

## Dataset for the histopathological reporting of carcinomas of the oropharynx and nasopharynx

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NICE has accredited the process used by the Royal College of Pathologists to produce its cancer datasets. Accreditation is valid for five years from 25 July 2017. More information on accreditation can be viewed at [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation).

For full details on our accreditation visit: [www.nice.org.uk/accreditation](http://www.nice.org.uk/accreditation).

## Foreword

The cancer datasets published by the Royal College of Pathologists (RCPATH) are a combination of textual guidance, educational information and reporting proformas. The datasets enable pathologists to grade and stage cancers in an accurate, consistent manner in compliance with international standards and provide prognostic information thereby allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. This guideline has been developed to cover most common circumstances. However, we recognise that guidelines cannot anticipate every pathological specimen type and clinical scenario. Occasional variation from the practice recommended in this guideline may therefore be required to report a specimen in a way that maximises benefit to the patient.

Each dataset contains core data items (see Appendices C and D) that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD – previously the National Cancer Data Set) v9.0 in England. Core data items are those that are supported by robust published evidence and are required for cancer staging, optimal patient management and prognosis. Core data items meet the requirements of professional standards (as defined by the Information Standards Board for Health and Social Care [ISB]) and it is recommended that at least 95% of reports on cancer resections should record a full set of core data items. Other non-core data items are described. These may be included to provide a comprehensive report or to meet local clinical or research requirements. All data items should be clearly defined to allow the unambiguous recording of data.

The following stakeholders were contacted to consult on this document:

- British Society for Oral and Maxillofacial Pathology (BSOMP)
- British Association of Head and Neck Oncologists (BAHNO)
- British Association of Oral and Maxillofacial Surgeons
- UK and Ireland Association of Cancer Registries
- comments from specialist and general histopathologists on the draft document that were published on the Royal College of Pathologists website were considered as part of the review of the dataset.

The information used by the authors to develop this dataset was obtained by undertaking a search of the PubMed database for relevant primary research evidence and systematic reviews on head and neck mucosal malignancies, either specifically in the oropharynx and nasopharynx or generally in the head and neck where these subsites can be separately identified, from January 2011 to December 2020 (inclusive). Key search terms searched included oropharynx, nasopharynx, clinical trial, prognosis, survival, surgery, chemotherapy and radiotherapy. In addition, abstracts from selected conference proceedings from American Society of Clinical Oncology (ASCO) were screened. The recommendations are in line with those of other national pathology organisations (College of American Pathologists, the Royal College of Pathologists of Australasia) and the ENT-UK Consensus document for the management of patients with head and neck malignancies ([www.entuk.org/publications](http://www.entuk.org/publications)). They incorporate the core data items and commentary from the International Collaboration on Cancer Reporting (ICCR).<sup>1</sup> The level of evidence for the recommendations has been summarised according to modified SIGN guidance (see Appendix E) and the grade of evidence is indicated in the text. No major conflicts in the evidence have been identified and minor discrepancies between studies have been resolved by expert consensus. Gaps in the evidence were identified by College members via feedback received during consultation.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset. The recommendation that primary carcinomas of the oropharynx are investigated for human papillomavirus (HPV) implies that the appropriate analytical facilities should be available and funded and the tests quality assured. Facilities for investigation of the presence of Epstein–Barr virus (EBV) should also be available.

All cancer datasets are formally revised every three years. However, each year, the College will ask the author of the dataset, in conjunction with the relevant subspecialty adviser to the College, to consider whether or not the dataset needs to be updated or revised. A full consultation process will be undertaken if major revisions are required. Major revisions to core data items, apart from changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies, will be implemented without further consultation. If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken whereby a short note of the proposed changes will be placed on the College website for two weeks for members' attention. If members do not object to the changes, the changes will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Clinical Effectiveness team, Working Group on Cancer Services and the Lay Network, and was placed on the College website for consultation with the membership from Tuesday 12 October to Tuesday 9 November. All comments received from the Working Group and membership were addressed by the author to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

This dataset was developed without external funding to the writing group. The College requires the authors of datasets to provide a list of potential conflicts of interest; these are monitored by the Clinical Effectiveness team and are available on request. The authors have declared no conflicts of interest.

## 1 Introduction

The dataset has been developed for the reporting of biopsy and resection 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 pharyngeal 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.

The primary purpose of this document is twofold:

- to define the set of data necessary for the uniform recording and staging of the core pathological features in cancers of the nasopharynx and oropharynx
- to describe its application in sufficient detail and clarity that reports from different departments will contain equivalent information, allowing comparison of clinical practice and outcomes.

Optimal reporting of specimens from the head and neck area requires a partnership between the pathologist and surgeon/oncologist. The surgeon can help the pathologist to provide the information necessary for patient management by the appropriate handling and labelling of the specimen in the operating theatre. The regular discussion of cases at multidisciplinary team (and other clinicopathological) meetings and correlation with pre-operative imaging studies are important in maintaining and developing this partnership.<sup>2</sup>

The core pathological data is summarised as proformas that may be used as the main reporting format or may be combined with free text as required. The core data differ between nasopharynx and oropharynx, but a common proforma for these primary sites has been employed, in keeping with the ICCR dataset, and the lymph node dataset is common to all sites. Individual centres may wish to expand the detail in some sections, e.g. for sites and subsites, to facilitate the recording of data for particular tumour types.

Certain features of invasive mucosal carcinomas (type, size and grade of the primary carcinoma, the pattern of invasion and proximity of carcinoma to resection margins) have been shown to be related to clinical outcome.<sup>3-11</sup> These features may therefore be important in:

- deciding on the most appropriate treatment for particular patients, including the extent of surgery and the use and choice of adjuvant radiotherapy, chemotherapy or targeted therapies<sup>12</sup>
- monitoring changing patterns of disease, particularly by cancer registries.

These features provide sufficiently accurate pathological information that can be used, together with clinical data, for the patient to be given a prognosis.

The guidelines within this dataset should be implemented for the following reasons:

- to allow correlation of resection specimens with pre-operative imaging
- to allow the accurate and equitable comparison of surgeons in different surgical units, to identify good surgical and pathological practice, and the selection and comparison of patients in clinical trials.

## **1.1 Design of this protocol**

RCPATH recognises the authority of internationally accepted guidance documents (WHO, AJCC/UICC TNM and ICCR) and, to promote consistent reporting practice, adopts the recommendations of these organisations. This structured reporting protocol has been developed using the framework and data items specified in the ICCR dataset on cancers of the nasopharynx and oropharynx (published in 2018).<sup>1</sup> This protocol includes all of the ICCR cancer dataset elements as well as additional information, elements and commentary. Core references have been updated to include relevant new information from 2018 to December 2020.

ICCR dataset elements for these cancers have been included verbatim and are indicated by the blue ICCR logo. ICCR core elements are mandatory, form part of the COSD data and are therefore represented as standards in this document. ICCR (and RCPATH) non-core elements are recommended and may be included as guidelines or used routinely according to local practice.

Additional non-core data items that have not been included in the ICCR dataset, but recommended by RCPATH, are involvement of bone (required for TNM staging) and assessment of tumour-infiltrating lymphocytes (TILs).

## **1.2 Target users and health benefits of this guideline**

The dataset is primarily intended for the use of consultant and trainee pathologists when reporting biopsies and resection specimens of mucosal malignancies of the head and neck region and has been developed to aid a consistent approach to the reporting of these cancers. Surgeons and oncologists may refer to the dataset when interpreting histopathology reports and core data should be available at multidisciplinary meetings to inform discussions on the management of head and neck cancer patients. The core data items are incorporated into the COSD data (and cognate datasets in the devolved administrations) and are collected for epidemiological analysis by Cancer Registries.

## 2 Clinical information required for the diagnosis of carcinomas of the nasopharynx and oropharynx

The request form should include patient demographic data, which includes:

- the patient's name
- date of birth
- sex
- hospital and NHS number (where appropriate), or other patient identification number.

Clinical information should include:

- the duration of symptoms
- details of the surgery and whether the intent is curative or palliative
- details of previous pathology reports
- the core clinical data items (see section 5)
- clinical TNM stage (for correlation with pathological findings)
- a history of previous biopsy, resection, radiotherapy or chemotherapy should be included as this may influence the interpretation of the histological changes and should prompt a comment on the extent of any response to treatment.

The request form should provide the opportunity for surgeons to provide annotated diagrams of specimens, either as free-hand drawings or on standard diagrams. Copies of reports that are sent to the Cancer Registries should include the patient's address if possible.

The following should also be recorded:

- the name of the clinician requesting the investigation
- the date and time of the operation
- the date and time at which the specimen was fixed
- the date and time the specimen was received in the laboratory.

Details of the legal basis of data sharing with the Cancer Registries can be accessed here: <https://www.gov.uk/guidance/national-cancer-registration-and-analysis-service-ncras#opt-out-of-cancer-registration>.

## 3 Receipt and preparation of specimens before dissection

Resection specimens should be orientated by the surgeon and may be pinned or sutured to an appropriate mount (e.g. cork board, polystyrene block, foam sponge, KliniTray), if desired. The surgeon should indicate surgically critical margins using metal tags or sutures. Fixation is in neutral buffered formalin for 24–48 hours in a container of adequate size (the volume of fixative should be ten times that of the tissue). Resection specimens identified as a biohazard risk should be fixed for at least 48 hours (e.g. HIV, tuberculosis). If tissue is sent fresh from theatres, this should reach the pathology laboratory promptly. Refer to the [COVID-19 Resources Hub](#) for the latest COVID-19-related guidance.

Photography and radiography of the specimen may be used to record the extent of the disease and the sites from which tissue blocks are selected. Surgical margins should be painted with

Indian ink or an appropriate dye to facilitate the later recording of the proximity of carcinoma to the margin.

## **4 Specimen handling and block selection**

### **4.1 Introduction**

The specimen handling and preparation protocol described below is based on contemporary practice and should be regarded as a guide only; it may need to be modified in individual cases. A detailed dissection protocol is beyond the scope of these guidelines, but a brief summary of dissection methods and block selection is included to facilitate recording of the core data items. More detail can be found in the relevant sections of the Tissue Pathways For Head and Neck Pathology.<sup>13</sup> It is particularly important to record the macroscopic dimensions of the tumour, the closest margins and any gross invasion of bone.

It is important to identify if the patient has been enrolled in clinical trials before starting to undertake a macroscopic examination of the tumour and the selection of blocks, as the clinical trial protocol may dictate specific requirements in this regard.

### **4.2 Nasopharynx**

The majority of nasopharyngeal carcinomas are treated non-surgically, so guidance relating to small biopsies is most appropriate for these tumours. Resection specimens of carcinomas from this area typically comprise piecemeal, tumour de-bulking with clearance informed by separate margin biopsies. En-bloc excisions should be carefully orientated by the surgeon so that surgically important resection margins can be appropriately sampled.

### **4.3 Oropharynx**

In general, these specimens may be assessed by slicing the specimen into 3 mm parallel slices, to demonstrate the size of the tumour (T category), the maximum depth of invasion and the tumour proximity to mucosal and deep resection margins.

### **4.4 Selection and recording of blocks for histology**

- At least one block per 10 mm diameter of tumour, including one selected to demonstrate the maximum depth of invasion; the whole tumour if less than 10 mm. If mega-blocks are used, then the number of blocks will be fewer.
- Blocks of defined mucosal and deep margins.
- Non-neoplastic mucosa (one block).
- A methodical text-based block key, and/or photographic record of blocks taken should be included.

### **4.5 Trans-oral laser resection specimens**

The handling of trans-oral laser and trans-oral robotic resection specimens requires particularly close collaboration between surgeon and pathologist.<sup>14</sup> The main tumour resection may be in one or more parts and it is common for separate biopsies from resection margins to be submitted for examination. The specimens should be secured to an appropriate mount (e.g. cork board, etc.) so that the anatomical relationships between the pieces are maintained and an annotated diagram should indicate the nature of each piece of tissue. The radial and deep margins should be inked to facilitate assessment of the histological sections. The main tumour should be serially sliced and blocked in its entirety. If possible, biopsies from critical resection margins should be sliced perpendicular to the margin and blocked in their entirety.

Trans-oral robotic surgery is being increasingly used to investigate the head and neck unknown primary tumour. For example, a patient presenting with metastatic HPV-related squamous cell carcinoma in a lymph node in the neck, with no evidence of a primary tumour following clinical staging, may be subject to a tongue base mucosectomy.<sup>15,16</sup> In these circumstances, the tissue should be serially sliced and blocked in its entirety in an attempt to discover sub-clinical disease. Judicious inking and detailed block annotation is still required, because if microscopic tumour is identified the surgeons and oncologists will need to know the precise tumour location and proximity to the margins in order to plan further treatment.<sup>14</sup>

*[Level of evidence C – The basis in evidence for block selection is extrapolated from the need to provide microscopic confirmation or evaluation of prognostic and predictive factors.]*

## 5 Core data items

We have set out to use the ICCR dataset in its current form, with appropriate qualifications and clarifications for implementation in UK clinical practice. In addition to the main dataset items, as outlined below, demographic and clinical data should be collected, as per the ICCR dataset. This includes the patient's name, date of birth, sex, hospital and NHS number (where appropriate), or other patient identification number.

1 ICCR	Descriptor	Core/Non-core	Responses
	Neoadjuvant therapy	Core	Not known Administered Not administered
		Core	Type of neoadjuvant therapy
<p><b>Neoadjuvant therapy comments:</b></p> <p>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/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.<sup>17-19</sup> 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 six and 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.</p> <p><i>[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]</i></p>			



2 ICCR	Descriptor	Core/Non-core	Responses
	Operative procedure	Core	Resection Biopsy Other
<p><b>Operative procedure comments:</b>  Oropharynx: Many oropharyngeal carcinomas are treated non-surgically<sup>20</sup> so that guidance relating to small biopsies is most appropriate for these tumours. 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, are utilised, particularly for small, early carcinomas, both HPV positive and negative.<sup>21,22</sup> 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.</p> <p>Nasopharynx: The vast majority of nasopharyngeal carcinomas are treated non-surgically so that guidance relating to small biopsies is most appropriate for these tumours.<sup>23</sup> 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.</p> <p><b>RCPATH additional comments:</b>  If a neck dissection specimen is submitted, please use the separate neck dissection dataset.</p> <p><i>[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]</i></p>			

3 ICCR	Descriptor	Core/Non-core	Responses
	Specimens submitted	Core	Oropharynx (plus subsites) Nasopharynx
<p><b>Specimens submitted comments:</b>  Oropharynx: 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.<sup>24</sup> The contents of the oropharynx include:</p> <ul style="list-style-type: none"> <li>• soft palate</li> <li>• palatine tonsils</li> <li>• anterior and posterior tonsillar pillars</li> <li>• tonsillar fossa</li> <li>• uvula</li> <li>• base of tongue (lingual tonsil)</li> <li>• vallecula</li> <li>• posterior oropharyngeal wall</li> <li>• lateral oropharyngeal wall.</li> </ul> <p>Nasopharynx: 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.<sup>24</sup> The contents of the nasopharynx include:</p>			

- 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.

*[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]*

4 ICCR	Descriptor	Core/Non-core	Responses
	Tumour site	Core	Oropharynx (plus subsites) Nasopharynx (plus subsites) Other

**Tumour site comments:**

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.

*[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]*

5 ICCR	Descriptor	Core/Non-core	Responses
	Tumour maximum dimension	Core	Size (mm)
	Tumour other dimensions	Core	Size (mm)

**Tumour dimensions comments:**

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.<sup>25</sup> Tumour size is also important in salvage nasopharyngectomy specimens as a correlate to prognosis after surgery.<sup>26,27</sup>

[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]

6 ICCR	Descriptor	Core/Non-core	Responses
	Histological tumour type	Core	WHO subtype list

**Histological tumour type comments:**

The latest World Health Organization (WHO) classification of carcinomas of the oropharynx<sup>5</sup> 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 (non-keratinising, 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 classification still refers to them by histologic type.<sup>6</sup> However, 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,<sup>28</sup> 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.<sup>29,30</sup> Refer to the ICCR *Carcinomas of the major salivary glands* dataset for more details.<sup>28</sup>

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.

[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]

7 ICCR	Descriptor	Core/Non-core	Responses
	Histological tumour grade	Core	Not applicable Cannot be assessed Well differentiated Moderately differentiated Poorly differentiated

**Histological grade comments:**

Only applicable for conventional, EBV-negative nasopharyngeal carcinomas, 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 non-keratinising morphology.<sup>31,32</sup>


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.

**RCPATH additional comments:**

Practically, the most aggressive area (at x10 objective field) 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 squamous cell carcinomas will be moderately differentiated, it is important for prognostication to separate well-differentiated and poorly differentiated tumours. Where a tumour has a varied appearance, then the highest grade is recorded.

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.

*[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]*

8	Descriptor	Core/Non-core	Responses
	Depth of invasion	Core	Depth (mm) Not applicable Cannot be assessed

**Depth of invasion comments:**


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 that 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.<sup>33</sup> 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.<sup>8</sup>

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.<sup>26,27</sup>

**RCPATH additional comments:**

This is included in the dataset as it has been demonstrated to be of prognostic significance in other head and neck sites. Literature specifically assessing this in the oropharynx and nasopharynx is very limited.

*[Level of evidence C/D – The basis in evidence for inclusion is case-control or cohort studies.]*

<b>9</b> 	Descriptor	Core/Non-core	Responses
	Perineural invasion*	Core	Not identified Present Cannot be assessed


**Perineural invasion comments:**

Traditionally, the presence of perineural invasion (neurotropism) is an important predictor of poor prognosis in head and neck cancer of virtually all sites.<sup>34,35</sup> 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.<sup>36</sup> 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.<sup>9-11</sup> 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.<sup>37,38</sup>

There are no data on perineural invasion for nasopharyngeal carcinomas, so it is considered not applicable for these tumours.

*[Level of evidence C/D – The basis in evidence for inclusion is case-control or cohort studies.]*

\*Not applicable for nasopharynx.

<b>10</b> 	Descriptor	Core/Non-core	Responses
	Lymphovascular invasion*	Core	Not identified Present Cannot be assessed


**Lymphovascular invasion comments:**

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.<sup>9-11,35,39</sup> 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.<sup>24</sup>

There are no data on lymphovascular invasion for nasopharyngeal carcinomas, so it is considered 'not applicable' for these tumours.

*[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]*

\*Not applicable for nasopharynx.

11 	Descriptor	Core/Non-core	Responses
	Margin status – invasive carcinoma	Core	Involved (specify) Not involved (distance) Cannot be assessed
	Margin status – in situ carcinoma	Core	Involved (specify) Not involved (distance) Cannot be assessed

**Margin status comments:**

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.<sup>9–11,35,39</sup> The definition of a positive margin is controversial.<sup>40,41</sup> 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).<sup>40</sup> 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,<sup>40,42,43</sup> but the definition of a close margin is not standardised 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. It is difficult, if not impossible, to tell in situ from invasive (metastasis-capable) squamous cell carcinoma in crypt-derived tumours of the oropharynx and nasopharynx. Therefore, 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.

**RCPATH additional comments:**


An alternative method for recording the margin status is to use the UICC Residual Tumour (R) Classification:<sup>44</sup>

- RX Presence of residual tumour cannot be assessed
- R0 No residual tumour
- R1 Microscopic residual tumour
- R2 Macroscopic residual tumour.

Whichever system is used, it should be by local agreement, with the surgical and pathology teams clear as to interpretation.

On occasion, additional descriptive comments on the margins will be required, for example where the tumour is 0 mm from the margin in the main specimen, but additional margin biopsies are clear.

*[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]*

12 	<b>Descriptor</b>	<b>Core/Non-core</b>	<b>Responses</b>
	Ancillary studies 1	Core	Viral/tumour markers

**Ancillary studies (including viral testing) comments:**

In resource-limited practices where p16/HPV (oropharynx) or EBV (nasopharynx) testing cannot be performed (or when only extremely limited biopsy samples are available that preclude further testing, etc.), staging and treatment of patients will be inherently different.<sup>45</sup> 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 non-keratinising 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 carcinoma patients, certain patients can be strongly suspected as having HPV-related tumours. In particular, non-keratinising histologic morphology, present in 50–60% of oropharyngeal squamous cell carcinoma, correlates very well with positive HPV status.<sup>46</sup> However, prediction of HPV status by such surrogate marker and clinical grounds is less reliable than direct p16/HPV testing.<sup>47</sup> 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.<sup>48,49</sup> A smaller subset of nasopharyngeal carcinomas is related to transcriptionally active high-risk HPV.<sup>50</sup> HPV-positive oropharyngeal carcinoma represents a unique squamous cell carcinoma type with proven more favourable prognosis than for HPV-negative tumours.<sup>51</sup> Staging of these patients is now different from that 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 SCC.<sup>52</sup> The most commonly used criterion for positivity as a surrogate marker is moderate to intense nuclear and cytoplasmic staining in 70% or more of the tumour cells, which is the recommended cut-off for these guidelines,<sup>53</sup> with the caveat that the correlation with HPV status is not 100%.<sup>54,55</sup> The combination of p16 immunohistochemistry with non-keratinising morphology is very strongly associated with transcriptionally-active high-risk HPV in the oropharynx.<sup>46</sup> 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, 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 Classification Blue Book terms squamous cell carcinomas of the oropharynx simply as HPV positive or HPV-negative.<sup>56</sup> 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 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 and because it is confirmation of the tumour having a nasopharyngeal association.<sup>31</sup> A subset of patients with nasopharyngeal carcinoma are related to transcriptionally-active high-risk HPV.<sup>57–59</sup> Most of these tumours are described as non-keratinising differentiated using the WHO terminology. They are EBV (EBER) negative and p16 positive. Testing for HPV/p16 in EBV-negative non-keratinising 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.<sup>57–59</sup>

**RCPATH additional comments:**

Given that both the ICCR and WHO guidance pragmatically advocates the use of p16 expression alone to infer HPV status for disease classification, there is a body of literature from case control studies that demonstrates the shortcomings of such an approach.<sup>60–63</sup> In particular, the identification of a p16-positive, HPV-negative population, with poor prognosis, demonstrates the usefulness of the addition of an HPV-specific test as part of diagnostic workup.<sup>60</sup> For this reason, and particularly where HPV status is used for prognosis or prediction, we have recommended the implementation of HPV-specific testing in addition to the assessment of p16 expression in oropharynx SCC.

*[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]*

**6 Additional non-core data items**

NC1 ICCR	Descriptor	Core/Non-core	Responses
	Co-existent pathology	Non-core	Dysplasia In situ carcinoma Other (specify)

**Coexistent pathology comments:**

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.

*[Level D – The basis in evidence for inclusion is expert opinion.]*

NC2	Descriptor	Core/Non-core	Responses
	Tumour infiltrating lymphocytes (TIL)	Non-core	3-group scoring system • High TIL – prominent TIL infiltrate in >80% of tumour • Moderate TIL – patchy TIL infiltrate in 20–80% of tumour • Low TIL – absent/low TIL infiltrate in <20% tumour

**TIL comments:**

There is accumulating evidence that assessment of tumour-infiltrating lymphocytes (TIL) has prognostic and potentially predictive significance, particularly in the context of immunotherapy. Immunophenotyping studies have examined the prognostic significance of lymphocyte subsets (e.g. CD8-positive T-cells, CD4-positive T-cells, FoxP3-positive regulatory T-cells, B-cells) in head and neck squamous cell carcinoma (HNSCC),<sup>64–67</sup> but simple semi-quantitative TIL assessment on H&E sections has consistently shown clinical validity as a prognostic marker in both HPV-negative and HPV-positive disease.<sup>41,67–69</sup> There is some anatomical subsite variation in the degree of immune infiltration; oropharyngeal tumours, which arise in lymphoid-rich tissues, have higher number of TILs<sup>70</sup> and most HPV-positive cancers contain high or moderate TIL levels.<sup>68</sup> There is some debate as to whether pre-existing lymphoid stroma in tumours (tonsillar tissue) should be excluded from assessment; in practice, it is not possible to determine whether this stroma is ‘active’ or ‘passive’, however RNA sequencing studies have shown broadly activated T-cells in HPV-positive and HPV-



negative oropharyngeal tumours suggesting that local lymphoid tissue is involved in an anti-tumour response.<sup>71</sup>

As yet there is no consensus for a common TIL scoring system across different cancers, and it is clear that infiltration patterns vary between tumour types. Most issues pertain to the relative importance of stromal TIL (sTIL) or intratumoral TIL (iTIL) or delineating different regions of the tumour – tumour margin and core. Recent guidelines by the International Immuno-oncology Biomarker Working Group recommended quantifying sTIL and iTIL in the tumour core and margin as a continuous variable percentage.<sup>72</sup> However, this scoring system has not been tested in HNSCC. Several large HNSCC studies have shown the prognostic utility of a three-group semi-quantitative scoring system, scoring tumours as TILhigh (TIL infiltrate in >80% of tumour), TILmoderate (TIL infiltrate in 20–80% of tumour) and TILlow (TIL infiltrate in <20% of tumour).<sup>41,67,68</sup> Assessment is made under low-power magnification, ideally from a full-face H&E section (small biopsies may not account for infiltrate heterogeneity) and taking into account the body of the tumour and the invasive front to provide a single score. Combining TILhigh and TILmoderate groups to generate a two-group scoring system retains prognostic significance,<sup>68,69</sup> although, given the possibility that immunotherapy may be more effective in TILhigh patients, it is probably better to retain a three-group scoring system at present. In practice, the majority of the lymphocytes assessed in this way sit within tumour stroma. Assessment of TIL at the tumour/host interface as three-groups (continuous/patchy/absent) has similarly been shown to be prognostic.

It is not yet established whether H&E-based assessment can accurately predict therapy response. In future, analysis of immune cell subsets or functional status (activation/exhaustion markers) may be required, particularly in the context of immunotherapy drug selection; combining TIL assessment with, for example, PD1/PDL1 or other therapeutic markers, may have utility. The advent of digital pathology technologies will also enable rapid quantitative assessment of lymphocyte numbers, subsets and tissue distribution, which may play a future role in for tumour immune characterisation.

*[Level of evidence C/D – The basis in evidence for inclusion is case-control or cohort studies.]*

NC3	Descriptor	Core/Non-core	Responses
	Bone invasion	Non-core	Present Absent
<p><b>Bone invasion comments:</b> The involvement of maxillary or mandibular bone may be by erosion of the cortex, or infiltration of medullary cavity. Cortical erosion is not classified as bone invasion per se. In the mandible, invasion of the inferior alveolar neurovascular bundle should be noted.<sup>44</sup> The presence or absence of carcinoma at the bone margins should be recorded.</p> <p><i>[Level of evidence B – The presence of bone involvement is important for accurate staging of oropharyngeal and nasopharyngeal malignancies.]</i></p>			


## 7 Diagnostic coding and staging

### 7.1 General comments

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 HPV type, there is no data to suggest that they are not simply separate primary tumours.<sup>73</sup> Thus, for oropharyngeal carcinomas, each distinct focus should be considered a separate primary tumour and should receive its own separate dataset.

For nasopharyngeal tumours, even if the tumour appears to be multifocal clinically and pathologically, these are regarded and treated as a single primary.<sup>74–76</sup>

## 7.2 Staging

14 	Descriptor	Core/Non-core	Responses
	Pathological staging (UICC TNM8)	Core	See Appendix B
<p><b>Pathological staging comments:</b></p> <p>This protocol recommends the T-classification schemes published by the UICC and the 8th edition of the AJCC for the pharynx.<sup>24,44</sup> 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.<sup>77</sup></p> <p>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.</p> <p>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 should be provided.</p> <p>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 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.</p> <p><i>[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]</i></p>			

## 8 Reporting of small biopsy specimens

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. The data that can be obtained from small biopsy specimens will be determined, in part, by their size. The type of carcinoma and its grade are the minimum data, as these may determine treatment. It is recognised that, in large tumours, the grade in superficial biopsy material may not be representative of the most aggressive part of the invasive front. If severe dysplasia is

present, this should be recorded as it may influence the siting of excision margins. It is not realistic to assess reliably the tumour thickness or presence of vascular invasion in small biopsies.

## **9 Frozen section diagnosis**

The initial diagnosis of carcinoma will usually be made before definitive surgery is performed. On occasions, intraoperative frozen section diagnosis of the nature of a neoplasm will be required. While it will usually be possible to identify the presence of neoplastic tissue, the nature of a poorly differentiated neoplasm may be impossible to determine on frozen sections.

The assessment of the presence or absence of carcinoma at surgical resection margins is the most common indication for intraoperative frozen section diagnosis. The surgeon should select the tissue for frozen section diagnosis with care, bearing in mind that it is not usually possible to section material more than 10 mm in diameter. There is evidence from a recent meta-analysis that frozen sections reduces the risk of positive margins during transoral surgery for oropharyngeal carcinomas.<sup>78</sup>

The report on the frozen section specimen(s) should normally form part of, or accompany, the final diagnostic report on the case.

## **10 Support of research and clinical trials**

It is important to be aware of local protocols for tissue banking and engagement with national initiatives for the further classification of tumours, (such as was implemented in the 100,000 Genomes Project). Other features, such as assessment of the effects of biological therapy/immunotherapy may be important but are currently beyond the remit of this dataset.

## **11 Specific aspects of individual tumours not covered elsewhere**

### **11.1 PD-L1 testing**

Immunohistochemical assessment for PD-L1 expression can predict response to anti-PD-L1 immunotherapy, although this is variable and has certain limitations.<sup>79,80</sup> However, a number of different anti-PD-L1 clones are available from different manufacturers and the published trials have examined specific clones linked to the activity of specific anti-PD-L1 immunotherapy agents. Moreover, these tests use different algorithms and cut-offs to identify which patients are more likely to benefit from each immunotherapeutic agent.<sup>79</sup> Since PD-L1 testing is required only for some patients with advanced head and neck cancer and each immunotherapeutic agent needs a different PD-L1 test, reflex testing of all specimens is not recommended at present. However, individual departments should set up a process to enable prompt PD-L1 testing by a trained pathologist in an accredited laboratory for any patient requiring this test. Participation in relevant immunohistochemistry EQA is mandatory for laboratories involved in PD-L1 assessment. The results of such testing should be incorporated into the pathology report (including the antibody used) when it is available; such testing should not delay the primary report.

## **12 Criteria for audit**

The following are recommended by the RCPATH as key performance indicators (see [Key Performance Indicators – Proposals for Implementation, July 2013](#)):

- cancer resections should be reported using a template or proforma, including items listed in the English COSD, which are, by definition, core data items in RCPATH cancer datasets. NHS trusts are required to implement the structured recording of core pathology data in the COSD
  - standard: 95% of reports must contain structured data.
- histopathology cases must be reported, confirmed and authorised within seven and ten calendar days of the procedure
  - standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

Given that the core dataset includes ancillary testing, a further suggested audit standard is presented below. This may be implemented by local agreement. Further suggested criteria for audit of the dataset are:

- utilisation of ancillary tests
  - standard: 90% of oropharyngeal squamous cell carcinoma are tested using p16 immunohistochemistry and are reported as p16/HPV-positive or -negative according to the recommended cut offs.

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## Appendix A SNOMED coding

SNOMED topography should be recorded for the site of the tumour. SNOMED morphology codes should be recorded for the diagnosis/tumour morphology.

Versions of SNOMED prior to SNOMED-CT will cease to be licenced by the International Health Terminology Standards Development Organisation from 26 April 2017. It is recognised that versions of SNOMED 2, SNOMED 3/RT and SNOMED CT are in use in the UK, these are therefore currently considered acceptable.

SNOMED Procedure codes (P codes in SNOMED 2/3/RT) should be recorded for the procedure. P codes vary according to the SNOMED system in use in different organisations, therefore local P codes should be recorded and used for audit purposes.

A list of applicable SNOMED morphology and topography codes should be provided.

Morphological item	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
Squamous cell carcinoma in situ	M-80702	Squamous cell carcinoma in situ, no International Classification of Diseases for Oncology subtype (morphologic abnormality)	59529006
Squamous cell carcinoma	M-80703	Squamous cell carcinoma, no International Classification of Diseases for Oncology subtype (morphologic abnormality)	28899001
		Squamous cell carcinoma of pharynx (disorder)	408649007
Microinvasive squamous carcinoma	M-80705	Squamous cell carcinoma, microinvasive (morphologic abnormality)	12478003
Keratinising squamous carcinoma	M-80713	Squamous cell carcinoma, keratinising (morphologic abnormality)	18048008
		Keratinising squamous cell carcinoma of nasopharynx (disorder)	698011002
Non-keratinising squamous carcinoma	M-80723	Squamous cell carcinoma, large cell, non-keratinising (morphologic abnormality)	45490001
Spindle cell squamous carcinoma	M-80743	Squamous cell carcinoma, spindle cell (morphologic abnormality)	10288008
Adenoid squamous carcinoma	M-80753	Adenoid squamous cell carcinoma (morphologic abnormality)	85956000

Adenosquamous carcinoma	M-85603	Adenosquamous carcinoma (morphologic abnormality)	59367005
N/A		Human papillomavirus positive squamous cell carcinoma (morphologic abnormality)	783212001

Note: This is not a comprehensive list of all malignancies and other codes should be used as necessary.

Topography item	SNOMED code	SNOMED-CT terminology	SNOMED-CT code
<b>Oropharynx</b>	T-60200	Oropharyngeal structure (body structure)	31389004
Anterior wall (glosso-epiglottic area)	T-53122	Structure of junctional region of epiglottis with oropharynx (body structure)	113280004
Base of tongue	T-53130	Mucosa of base of tongue (body structure)	245832000
Vallecula	T-60230	Structure of vallecula of epiglottis (body structure)	42275007
Lateral wall	T-61100	Structure of lateral wall of oropharynx (body structure)	19120004
Tonsil	T-60220	Tonsillar structure (palatine) (body structure)	75573002
Tonsillar fossa and pillars	T-61240	Tonsillar fossa structure (body structure)	32163006
Tonsillar pillars	T-61150	Palatine arch structure (body structure)	21294006
Posterior wall	T-60210	Structure of posterior wall of oropharynx (body structure)	12999009
Inferior surface of soft palate	T-51120	Inferior surface of soft palate (body structure)	303339004
Uvula	T-51130	Uvula palatina structure (body structure)	26140008
<b>Nasopharynx</b>	T-23000	Entire nasopharynx (body structure)	1812000003
Postero-superior wall	T-23001	Entire posterior wall of nasopharynx (body structure)	361936002
		Entire superior wall of nasopharynx (body structure)	179268001
Lateral wall (includes fossa of Rosenmüller)	T-23002	Entire lateral wall of nasopharynx (body structure)	361937006

Inferior wall (superior surface of soft palate)	T-51122	Entire superior surface of soft palate (body structure)	362081003
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### **Procedure codes (P)**

These are used in SNOMED 2 and SNOMED 3 to distinguish biopsies, partial resections and radical resections to indicate the nature of the procedure. Local P codes should be recorded. At present, P codes vary according to the SNOMED system in use in different institutions.

## Appendix B      TNM classification

This provides updated information on staging using UICC TNM 8, which should be used for all tumours diagnosed after 1 January 2020.

### Primary tumour (T)

#### HPV-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

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

#### HPV-negative oropharynx

- 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

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

#### 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 para-pharyngeal involvement
- T2 Tumour with extension to para-pharyngeal 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

### **Residual tumour (R)**

An R classification can be used to record the presence/absence of tumour remaining after curative therapy.

- RX Presence of residual tumour cannot be assessed
- R0 No residual tumour
- R1 Microscopic residual tumour
- R2 Macroscopic residual tumour

## Appendix C Reporting proforma for carcinomas of the oropharynx and nasopharynx

Surname..... Forenames..... Date of birth..... Sex.....  
Hospital..... Hospital no..... NHS/CHI no.....  
Date of receipt..... Date of reporting..... Report no.....  
Pathologist..... Surgeon.....

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### Neoadjuvant therapy

Information not provided  Not administered  Administered   
Specify type: Chemotherapy  Radiotherapy  Chemoradiotherapy  Targeted therapy   
Immunotherapy  specify if available .....

### Operative procedure (select all that apply)

Not specified  Resection, specify:  ..... Transoral laser microsurgical resection   
Transoral robotic surgical resection  Other  specify.....  
Biopsy (excisional, incisional)  specify .....

Neck (lymph node) dissection<sup>1</sup>  specify .....

Other  specify.....

### Specimens submitted (select all that apply)

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)

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 .....

### Tumour dimensions

Maximum tumour dimension (largest tumour) .....mm  
Additional dimensions (largest tumour) .....mm x .....mm  
Cannot be assessed, specify .....

### Histological tumour type

Salivary gland carcinoma  specify type .....

Neuroendocrine carcinoma  specify type .....

Other  specify type .....

### Carcinomas of the oropharynx

Squamous cell carcinoma, conventional   
    Keratinising  Non-keratinising  Non-keratinising with maturation ('partially keratinising')

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<sup>1</sup>If a neck dissection is submitted, then a separate dataset is used to record the information.



Acantholytic squamous cell carcinoma  Adenosquamous carcinoma   
Basaloid squamous cell carcinoma  Papillary squamous cell carcinoma  Spindle cell carcinoma   
Verrucous cell carcinoma  Lymphoepithelial carcinoma   
Other , please state .....

**Carcinomas of the nasopharynx**

Non-keratinising squamous cell carcinoma   
    Differentiated  Undifferentiated   
Keratinising squamous cell carcinoma  Basaloid squamous cell carcinoma   
Nasopharyngeal papillary adenocarcinoma  Cannot be assessed , specify .....

**Histological tumour grade**

Not applicable  GX: Cannot be assessed  G1: Well differentiated  G2: Moderately differentiated   
G3: Poorly differentiated  Other , specify ..... Cannot be assessed , specify .....

**Depth of invasion**

.....mm Not applicable  Cannot be assessed , specify .....

**Perineural invasion (oropharynx only)**

Not identified  Present  Cannot be assessed , specify .....

**Lymphovascular invasion (oropharynx only)**

Not identified  Present  Not applicable  Cannot be assessed , specify .....

**Margin status**

Invasive carcinoma<sup>2</sup>   
    Involved  specify margin(s) if possible .....  
    Not Involved  Distance of tumour from closest margin ..... mm  Distance not assessable   
    Specify closest margin if possible .....

Carcinoma in situ/high-grade dysplasia<sup>3</sup>

    Involved  specify margin(s) if possible .....  
    Not Involved  Distance of tumour from closest margin ..... mm  Distance not assessable   
    Specify closest margin if possible .....  
    Not applicable<sup>3</sup>  Cannot be assessed , specify .....

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<sup>2</sup>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'.

<sup>3</sup>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.

**Co-existent pathology (select all that apply)**

None identified

Dysplasia<sup>4</sup>

Mild  Moderate  Severe

Focal  Multifocal  Discontinuous with the primary site

Carcinoma in situ

Focal  Multifocal  Discontinuous with the primary site  Other , specify .....

**Ancillary studies**

**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 hybridisation  Not identified  Present

E6/E7 mRNA in situ hybridisation  Not identified  Present

E6/E7 mRNA RTPCR  Not identified  Present

**Viral testing/viral tumour markers – nasopharynx**

Not performed/unknown  Performed

EBV (EBER) in situ hybridisation – positive

EBV (EBER) in situ hybridisation – negative

**Other ancillary studies**

Not performed  Performed , specify .....

**Pathological staging (UICC TNM 8th edition)**

TNM Descriptors  (only if applicable) specify:

**Primary tumour (pT)** .....

**P16 negative oropharynx**

**Nasopharynx**

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<sup>4</sup>Applicable for oropharyngeal surface mucosal disease only; not for tonsillar crypt epithelium.

**Appendix D Reporting proforma for carcinomas of the nasopharynx and oropharynx in list format**

Element name	Values	Implementation notes
<b>Neoadjuvant therapy</b>	Single selection value list: <ul style="list-style-type: none"> <li>• Information not provided</li> <li>• Not administered</li> <li>• Administered, specify type</li> </ul> Multi selection value list (select all that apply): <ul style="list-style-type: none"> <li>– Chemotherapy</li> <li>– Radiotherapy</li> <li>– Chemoradiotherapy</li> <li>– Targeted therapy, specify if available</li> <li>– Immunotherapy, specify if available</li> </ul>	
<b>Operative procedure</b>	Multi-selection value list (select all that apply): <ul style="list-style-type: none"> <li>• Not specified</li> </ul> OR <ul style="list-style-type: none"> <li>• Resection, specify               <ul style="list-style-type: none"> <li>– Transoral laser microsurgical resection</li> <li>– Transoral robotic surgical resection</li> <li>– Other, specify</li> </ul> </li> <li>• Biopsy (excisional, incisional), specify</li> <li>• Neck (lymph node) dissection*, specify</li> <li>• Other, specify</li> </ul>	*If a neck dissection is submitted, then a separate dataset is used to record the information.
<b>Specimens submitted</b>	Multi-selection value list (select all that apply): <ul style="list-style-type: none"> <li>• Not specified</li> </ul> OR <ul style="list-style-type: none"> <li>• Oropharynx               <ul style="list-style-type: none"> <li>– Palatine tonsil</li> <li>– Base of tongue/lingual tonsil</li> <li>– Soft palate</li> <li>– Uvula</li> <li>– Pharyngeal wall (posterior)</li> <li>– Pharyngeal wall (lateral)</li> <li>– Other, specify</li> </ul> </li> <li>• Nasopharynx, specify if necessary</li> </ul>	

	<ul style="list-style-type: none"> <li>• Other, specify</li> </ul>	
<b>Tumour site</b>	<p>Multi-selection value list (select all that apply):</p> <ul style="list-style-type: none"> <li>• Cannot be assessed</li> </ul> <p>OR</p> <ul style="list-style-type: none"> <li>• Oropharynx <ul style="list-style-type: none"> <li>– Left</li> <li>– Right</li> <li>– Midline</li> <li>– Laterality not specified</li> <li>▪ Palatine tonsil</li> <li>▪ Base of tongue/lingual tonsil</li> <li>▪ Soft palate</li> <li>▪ Uvula</li> <li>▪ Pharyngeal wall (posterior)</li> <li>▪ Pharyngeal wall (lateral)</li> <li>▪ Other, specify</li> </ul> </li> <li>• Nasopharynx <ul style="list-style-type: none"> <li>– Left</li> <li>– Right</li> <li>– Midline</li> <li>– Laterality not specified</li> <li>▪ Nasopharyngeal tonsils (adenoids)</li> <li>▪ Fossa of Rosenmüller</li> <li>▪ Lateral wall</li> <li>▪ Other, specify</li> </ul> </li> <li>• Other, specify including laterality</li> </ul>	
<b>Tumour dimensions</b>	<ul style="list-style-type: none"> <li>• Maximum tumour dimension (largest tumour) ___ mm</li> <li>• Additional dimensions (largest tumour) ___ mm x ___ mm</li> <li>• Cannot be assessed, specify</li> </ul>	
<b>Histological tumour type</b>	<p>Multi-selection value list (select all that apply):</p> <ul style="list-style-type: none"> <li>• <b>Salivary gland carcinoma</b>, specify type</li> <li>• <b>Neuroendocrine carcinoma</b>, specify type</li> <li>• Other, specify type</li> </ul> <p><b>Carcinomas of the oropharynx</b></p>	<p>Value list from the WHO Classification of Head and Neck Tumours (2017).</p> <p>Note that permission to publish the WHO classification of tumours may be needed in your implementation. It is advisable to check with the International Agency on Cancer research (IARC).</p>

	<ul style="list-style-type: none"> <li>• Squamous cell carcinoma, conventional</li> <li style="padding-left: 20px;">Single selection value list: <ul style="list-style-type: none"> <li>– Keratinising</li> <li>– Non-keratinising</li> <li>– Non-keratinising with maturation ('partially keratinising')</li> </ul> </li> <li>• Acantholytic squamous cell carcinoma</li> <li>• Adenosquamous carcinoma</li> <li>• Basaloid squamous cell carcinoma</li> <li>• Papillary squamous cell carcinoma</li> <li>• Spindle cell carcinoma</li> <li>• Verrucous carcinoma</li> <li>• Lymphoepithelial carcinoma</li>   <li><b>Carcinomas of the nasopharynx</b></li> <li>• Non-keratinising squamous cell carcinoma</li> <li style="padding-left: 20px;">Single selection value list: <ul style="list-style-type: none"> <li>– Differentiated</li> <li>– Undifferentiated (lymphoepithelial)</li> </ul> </li> <li>• Keratinising squamous cell carcinoma</li> <li>• Basaloid squamous cell carcinoma</li> <li>• Nasopharyngeal papillary adenocarcinoma</li> <li>• Cannot be assessed, specify</li> </ul>	
<b>Histological tumour grade</b>	<p>Single selection value list:</p> <ul style="list-style-type: none"> <li>• Not applicable</li> <li>• GX: Cannot be assessed</li> <li>• G1: Well differentiated</li> <li>• G2: Moderately differentiated</li> <li>• G3: Poorly differentiated</li> <li>• Other, specify</li> <li>• Cannot be assessed, specify</li> </ul>	
<b>Depth of invasion</b>	<p>Numeric/single selection value list:</p> <ul style="list-style-type: none"> <li>• ___ mm</li> <li>• Not applicable</li> <li>• Cannot be assessed, specify</li> </ul>	

<b>Perineural invasion</b>	Single selection value list: • Not identified • Present • Cannot be assessed, specify	Not applicable for nasopharynx.
<b>Lymphovascular invasion</b>	Single selection value list: • Not identified • Present • Cannot be assessed, specify	Not applicable for nasopharynx.
<b>Margin status</b>	Single selection value list/text/numeric: <b>Invasive carcinoma**</b> • Involved – Specify margin(s), if possible • Not involved – Distance of tumour from closest margin ___ mm – Distance not assessable – Specify closest margin, if possible  <b>Carcinoma in situ/high-grade dysplasia***</b> • Involved – Specify margin(s), if possible • Not involved – Distance of tumour from closest margin ___ mm – Distance not assessable – Specify closest margin, if possible • Not applicable ***  OR • Cannot be assessed, specify	<b>**</b> 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'.  <b>***</b> 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.
<b>Coexistent pathology</b>	Multi-selection value list (select all that apply): • None identified OR • Dysplasia**** Single selection value list: – Mild – Moderate – Severe ▪ Focal ▪ Multifocal	<b>****</b> Applicable for oropharyngeal surface mucosal disease only; not for tonsillar crypt epithelium.

	<ul style="list-style-type: none"> <li>▪ Discontinuous with the primary site</li> <li>• Carcinoma in situ <ul style="list-style-type: none"> <li>Single selection value list: <ul style="list-style-type: none"> <li>– Focal</li> <li>– Multifocal</li> <li>– Discontinuous with the primary site</li> </ul> </li> </ul> </li> <li>• Other, specify</li> </ul>	
<b>Ancillary studies</b>	<p>Single selection value list:</p> <p><b>Viral testing/Viral tumour markers</b></p> <p><b>Oropharynx</b></p> <ul style="list-style-type: none"> <li>• Not performed/unknown</li> <li>• Performed (select all that apply) <ul style="list-style-type: none"> <li>– Immunohistochemistry <ul style="list-style-type: none"> <li>▪ Positive <ul style="list-style-type: none"> <li>• &gt;70% nuclear and cytoplasmic staining of at least moderate to strong intensity</li> <li>• Other criterion used, specify</li> </ul> </li> <li>▪ Negative</li> <li>▪ Criteria used to determine results, specify <ul style="list-style-type: none"> <li>– High-risk HPV-specific testing</li> </ul> </li> </ul> </li> </ul> </li> </ul> <p>Single selection value list:</p> <ul style="list-style-type: none"> <li>• DNA PCR <ul style="list-style-type: none"> <li>– Not identified</li> <li>– Present</li> </ul> </li> <li>• DNA in situ hybridisation <ul style="list-style-type: none"> <li>– Not identified</li> <li>– Present</li> </ul> </li> <li>• E6/E7 mRNA in situ hybridisation <ul style="list-style-type: none"> <li>– Not identified</li> <li>– Present</li> </ul> </li> <li>• E6/E7 mRNA RTPCR <ul style="list-style-type: none"> <li>– Not identified</li> <li>– Present</li> </ul> </li> </ul> <p><b>Viral testing/Viral tumour markers</b></p> <p><b>Nasopharynx</b></p> <ul style="list-style-type: none"> <li>• Not performed/unknown</li> </ul>	

	<ul style="list-style-type: none"> <li>• Performed <ul style="list-style-type: none"> <li>– EBV (EBER) in situ hybridisation – positive</li> <li>– EBV (EBER) in situ hybridisation – negative</li> </ul> </li> </ul> <p><b>Other ancillary studies</b></p> <ul style="list-style-type: none"> <li>• Not performed</li> <li>• Performed, specify</li> </ul>	
<b>Pathological staging</b> (UICC TNM 8th edition) TNM descriptors	<p>Choose if applicable:</p> <ul style="list-style-type: none"> <li>• m – multiple primary tumours</li> <li>• r – recurrent</li> <li>• y – post-therapy</li> </ul>	
<b>Primary tumour (pT)</b>	Free text	
<b>P16 negative oropharynx</b>	Single selection	
<b>Nasopharynx</b>	Single selection	



**Appendix E      Summary table – explanation of grades of evidence**  
(modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	<p>At least one high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type</p> <p>or</p> <p>A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.</p>
Grade B	<p>A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal, and which are directly applicable to the target cancer type</p> <p>or</p> <p>Extrapolation evidence from studies described in A.</p>
Grade C	<p>A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high-quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal, and which are directly applicable to the target cancer type</p> <p>or</p> <p>Extrapolation evidence from studies described in B.</p>
Grade D	<p>Non-analytic studies such as case reports, case series or expert opinion</p> <p>or</p> <p>Extrapolation evidence from studies described in C.</p>
Good practice point (GPP)	<p>Recommended best practice based on the clinical experience of the authors of the writing group.</p>

## Appendix F      AGREE II guideline monitoring sheet

The cancer datasets of the Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this dataset that indicate compliance with each of the AGREE II standards are indicated in the table.

<b>AGREE standard</b>	<b>Section of guideline</b>
<b>Scope and purpose</b>	
1. The overall objective(s) of the guideline is (are) specifically described	Introduction
2. The health question(s) covered by the guideline is (are) specifically described	Introduction
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
<b>Stakeholder involvement</b>	
4. The guideline development group includes individuals from all the relevant professional groups	Foreword
5. The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6. The target users of the guideline are clearly defined	Introduction
<b>Rigour of development</b>	
7. Systematic methods were used to search for evidence	Foreword
8. The criteria for selecting the evidence are clearly described	Foreword
9. The strengths and limitations of the body of evidence are clearly described	Foreword
10. The methods for formulating the recommendations are clearly described	Foreword
11. The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12. There is an explicit link between the recommendations and the supporting evidence	All sections
13. The guideline has been externally reviewed by experts prior to its publication	Foreword
14. A procedure for updating the guideline is provided	Foreword
<b>Clarity of presentation</b>	
15. The recommendations are specific and unambiguous	2–11
16. The different options for management of the condition or health issue are clearly presented	2–11
17. Key recommendations are easily identifiable	2–11
<b>Applicability</b>	
18. The guideline describes facilitators and barriers to its application	Foreword
19. The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–D
20. The potential resource implications of applying the recommendations have been considered	Foreword
21. The guideline presents monitoring and/or auditing criteria	12
<b>Editorial independence</b>	
22. The views of the funding body have not influenced the content of the guideline	Foreword
23. Competing interest of guideline development group members have been recorded and addressed	Foreword