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Carcinomas of the Nasopharynx and Oropharynx Histopathology Reporting Guide



Family/Last name

Date of birth

Given name(s)

Patient identifiers

Date of request

Accession/Laboratory number

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

[SCOPE OF THIS DATASET](#)

NEOADJUVANT THERAPY (Note 1)

Information not provided

Not administered

Administered, *specify type*

Chemotherapy

Radiotherapy

Chemoradiotherapy

Targeted therapy, *specify if available*

Immunotherapy, *specify if available*

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

Not specified

Resection, *specify*

Transoral laser microsurgical resection

Transoral robotic surgical resection

Other, *specify*

Biopsy (excisional, incisional), *specify*

Neck (lymph node) dissection*, *specify*

Other, *specify*

* If a **neck dissection** is submitted, then a separate dataset is used to record the information.

SPECIMENS 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 if necessary*

Other, *specify*

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

Cannot be assessed

Oropharynx

Left

Right

Midline

Laterality not specified

Palatine tonsil

Base of tongue/lingual tonsil

Soft palate

Uvula

Pharyngeal wall (posterior)

Pharyngeal wall (lateral)

Other, *specify*

Nasopharynx

Left

Right

Midline

Laterality not specified

Nasopharyngeal tonsils (adenoids)

Fossa of Rosenmüller

Lateral wall

Other, *specify*

Other, *specify including laterality*

TUMOUR DIMENSIONS (Note 5)

Maximum tumour dimension (largest tumour)

Additional dimensions (largest tumour)

 x Cannot be assessed, *specify***HISTOLOGICAL TUMOUR TYPE** (Note 6)*(Value list from the World Health Organization Classification of Head and Neck Tumours (2017))* **Salivary gland carcinoma, specify type** **Neuroendocrine carcinoma, specify type** **Other, specify type****Carcinomas of the oropharynx** Squamous cell carcinoma, conventional Keratinizing Nonkeratinizing Nonkeratinizing with maturation ("partially keratinizing") Acantholytic squamous cell carcinoma Adenosquamous carcinoma Basaloid squamous cell carcinoma Papillary squamous cell carcinoma Spindle cell carcinoma Verrucous carcinoma Lymphoepithelial carcinoma**Carcinomas of the nasopharynx** Nonkeratinizing squamous cell carcinoma Differentiated Undifferentiated (lymphoepithelial) Keratinizing squamous cell carcinoma Basaloid squamous cell carcinoma Nasopharyngeal papillary adenocarcinoma Cannot be assessed, *specify***HISTOLOGICAL TUMOUR GRADE** (Note 7) Not applicable GX: Cannot be assessed G1: Well differentiated G2: Moderately differentiated G3: Poorly differentiated Other, *specify* Cannot be assessed, *specify***DEPTH OF INVASION** (Note 8) Not applicable Cannot be assessed, *specify***PERINEURAL INVASION** (Note 9)*(Not applicable for nasopharynx)* Not identified Present Cannot be assessed, *specify***LYMPHOVASCULAR INVASION** (Note 10)*(Not applicable for nasopharynx)* Not identified Present Cannot be assessed, *specify***MARGIN STATUS** (Note 11) **Invasive carcinoma**** Involved

Specify margin(s), if possible

 Not involved

Distance of tumour from closest margin

 Distance not assessable

Specify closest margin, if possible

 Carcinoma in situ/high-grade dysplasia*** Involved

Specify margin(s), if possible

 Not involved

Distance of tumour from closest margin

 Distance not assessable

Specify closest margin, if possible

 Not applicable *** Cannot be assessed, *specify*

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

*** Only applicable for HPV-negative oropharyngeal and EBV-negative nasopharyngeal tumours and for tonsillar surface disease. High-grade dysplasia is synonymous with moderate/severe dysplasia.

COEXISTENT PATHOLOGY (select all that apply) (Note 12)

- None identified
- Dysplasia[^]
 - Mild
 - Moderate
 - Severe
- Carcinoma in situ
 - Focal Multifocal
 - Discontinuous with the primary site
- Other, *specify*

[^] Applicable for oropharyngeal surface mucosal disease only; not for tonsillar crypt epithelium.

ANCILLARY STUDIES (Note 13)

Viral testing/Viral tumour markers

OROPHARYNX

- Not performed/unknown
- Performed (select all that apply)
 - p16 immunohistochemistry
 - Positive
 - >70% nuclear and cytoplasmic staining of at least moderate to strong intensity
 - Other criterion used, *specify*
 - Negative

Criteria used to determine results, *specify*

- High risk HPV specific testing
 - DNA PCR
 - Not identified Present
 - DNA in situ hybridization
 - Not identified Present
 - E6/E7 mRNA in situ hybridization
 - Not identified Present
 - E6/E7 mRNA RTPCR
 - Not identified Present

Viral testing/Viral tumour markers

NASOPHARYNX

- Not performed/unknown
- Performed
 - EBV (EBER) in situ hybridization - Positive
 - EBV (EBER) in situ hybridization - Negative

Other ancillary studies

- Not performed
- Performed, *specify*

PATHOLOGICAL STAGING (UICC TNM 8th edition)^{##} (Note 14)

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

- m - multiple primary tumours
- r - recurrent
- y - post-therapy

Primary tumour (pT)^{**}**

p16 Positive oropharynx

- 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^{^^}, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, mandible^{^^}, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery

p16 Negative oropharynx

- 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^{^^}, 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 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

^{****} If a lymph node/neck dissection is submitted, then a separate dataset is to be completed for the corresponding neck nodal disease specimen(s).

^{^^} 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.

^{##} Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2017, Publisher Wiley-Blackwell.

Scope

The dataset has been developed for the reporting of resection and biopsy specimens of the nasopharynx and oropharynx. The protocol applies to all invasive carcinomas of the nasopharynx and oropharynx including the base of tongue, tonsils, soft palate, posterior wall, and uvula. Lymphomas and sarcomas are not included. Neck dissections and nodal excisions are dealt with in a separate dataset, and this dataset should be used in conjunction, where applicable.

When a biopsy specimen is all that is received, elements specific to the biopsy should be reported and the remaining items that are applicable to surgically resected tumours omitted. For carcinomas of the oropharynx, there is no allowance for a single tumour that is “multifocal”. Although multiple synchronous and metachronous primary oropharyngeal squamous cell carcinomas 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.¹ 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.²⁻⁴

Note 1 – Neoadjuvant therapy (Core and Non-core)

Reason/Evidentiary Support

Treatment with primary chemoradiation is the most common approach for patients with carcinomas of the nasopharynx and oropharynx. However, for oropharynx cancer patients, primary surgery can be used with appropriate adjuvant therapy based on the staging, particularly for small primary tumours and clinically early stage patients. Patients should be clinically staged based on the features at primary presentation. 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 neoadjuvant therapy, whether chemotherapy, targeted therapies, immunotherapies, radiation or multiple modalities. Unlike other anatomic sites where pathologic treatment response quantification/characterization 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. For nasopharyngeal carcinomas, primary surgical resection is very uncommon. Most patients will receive primary chemotherapy and radiation with post-treatment endoscopy, biopsy, and imaging between 6 to 12 weeks later, with the simple binary presence of viable tumour or not dictating need for additional therapy. 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)

Reason/Evidentiary Support

Oropharynx

Many oropharyngeal carcinomas are treated non-surgically so that guidance relating to small biopsies is most appropriate for these tumours.⁵

Open surgical resections have become less common. Transoral approaches such as transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) that are less morbid and have shown promising oncologic outcomes and are utilized, particularly for small, early carcinomas, both HPV positive and negative.^{6,7} 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.⁸ 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 – Specimens submitted (Core)

Reason/Evidentiary Support

Oropharynx (Figure 1)

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.⁹ 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.⁹ 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
- fossa of Rosenmüller.

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
- pharyngeal tonsil (adenoids)
- base of tongue/lingual tonsil
- adjacent submucosal lymphatic tissues.

The oropharynx is clearly delineated from the nasopharynx by the soft palate. The inferior portion of the soft palate is oropharyngeal and the superior portion nasopharyngeal. Posteriorly, the nasopharynx extends from the level of the free edge of the soft palate to the skull base.

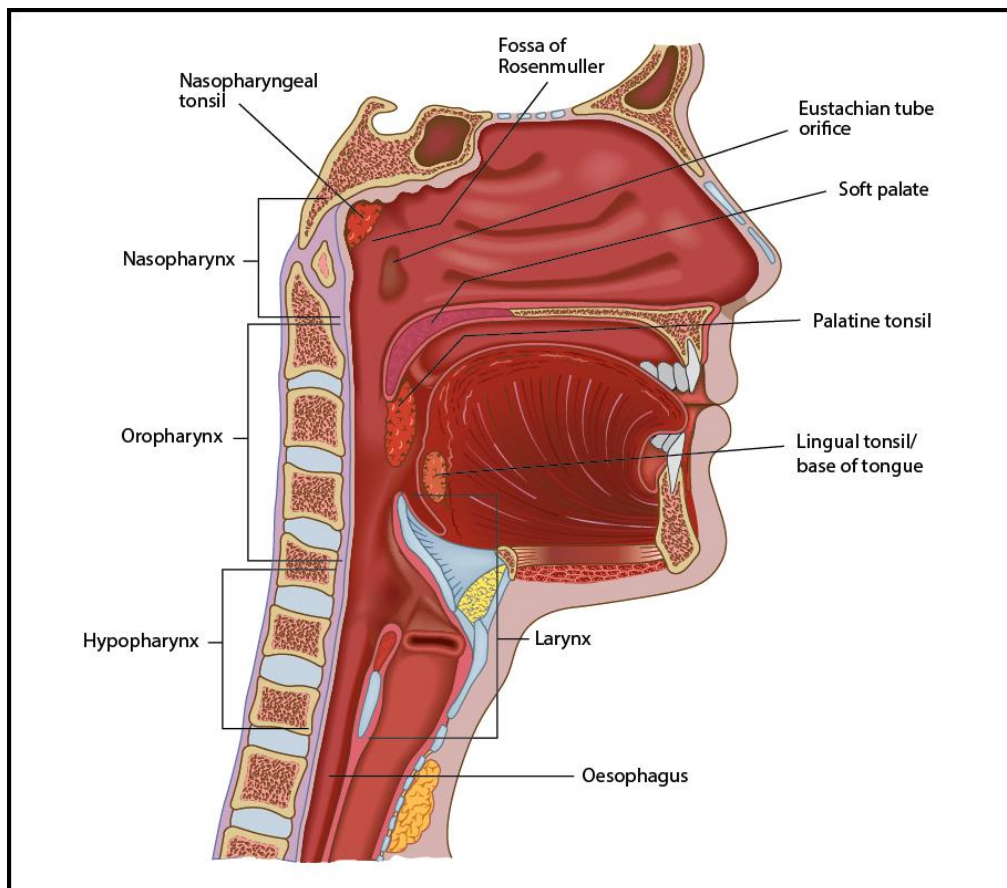


Figure 1. Normal anatomy of the pharynx

Note 4 – Tumour site (Core)

Reason/Evidentiary Support

Tumour site is important for understanding the locations within the pharynx in pathology specimens that are involved by tumour and provides information beyond T-classification that may be useful for the management of patients, such as for narrowly targeting radiation therapy and for surgical resection or re-resection.

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

Reason/Evidentiary Support

Tumour dimensions are used for T-classification of oropharyngeal carcinomas, at least for early stage tumours. 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. 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 transoral resection specimens that are received in multiple pieces, the exact size of the tumour cannot be precisely assessed pathologically. Even if an exact tumour size cannot be provided, an estimate should be provided that will allow for provision of one of the T-classifiers that are based on size.¹¹ Tumour size is also important in salvage nasopharyngectomy specimens as a correlate to prognosis after surgery.^{12,13}

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Note 6 – Histological tumour type (Core)

Reason/Evidentiary Support

The latest World Health Organization (WHO) classification of carcinomas of the oropharynx¹⁴ has simplified the nomenclature of oropharyngeal squamous cell carcinoma to HPV-positive (p16 positivity an acceptable surrogate marker) and HPV-negative (p16 negativity an acceptable surrogate marker), removing further histologic typing. This is because for HPV/p16 positive squamous cell carcinomas, histologic subtype (nonkeratinizing, basaloid, papillary, etc) does not appear to further segregate outcomes in any meaningful or reproducible way. However, even if HPV/p16 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 dataset we recommend recording histological type and viral status as separate data items.

For nasopharyngeal carcinomas, the WHO classification¹⁵ still refers to them by histologic type. However, Epstein-Barr Virus (EBV) status should be assessed and reported as well, if possible.

Salivary gland carcinomas are typed based on the recent WHO classification, and matching the International Collaboration on Cancer Reporting (ICCR) *Carcinomas of the major salivary glands* dataset,¹⁶ including the many new histologic and molecular subtypes. Histologic type essentially defines biologic behaviour amongst salivary gland carcinomas and thus influences prognosis, patterns of recurrence and thus clinical management.^{17,18} Refer to the ICCR *Carcinomas of the major salivary glands* dataset¹⁶ for more details.

For neuroendocrine carcinomas, there is a paucity of data regarding stage variables and outcome, but histologic typing provides strong and useful information for treatment and prognosis.

WHO classification of tumours of the nasopharynx^{a19}

Descriptor	ICD-O codes
Nasopharyngeal carcinoma	
Nonkeratinizing squamous cell carcinoma	8072/3
Keratinizing squamous cell carcinoma	8071/3
Basaloid squamous cell carcinoma	8083/3
Nasopharyngeal papillary adenocarcinoma (low grade)	8260/3
Salivary gland tumours	
Adenoid cystic carcinoma	8200/3
Salivary gland anlage tumour	

a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.

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WHO classification of tumours of the oropharynx (base of tongue, tonsils, adenoids)^{a20}

Descriptor	ICD-O codes
Squamous cell carcinoma	
Squamous cell carcinoma, HPV-positive	8085/3*
Squamous cell carcinoma, HPV-negative	8086/3*
Salivary gland tumours	
Pleomorphic adenoma	8940/0
Adenoid cystic carcinoma	8200/3
Polymorphous adenocarcinoma	8525/3
Haematolymphoid tumours	
Hodgkin lymphoma, nodular lymphocyte predominant	9659/3
Classical Hodgkin lymphoma	
Nodular sclerosis classical Hodgkin lymphoma	9663/3
Mixed cellularity classical Hodgkin lymphoma	9652/3
Lymphocyte-rich classical Hodgkin lymphoma	9651/3
Lymphocyte-depleted classical Hodgkin lymphoma	9653/3
Burkitt lymphoma	9687/3
Follicular lymphoma	9690/3
Mantle cell lymphoma	9673/3
T-lymphoblastic leukaemia/lymphoma	9837/3
Follicular dendritic cell sarcoma	9758/3

a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.

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Note 7 – Histological tumour grade (Core)

Reason/Evidentiary Support

Only applicable for conventional, EBV negative nasopharyngeal carcinomas and for HPV negative 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.

For virus-related oropharyngeal and nasopharyngeal squamous cell carcinomas, formal grading is not applicable. HPV-positive oropharyngeal carcinomas and EBV-related nasopharyngeal carcinomas are prognostically favourable relative to the virus negative ones, yet appear poorly differentiated morphologically due to their lymphoepithelial or nonkeratinizing morphology.^{21,22}

For the virus negative squamous cell carcinomas (“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. This is identical to conventional squamous cell carcinomas at other head and neck anatomic subsites. Specific variants of squamous cell carcinoma such as spindle cell, verrucous, basaloid, papillary, and adenosquamous have intrinsic biological behaviours and currently do not require grading.

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Note 8 – Depth of invasion (Non-core)

Reason/Evidentiary Support

Depth of invasion is less well established as a staging and prognostic parameter for oropharyngeal tumours than for oral cavity carcinomas. The maximum depth of invasion should be recorded in millimetres from the normal surface epithelium to the deepest point of tumour invasion, but *only* for those tumours clearly arising from the surface epithelium. This does *not* apply for those arising submucosally from the tonsillar crypt epithelium which lack landmarks from which to measure “depth”. For surface tumours, if the tumour is ulcerated, then the reconstructed surface should be used. Note that depth of invasion, defined in this way, is not the same as tumour thickness (measured from surface of tumour to deepest invasion) which will be larger than depth of invasion in exophytic tumours and smaller in ulcerated tumours.²³ The aim should be to provide a best estimate of tumour depth. A more detailed comment on the nature of the tissues invaded (mucosa, muscle, etc.) should occur in the 'comments' sections. Depth of invasion is significantly related to nodal metastasis for oropharyngeal carcinomas, although the optimal cut-off point for prognostic purposes is uncertain with 3 mm, 4 mm or 5 mm being suggested by different authors.²³⁻³¹ Depth of invasion is not clearly prognostic or clinically useful for nasopharyngeal carcinomas, but is a surrogate of tumour size in salvage nasopharyngectomy specimens, so reporting is encouraged (but not required) in these specimens. In addition, in centres that perform nasopharyngectomy procedures, additional information that should be provided would include the presence of sphenoid sinus or cavernous sinus invasion.^{12,13}

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Note 9 – Perineural invasion (Core)

Reason/Evidentiary Support

Traditionally, the presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.³² This refers to the H&E presence of tumour growing in the perineural plane/space and not to tumour simply surrounding or near to nerves. The relationship between perineural invasion and prognosis appears to be largely independent of nerve diameter.³³ The few studies (mostly surgical resection-related) looking at perineural invasion exclusively in oropharyngeal squamous cell carcinomas show either borderline significance or none,

when controlling for p16/HPV status, etc.³⁴⁻³⁶ It may be that it remains important in HPV negative tumours but has less or no significance for HPV positive ones. 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 American Society for Radiation Oncology (ASTRO) guidelines it may be used to administer post-operative radiation after careful discussion of patient preference.³⁷⁻³⁹ There are no data on perineural invasion for nasopharyngeal carcinomas so it is considered “not applicable” for these tumours.

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Note 10 – Lymphovascular invasion (Core)

Reason/Evidentiary Support

The presence or absence of lymphovascular invasion should be mentioned 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 squamous cell carcinoma show a statistically significant decrease in prognosis for patients with lymphovascular space invasion, independent of other clinical and pathologic features.^{34-36,40,41} The presence of lymphovascular invasion may impact decisions on therapy. If it is the only risk factor present, then by ASTRO guidelines it may be used to advise post-operative radiation after careful discussion of patient preference.³⁹

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Note 11 – Margin status (Core)

Reason/Evidentiary Support

Positive resection margins are a consistently adverse prognostic feature in patients with oropharyngeal squamous cell carcinoma, when tightly defined, although this impact might be less in the p16/HPV positive patient.^{34-36,40,41} The definition of a positive margin is controversial.^{42,43} However, several studies support the definition of a positive margin to be invasive carcinoma or carcinoma in situ/severe dysplasia present at margins (microscopic cut-through of tumour).⁴² The reporting of surgical margins should also include information regarding the distance of invasive carcinoma or severe dysplasia/carcinoma in situ from the surgical margin. Tumours with “close” margins also carry an increased risk for local recurrence,^{42,44,45} but the definition of a “close” margin is not standardized as the effective cut-off varies between studies and between anatomic subsites. 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. Distance from margins essentially cannot be ascertained in TLM, but may not be of the same significance as for en-bloc resections or TORS specimens.

Because of the uncertainty and difficulty (if not impossibility) of telling in situ from invasive (“metastasis-capable”) squamous cell carcinoma in crypt-derived 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 12 – Coexistent pathology (Non-core)

Reason/Evidentiary Support

Some coexistent pathologic findings can be significant for the index cancer, the most obvious of which is 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 section.

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Note 13 – Ancillary studies, including viral testing (Core and Non-core)

Reason/Evidentiary Support

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.⁴⁶ The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) recommend that oropharyngeal squamous cell carcinomas that cannot be tested for p16/HPV be regarded and treated as HPV-negative. This recommendation should be followed for the completion of the ICCR dataset.

Given that most HPV-related oropharyngeal squamous cell carcinomas are nonkeratinizing morphologically, arise deep in the tonsillar parenchyma, have cystic nodal metastases, and may have particular clinical features such as arising in non-smokers who are younger than typical head and neck squamous cell carcinomas, certain patients can be strongly suspected as having HPV-related tumours. In particular, nonkeratinizing histologic morphology, present in 50-60% of oropharyngeal squamous cell carcinoma, correlates very well with positive HPV status.⁴⁷ However, prediction of HPV status by such surrogate marker and clinical grounds is less reliable than direct p16/HPV testing.⁴⁸ 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-related in their populations.

It is now well established that HPV plays a pathogenic role in a large subset of oropharyngeal squamous cell carcinomas.^{49,50} A smaller subset of nasopharyngeal carcinomas is related to transcriptionally active high risk HPV.

HPV-positive oropharyngeal carcinoma represents a unique squamous cell carcinoma type with proven more favourable prognosis than for HPV-negative tumours.⁵¹ Staging of these patients is now different than for HPV-negative tumours and treatment differences are emerging.

There are many methods for testing HPV status with p16 immunohistochemistry emerging as a simple, thoroughly validated prognostic marker in oropharyngeal squamous cell carcinoma (SCC).⁵² The most commonly used criterion for positivity as a surrogate marker moderate to intense nuclear and cytoplasmic staining in 70% or more of the tumour cells, which is the recommended cutoff for these guidelines,⁵³ with the caveat that the correlation with HPV status is not 100%.^{54,55} The combination of p16 immunohistochemistry with nonkeratinizing morphology is very strongly associated with transcriptionally-active high risk HPV in the oropharynx.⁴⁷ HPV specific tests include in situ hybridization for DNA, PCR for HPV-DNA, RT-PCR for HPV-mRNA, and in situ hybridization for mRNA. There is no consensus on the best methodology for HPV testing but the WHO, AJCC, UICC, and a College of American Pathologists Expert Panel have all recommended p16 immunohistochemistry. Additional HPV-specific testing is performed at the discretion of the pathologist.

The new WHO Blue Book terms squamous cell carcinomas of the oropharynx simply as HPV-positive or HPV-negative.^{14,56} However, they specifically note that p16 immunohistochemistry alone (with appropriate criteria for a positive versus negative test) is a suitable surrogate marker. They recommend the terminology HPV-positive even if only p16 is performed.

EBV is associated with the nonkeratinizing types of nasopharyngeal carcinomas in the vast majority of patients. The most reliable detection method for EBV is in situ hybridization 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 and because it is confirmation of the tumour having a nasopharyngeal association.²¹ A subset of patients with nasopharyngeal carcinoma are related to transcriptionally-active high risk HPV.⁵⁷⁻⁵⁹ Most of these tumours are described as nonkeratinizing differentiated using the WHO terminology. They are EBV (EBER) negative and p16 positive. Testing for HPV/p16 in EBV negative nonkeratinizing carcinomas, however, is at the discretion of the local practice. 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.⁵⁷⁻⁵⁹

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Note 14 – Pathological staging (Core)

Reason/Evidentiary Support

This protocol recommends the T-classification schemes published by the UICC and the 8th edition of the AJCC for the pharynx.^{9,60} It is quite noteworthy that the oropharyngeal carcinomas staging has been modified significantly from past systems, as the identification of HPV-positive oropharyngeal SCC as a specific subgroup means that the older versions ineffectively stratify outcomes.⁶¹

By convention, 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.

For identification of special cases of TNM or pTNM classifications, “y” and “r” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

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 tumour actually present at the time of that examination. The “y” categorization 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.

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References

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