal SCCs. Tumour depth of invasion (DOI) is also not a component of the T category for either nasopharyngeal or oropharyngeal carcinomas regardless of virus status. DOI should not be reported, especially for HPV and EBV-associated SCCs, which often arise from crypt mucosa deep to the surface and the point of origin cannot be determined nor can an accurate depth measured.

For oropharyngeal carcinomas, a combination of tumour size and extent determine the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) T category.[18,19] Extension to the lingual surface of the epiglottis warrants classification as pT3 and invasion of the larynx, extrinsic muscle of the tongue, medial pterygoid, hard palate, mandible or beyond is a pT4 tumour. The pT4 category is further subdivided into pT4a and 4b for HPV-independent tumours only, with invasion of the larynx, extrinsic muscle of the tongue, medial pterygoid, hard palate or mandible defining pT4a tumours and invasion of the lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base or encasement of the carotid artery indicating a pT4b tumour.

For nasopharyngeal carcinomas, tumour extent alone determines UICC and AJCC T category.[18,19] Tumour confined to the nasopharynx with or without extension to the oropharynx and/or nasal cavity is a pT1 tumour. pT2 tumours extend into the parapharyngeal space and/or adjacent soft tissue (medial or lateral pterygoids or prevertebral muscle). pT3 tumours involve bony structures at the skull base, cervical vertebrae, pterygoids and/or paranasal sinuses. pT4 tumours have intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland and/or extensive soft tissue involvement beyond the lateral surface of the lateral pterygoid muscle.

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## Note 10 – Lymphovascular invasion (Core)

The presence or absence of lymphovascular invasion should be documented if carcinoma is clearly identified within endothelial-lined spaces. This must be carefully distinguished from retraction artefacts. It is not necessary to distinguish between small lymphatics and venous channels. While the presence of nodal metastases indicates that lymphatic invasion must be present, this element should only be reported as positive when lymphovascular invasion is identified microscopically in the primary tumour specimen. Otherwise, it should be listed as 'not identified'. Several retrospective studies on surgically-treated oropharyngeal SCC show a statistically significant decrease in prognosis for patients with lymphovascular

space invasion, independent of other clinical and pathologic features.[52-56] The presence of lymphovascular invasion may impact decisions on therapy. If it is the only risk factor present, then by American Society for Radiation Oncology (ASTRO) guidelines it may be used to advise post-operative radiation after informed patient discussion.[57]

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 11 – Perineural invasion (Core)

Traditionally, the presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.[58] This refers to standard haematoxylin and eosin (H&E) stained material showing the presence of tumour growing in the perineural plane/space and not to tumour simply surrounding or near nerves. The relationship between perineural invasion and prognosis appears to be largely independent of nerve diameter.[59] The few studies (mostly surgical resection-related) looking at perineural invasion exclusively in oropharyngeal SCCs show either borderline significance or none, when controlling for HPV status, etc.[52-54,60,61] Perineural invasion is uncommon in HPV-associated tumours and, thus, its significance may be difficult to establish. Although its impact in oropharyngeal tumours may not be equivalent to other anatomic subsites in the head and neck, it is still an important data element and may impact decisions on therapy. If it is the only risk factor present, then by ASTRO guidelines it may be used to administer post-operative radiation after informed patient discussion.[57] There are no data on perineural invasion for nasopharyngeal carcinomas so it is considered non-core for these tumours.

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## Note 12 – Margin status (Core)

Positive resection margins are a consistently adverse prognostic feature in patients with oropharyngeal SCC, when tightly defined, although this impact might be less in the HPV-associated patient.[45,62-65] The definition of a positive margin is controversial.[66,67] However, 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 tumour).[66] The reporting of surgical margins should also include information regarding the distance of invasive carcinoma or carcinoma in situ/high grade dysplasia from the surgical margin. Tumours with 'close' margins also carry an increased risk for local recurrence,[66,68,69] but the definition of a 'close' margin is not standardised as the effective cut-off varies between studies and between anatomic subsites and the risk of a close margin may be lower in HPV-associated tumours.[70] Thus, distance of tumour from the nearest margin should be recorded when it can be measured. Distance may not be feasible to report if separate margin specimens are submitted in addition to the main specimen. In this instance, state that margins are negative, but do not provide a distance. Margin evaluation may not be possible in TLM specimens, if the tumour is excised in pieces and the true margins are not designated by the surgeon. It may be possible to refine the margin status following discussion with the surgical team.

Because of the uncertainty and difficulty (if not impossibility) of telling in situ from invasive ('metastasis-capable') SCC in crypt-derived (usually viral-associated) tumours of the oropharynx and nasopharynx, the

reporting is simplified here just as 'distance of closest carcinoma' to the margin, without reference to invasive or in situ.

Reporting of surgical margins for non-squamous carcinomas should follow those used for such tumours at all head and neck subsites.

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## Note 13 – Coexistent pathology (Non-core)

Some coexistent pathologic findings can be significant for the index cancer, the most obvious of which are areas of extensive or discontinuous surface squamous dysplasia, but coexistent diseases or other malignancies (such as lymphoma) could be clinically relevant. Judgment of the reporting pathologist will dictate the information provided in this element.

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## Note 14 – Ancillary studies (Core and Non-core)

In resource-limited practices (or when only extremely limited biopsy samples are available that preclude further testing etc.) where p16/HPV (oropharynx) or EBV (nasopharynx) testing cannot be performed, staging and treatment of patients will be inherently different.[71] The UICC and AJCC recommend that oropharyngeal SCCs that cannot be tested for p16/HPV be regarded and treated as HPV-negative.[18,19] This guidance should be followed for completing the ICCR Carcinomas of the oropharynx and nasopharynx dataset.

Given that most HPV-associated oropharyngeal SCCs are non-keratinising morphologically, arise deep in the tonsillar or base of tongue parenchyma, have cystic nodal metastases, and may have particular clinical features such as arising in non-smokers, certain patients can be strongly suspected as having HPV-associated tumours. In particular, non-keratinising histologic morphology, present in 50-60% of oropharyngeal SCC, correlates very well with positive HPV status.[72] However, prediction of HPV status by such surrogate markers and clinical grounds is less reliable than p16/HPV testing.[73] Thus, when determining optimal treatment for patients, local practices must carefully exercise their own judgment and decide on what grounds they can classify patients as (likely) HPV-associated in their populations.

It is now well established that HPV plays a pathogenic role in a large subset of oropharyngeal SCCs.[74,75] A smaller subset of nasopharyngeal carcinomas is related to transcriptionally active high-risk HPV but the prognostic significance is less certain than in the oropharynx.

Human papillomavirus (HPV)-associated oropharyngeal carcinoma represents a unique SCC type with proven more favourable prognosis than for HPV-independent tumours.[38,76] Staging of these patients is different than for HPV-independent tumours and treatment differences are emerging.

There are many methods for testing HPV status. p16 immunohistochemistry is a simple validated HPV surrogate and prognostic marker in oropharyngeal SCC.[77] The most commonly used criterion for positivity as a surrogate marker is: moderate to intense, block-like, nuclear and cytoplasmic staining in ≥70% of the tumour cells,[78] with the caveat that the correlation with HPV status is not 100%.[79,80] The combination of p16 immunohistochemistry with non-keratinising morphology is very strongly associated with transcriptionally-

active high-risk HPV in the oropharynx. Even so, a small minority of patients will be misclassified.[72,81,82] Emerging evidence indicates that p16/HPV discordant tumours are associated with reduced survival compared to double positive tumours.[81-84] Furthermore, the p16/HPV discordant population may be significantly larger in low HPV prevalence geographic regions.[85] HPV specific tests include in situ hybridisation for DNA, PCR for HPV-DNA, RT-PCR for HPV-mRNA, and in situ hybridisation for mRNA. There is no consensus on the best methodology for HPV testing but the WHO, UICC, AJCC, and the College of American Pathologists have all recommended p16 immunohistochemistry.[7,18,19,35] Thus, p16 is considered 'core' in oropharyngeal SCCs. Additional HPV-specific testing is recommended at the discretion of the pathologist and may be important for accurate determination of viral status in certain scenarios (i.e., non-core). HPV specific testing should be considered when p16 is equivocal or there is discordance between the p16 result and tumour morphology, in low HPV prevalence geographic regions, and as required for clinical trials.[7]

Epstein-Barr virus (EBV) is associated with the non-keratinising types of nasopharyngeal carcinomas in the vast majority of patients. The most reliable detection method for EBV is in situ hybridisation for EBV encoded early RNA (EBER) present in cells latently infected by EBV, and is recommended because it is a modestly strong favourable prognostic marker.[36] EBV serology may also be a clinically useful post-treatment surveillance option in EBV-positive tumours.[9,86] A subset of nasopharyngeal carcinomas are related to transcriptionally-active high risk HPV.[87-89] Most of these tumours are described as non-keratinising differentiated using the WHO terminology. They are EBV (EBER) negative and p16 positive. HPV is not clearly prognostic in nasopharyngeal carcinomas.[90] Testing for HPV/p16 in EBV negative non-keratinising carcinomas, however, is at the discretion of the local practice (non-core). It may be indicated in routine clinical practice to help alert the clinician that this may be an oropharyngeal primary tumour that is secondarily involving the nasopharynx and not because the HPV is of proven prognostic benefit in such tumours.[87-89]

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 SSC,[91-94] with various cutoffs of expression associated with betters responses, although not in all patients.[95] There are two scoring systems for PD-L1 expression, tumour proportion score (TPS) and combined positive score (CPS). CPS is the preferred scoring system in head and neck cancers.

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.[40,44,96]

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## Note 15 – Pathological staging (Core)

This protocol recommends the T category schemes published for the pharynx in the 8th edition of the UICC and AJCC.[18,19] It is quite noteworthy that the oropharyngeal carcinomas staging has been modified significantly from past systems, as the identification of HPV-associated oropharyngeal SCC as a specific subgroup means that the older versions ineffectively stratify outcomes.[49,97-101] In essence, a separate TNM

classification was introduced for the first time in the 8th edition to address the need for HPV-associated oropharyngeal cancers.[18,19]

By UICC/AJCC convention,[18,19] 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 referring physician 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 without total removal of the primary cancer, and thus this information provided.

**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.[102]

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,[18,19] 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.[18,19]

The reference document TNM Supplement: A commentary on uniform use, 5th Edition (C Wittekind et al. editors) may be of assistance when staging.[103]

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