**** **Carcinomas of the Hypopharynx, Larynx and Trachea Histopathology Reporting Guide**

 **Elements in black text are CORE Elements in grey text are NON-CORE o indicates single select values □ indicates multi-select values**

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| --- | --- |
| Definition of Core elements | CORE elements are those which are essential for the clinical management, staging or prognosis of the cancer. These elements will either have evidentiary support at Level III-2 or above (based on prognostic factors in the National Health and Medical Research Council (NHMRC) levels of evidence1). In rare circumstances, where level III-2 evidence is not available an element may be made a CORE element where there is unanimous agreement by the Dataset Authoring Committee (DAC). An appropriate staging system e.g., Pathological TNM staging would normally be included as a CORE element. Molecular and immunohistochemical testing is a growing feature of cancer reporting. However, in many parts of the world this type of testing is limited by the available resources. In order to encourage the global adoption of ancillary tests for patient benefit, International Collaboration on Cancer Reporting (ICCR) includes the most relevant ancillary testing in ICCR Datasets as CORE elements, especially when they are necessary for the diagnosis. Where the technical capability does not yet exist, laboratories may consider temporarily using these data elements as NON-CORE items.The summation of all CORE elements is considered to be the minimum reporting standard for a specific cancer.**Reference**1 Merlin T, Weston A and Tooher R (2009). Extending an evidence hierarchy to include topics other than treatment: revising the Australian 'levels of evidence'. *BMC Med Res Methodol* 9:34.  |
| Definition of Non-core elements | NON-CORE elements are those which are unanimously agreed should be included in the dataset but are not supported by level III-2 evidence. These elements may be clinically important and recommended as good practice but are not yet validated or regularly used in patient management.Key information other than that which is essential for clinical management, staging or prognosis of the cancer such as macroscopic observations and interpretation, which are fundamental to the histological diagnosis and conclusion e.g., macroscopic tumour details, may be included as either CORE or NON-CORE elements by consensus of DAC |
| Scope of this dataset | The dataset has been developed for the reporting of resection and biopsy specimens of invasive epithelial malignancies of the larynx, hypopharynx and trachea. Salivary-type malignancies arising from minor mucoserous glands of the hypopharynx and larynx should be recorded in this dataset; the paucity of prognostic or predictive data suggest that tumour type and grade (as described in the ICCR Carcinomas of the major salivary glands dataset1), size and margin status should be recorded. Neuroendocrine neoplasms, as newly defined, include paraganglioma, neuroendocrine tumours (NET), and neuroendocrine carcinomas (NEC). NETs are separated into grades (1, 2, and 3) based on mitotic rate and Ki-67 proliferation index, but these criteria are not yet fully developed for each of the anatomic sites in the head and neck. At present, the site, tumour category, and grade should be reported, with additional advances in this field incorporated when validated further. Mucosal melanoma is presented in a separate ICCR dataset.2 Lymphomas and sarcomas are not included. Malignancies arising at other sites in the head and neck region, and neck dissections and nodal excisions are dealt with in separate ICCR datasets which may be used, as appropriate, in conjunction with this dataset.3  Where more than one anatomically or histologically distinct primary tumour occur, a separate dataset should be completed for each tumour (see **TUMOUR FOCALITY**). This dataset is intended for use for primary cancer resections. For resections of recurrent disease, the reporting guide may be used pragmatically but some data items may be not applicable or not assessable.The second edition of this dataset includes changes to align the dataset with the World Health Organization (WHO) Classification of Head and Neck Tumours, 5th edition, 2024.4 **Tracheal carcinomas**Tracheal malignancies are rare and represented in the literature as single case reports and small case series. Most reports describe squamous cell carcinomas (SCC) and carcinomas of salivary type arising from mucosal glands.5-14 Too few cases are reported to analyse prognostic or predictive data and there is no TNM classification for tracheal malignancies under either the Union for International Cancer Control (UICC) or American Joint Committee on Cancer (AJCC) systems. Thus, staging criteria for tracheal carcinomas are not yet performed, although recording core elements as available, may aid in further development.14**References** 1 International Collaboration on Cancer Reporting (2024). *Carcinomas of the major salivary glands Histopathology Reporting Guide. 2nd edition*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/head-neck/salivary-glands/ (Accessed 31st July 2024).2 International Collaboration on Cancer Reporting (2024). *Mucosal melanomas of the head and neck Histopathology Reporting Guide. 2nd edition*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/head-neck/mucosal/ (Accessed 31st July 2024).3 International Collaboration on Cancer Reporting (2024). *Head & Neck datasets*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/head-neck/ (Accessed 31st July 2024). 4 WHO Classification of Tumours Editorial Board (2024). *Head and Neck Tumours, WHO Classification of Tumours, 5th Edition, Volume 10.* IARC Press, Lyon.5 Qi D, Feng L, Li J, Liu B and Zhang Q (2016). Primary adenoid cystic carcinoma of the trachea with thyroid invasion: a case report and literature review. *Onco Targets Ther* 9:6291-6296.6 Qiu J, Lin W, Zhou ML, Zhou SH, Wang QY and Bao YY (2015). Primary small cell cancer of cervical trachea: a case report and literature review. *Int J Clin Exp Pathol* 8(6):7488-7493.7 Huo Z, Meng Y, Wu H, Shen J, Bi Y, Luo Y, Cao J and Liang Z (2014). Adenoid cystic carcinoma of the tracheobronchial tree: clinicopathologic and immunohistochemical studies of 21 cases. *Int J Clin Exp Pathol* 7(11):7527-7535.8 Junker K (2014). Pathology of tracheal tumors. *Thorac Surg Clin* 24(1):7-11.9 Gaissert HA, Grillo HC, Shadmehr MB, Wright CD, Gokhale M, Wain JC and Mathisen DJ (2004). Long-term survival after resection of primary adenoid cystic and squamous cell carcinoma of the trachea and carina. *Ann Thorac Surg* 78(6):1889-1896; discussion 1896-1887.10 Gelder CM and Hetzel MR (1993). Primary tracheal tumours: a national survey. *Thorax* 48(7):688-692.11 Webb BD, Walsh GL, Roberts DB and Sturgis EM (2006). Primary tracheal malignant neoplasms: the University of Texas MD Anderson Cancer Center experience. *J Am Coll Surg* 202(2):237-246.12 Zhengjaiang L, Pingzhang T, Dechao Z, Reddy-Kolanu G and Ilankovan V (2008). Primary tracheal tumours: 21 years of experience at Peking Union Medical College, Beijing, China. *J Laryngol Otol* 122(11):1235-1240.13 Li J, Tan F, Wang Y, Xue Q, Gao Y, Mu J, Mao Y, Zhao J, Wang D, Feng X, Shi S, Suda K, Cardillo G, Bertolaccini L, Infante MV, Van Schil PE, Gao S and He J (2022). Clinical characteristics, surgical treatments, prognosis, and prognostic factors of primary tracheal cancer patients: 20-year data of the National Cancer Center, China. *Transl Lung Cancer Res* 11(5):735-743.14 Piórek A, Płużański A, Teterycz P, Kowalski DM and Krzakowski M (2022). Do We Need TNM for Tracheal Cancers? Analysis of a Large Retrospective Series of Tracheal Tumors. *Cancers (Basel)* 14(7):1665. |

| **Core/** **Non-core** | **Element name** | **Values** | **Commentary** | **Implementation notes** |
| --- | --- | --- | --- | --- |
| Core and Non-core | CLINICAL INFORMATION | * Information not provided
* Information provided (select all that apply)
* Previous therapy
* Surgery
* Chemotherapy
* Radiotherapy
* Targeted therapy, *specify if available*
* Immunotherapy, *specify if available*
* Clinical staging, *specify*
* Other clinical information, *specify*
 | Clinical information about previous surgery or the use of neoadjuvant therapy will help the pathologist correctly interpret the histologic findings. While the extent of tumour necrosis or post-therapy fibrosis are not currently used as an important guide to management, it is good practice to document the effects of previous treatment within the ‘other’ free text box, pragmatically, estimating the percentage tumour volume affected by necrosis or fibrosis.In the case of prior treatment, the initial stage of the disease or at least information about the mobility of the larynx are helpful guides to staging. |  |
| Core  | OPERATIVE PROCEDURE  | * Not specified
* Biopsy (excisional, incisional, core needle), *specify*
* Resection
* Cordectomy
* Supraglottic laryngectomy
* Hemilaryngectomy, *specify side*
* Partial laryngectomy, *specify type*
* Total laryngectomy
* Neck (lymph node) dissection, a *specify*
* Other, *specify*
 | The nature of the operative procedure will influence the required level of detail in the pathological report. Diagnostic/incisional biopsies will usually generate a limited set of data items compared to excision/resection specimens. As an example, the status of resection margins does not require detailed consideration for diagnostic biopsies except for very small carcinomas where the entire cancer may be present in the diagnostic specimen. When a lymph node biopsy or neck dissection is included, a separate dataset is used to record the elements.  | a If a neck (lymph node) dissection is submitted, then a separate dataset is used to record the information. |
| Core | SPECIMEN(S) SUBMITTED | * Not specified
* Larynx
* Endolaryngeal excision
* Transoral laser excision
* Supraglottic laryngectomy
* Supracricoid laryngectomy
* Vertical hemilaryngectomy, *specify side*
* Partial laryngectomy, *specify type*
* Total laryngectomy
* Other. *specify*
* Hypopharynx
* Laryngopharyngectomy
* Other, *specify*
* Trachea
* Neck (lymph node) dissection,a *specify*
* Other, *specify*
 | The pathologist needs to be informed about the nature of surgery (type of specimen) so that their description and dissection are focused on selecting appropriate tissues to guide accurate cancer staging.1,2The following commentary is intended to assist pathologists in understanding the complex anatomy of the larynx and related structures. Anatomical sites and tissue compartments of the larynx are shown in Figures 1 and 2.The **supraglottis** includes the epiglottis, aryepiglottic fold (laryngeal aspect), arytenoid, ventricular bands (false cords) and laryngeal ventricles. The **glottis** extends from the ventricle to approximately 10 millimetres (mm) below the free level of the true vocal cord and includes the vocal cords, anterior commissure and posterior commissure.The **subglottis** extends from approximately 10 mm below the level of the true vocal cord to the inferior rim of the cricoid cartilage.Note that transglottic carcinomas cross the ventricles in a vertical direction to involve both true and false vocal cords.The **hypopharynx** is the part of the pharynx extending from the plane of the superior border of the hyoid bone (or floor of the vallecula) to the plane corresponding to the lower border of the cricoid cartilage. The contents of the hypopharynx include:* left and right pyriform sinuses which expand bilaterally and forward around the sides of the larynx and lie between the larynx and the thyroid cartilage;
* lateral and posterior hypopharyngeal walls; and
* postcricoid region extending from the level of the arytenoid cartilages to the inferior border of the cricoid cartilage.

The **paraglottic space** is a potential space antero-lateral and deep to the ventricles and saccules and filled with adipose tissue and connective tissue (Figure 1). It is bounded by the conus elasticus inferiorly, the thyroid cartilage laterally, the quadrangular membrane medially, and the pyriform sinus posteriorly.The **pre-epiglottic space** is anterior to the base of the epiglottis and filled with adipose tissue and connective tissue (Figure 2); it is triangular and is bounded by the thyroid cartilage and thyrohyoid membrane anteriorly, the epiglottis and thyroepiglottic ligament posteriorly, and the hyoepiglottic ligament at its base (Figures 1 and 2). Additionally, involvement of the adjacent soft tissues of the neck or thyroid gland (including the infrahyoid muscles (strap muscles), extrinsic muscle of the tongue, oesophagus, and/or trachea) are noted when more advanced disease is present, with significantly advanced disease identified when the tumour involves the prevertebral space, encases the carotid artery or invades any of the mediastinal structures. **Figure 1-2 (See end of the document for Figures)****References** 1 Helliwell TR (2000). ACP Best Practice No 157. Guidelines for the laboratory handling of laryngectomy specimens. *J Clin Pathol* 53(3):171-176.2 The Royal College of Pathologists of Australasia. Macroscopic Cut-up Manual. Available from: http://www.rcpa.edu.au/Library/Practising-Pathology/Macroscopic-Cut-Up/Specimen/Head-and-neck/Larynx (Accessed 7th January 2024).  | a If a neck (lymph node) dissection is submitted, then a separate dataset is used to record the information. |
| Core | TUMOUR SITE | * Not specified
* Larynx, supraglottis
* Epiglottis
* Lingual aspect
* Laryngeal aspect
* Aryepiglottic fold
* Arytenoid
* False vocal cord/fold
* Ventricle
* Larynx, glottis
* True vocal cord/fold
* Anterior commissure
* Posterior commissure
* Larynx, subglottis
* Hypopharynx
* Piriform sinus
* Postcricoid
* Pharyngeal wall (posterior and/or lateral)
* Other, *specify*
* Trachea
* Other, *specify*
 | Accurate documentation of the laterality and site of the specimen and tumour avoids errors in the delivery of therapy. The site of the primary tumour is a key determinant in clinicopathological staging systems for hypopharynx and larynx. For carcinomas that involve more than one site, the principal site of involvement should be recorded and coded; this may not be the site of origin. If required, the involvement of associated sites can be noted to help in further data analysis. Sites and subsites should be recorded according to the Union for International Cancer Control (UICC) nomenclature.1,2**References** 1 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control.* *TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.2 WHO Classification of Tumours Editorial Board (2024). *Head and Neck Tumours, WHO Classification of Tumours, 5th Edition, Volume 10.* IARC Press, Lyon. |  |
| Core  | TUMOUR LATERALITY | * Not specified
* Left
* Right
* Midline
 | Accurate documentation of the laterality and site of the specimen and tumour avoids errors in the delivery of therapy. The site of the primary tumour is a key determinant in clinicopathological staging systems for hypopharynx and larynx. For carcinomas that involve more than one site, the principal site of involvement should be recorded and coded; this may not be the site of origin. If required, the involvement of associated sites can be noted to help in further data analysis. Sites and subsites should be recorded according to the UICC nomenclature.1,2**References** 1 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control.* *TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.2 WHO Classification of Tumours Editorial Board (2024). *Head and Neck Tumours, WHO Classification of Tumours, 5th Edition, Volume 10.* IARC Press, Lyon.  |  |
| Core  | TUMOUR FOCALITY | * Unifocal
* Bilateral
* Multifocal

 Specify number of tumours \_\_\_* Cannot be assessed, *specify*
 | The presence of multiple or multifocal tumours is an important clue to a cancerization or field-effect phenomenon, potentiated by radiotherapy, alcohol, and various forms of tobacco use.1-5 Multifocality is defined as separate foci of tumour in the same organ, while multicentricity is defined as multiple tumours in separate organs/sites (e.g., hypopharynx, larynx, oral cavity).6 These designations apply to primary tumours, not metastases, and require histologic confirmation that tumour is present. In some cases, it may not be possible to determine whether there is direct extension or a new primary (hypopharynx and supraglottis). Similarly, it may not be possible to determine whether a fragmented specimen may contain multifocal tumours. At present, there is no defining distance of intervening, normal, uninvolved mucosa between tumour sites. By inference, using 10 mm of uninvolved mucosa between invasive tumours may be a useful guide to suggest multifocality when there is more than one tumour present. Specimens should be carefully examined both macroscopically and microscopically to determine whether multiple tumours are present, as patients with multiple tumours tend to have a worse overall long-term prognosis.7,8Where more than one anatomically or histologically distinct primary tumours occur, a separate dataset should be completed for each tumour. **References**1 Katada C, Yokoyama T, Yano T, Kaneko K, Oda I, Shimizu Y, Doyama H, Koike T, Takizawa K, Hirao M, Okada H, Yoshii T, Konishi K, Yamanouchi T, Tsuda T, Omori T, Kobayashi N, Shimoda T, Ochiai A, Amanuma Y, Ohashi S, Matsuda T, Ishikawa H, Yokoyama A and Muto M (2016). Alcohol Consumption and Multiple Dysplastic Lesions Increase Risk of Squamous Cell Carcinoma in the Esophagus, Head, and Neck. *Gastroenterology* 151(5):860-869.e867.2 Feller L and Lemmer J (2012). New 'second primary' cancers. *Sadj* 67(4):175-178.3 Pai SI and Westra WH (2009). Molecular pathology of head and neck cancer: implications for diagnosis, prognosis, and treatment. *Annu Rev Pathol* 4:49-70.4 Kong L, Lu JJ, Hu C, Guo X, Wu Y and Zhang Y (2006). The risk of second primary tumors in patients with nasopharyngeal carcinoma after definitive radiotherapy. *Cancer* 107(6):1287-1293.5 Thomas G, Hashibe M, Jacob BJ, Ramadas K, Mathew B, Sankaranarayanan R and Zhang ZF (2003). Risk factors for multiple oral premalignant lesions. *Int J Cancer* 107(2):285-291.6 Lee N, Waber P, Ye Y, Li X and Nisen P (1994). Clonality of head and neck-carcinoma and adjacent mucosa. *Oncol Rep* 1(3):637-638.7 Wang WL, Chang WL, Yang HB, Chang IW, Lee CT, Chang CY, Lin JT and Sheu BS (2015). Quantification of tumor infiltrating Foxp3+ regulatory T cells enables the identification of high-risk patients for developing synchronous cancers over upper aerodigestive tract. *Oral Oncol* 51(7):698-703.8 Mignogna MD, Fedele S, Lo Russo L, Mignogna C, de Rosa G and Porter SR (2007). Field cancerization in oral lichen planus. *Eur J Surg Oncol* 33(3):383-389.  |  |
| Core and Non-core | TUMOUR DIMENSIONS | Maximum tumour dimension (largest tumour)b (pathology and/or imaging determination)\_\_\_ mmAdditional dimensions (largest tumour) \_\_\_ mm x \_\_\_ mm* Cannot be assessed, *specify*
 | Tumour dimension is an important component in pathologic staging of the tumours of hypopharynx (core element). The macroscopic diameter (in millimetres) should be used unless the histological extent is greater than macroscopically apparent, in which case the microscopic dimension is used. As for other tissues, measurements are made pragmatically, acknowledging distortion of tissues by fixation and processing.1,2 Tumour dimension is not important in pathologic staging of the tumours of larynx (non-core).1,2 **References** 1 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control.* *TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.2 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.  | b Non-core for larynx.  |
| Non-core | BLOCK IDENTIFICATION KEY | List overleaf or separately with an indication of the nature and origin of all tissue blocks. | The origin/designation of all tissue blocks should be recorded. This information should ideally be documented in the final pathology report and is particularly important when further internal or external review arises. The reviewer needs to have unequivocal description of the origin of each block in order to provide an informed specialist opinion. If this information is not included in the final pathology report, it should be available on the laboratory computer system and relayed to the reviewing pathologist. It is highly encouraged to have a digital image (photograph) of the specimen and record of the key of the tumour blocks.Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.  |  |
| Core | HISTOLOGICAL TUMOUR TYPE | Select all that apply* Squamous cell carcinoma, conventional type
* Squamous cell carcinoma, subtypes
* Verrucous squamous cell carcinoma
* Basaloid squamous cell carcinoma
* Papillary squamous cell carcinoma
* Spindle cell squamous cell carcinoma
* Adenosquamous carcinoma
* Lymphoepithelial carcinoma
* Salivary gland-type carcinoma,c *specify type*
* Neuroendocrine neoplasm
* Neuroendocrine tumour, grade 1
* Neuroendocrine tumour, grade 2
* Neuroendocrine tumour, grade 3
* Small cell neuroendocrine carcinoma
* Large cell neuroendocrine carcinoma
* Mixed neuroendocrine and non-neuroendocrine, *specify type*
* Other, *specify*
 | All tumours of the hypopharynx, larynx and trachea should be given a type based on the most recent edition of the World Health Organization (WHO) Classification of Head and Neck Tumours, 5th edition, 2024 (Table 1).1Histopathological type is important for cancer registration and prognosis, with strength of evidence varying for different types. Verrucous and papillary carcinomas tend to have a good prognosis while, adenosquamous carcinomas have a worse prognosis than conventional and spindle cell carcinomas. For most of the subtypes of squamous cell carcinoma (SCC), surgery with adequate margins is the main treatment. In some malignancies, such as large cell neuroendocrine carcinomas (NEC), a combination of irradiation and chemotherapy is indicated.1-4 Epithelial neuroendocrine neoplasms are classified as neuroendocrine tumours (NET), NECs and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN). Neuroendocrine tumours (NET) are separated into grades (1, 2, and 3) based on mitotic rate and Ki-67 proliferation index, but these criteria are not yet fully developed for each of the anatomic sites in the head and neck. At present, the general cutoffs are: grade 1: <2 mitoses/2 mm2 and <2% Ki-67 proliferation index; grade 2: ≥2-10 mitoses/2 mm2 and 2-20% Ki-67 proliferation index; and grade 3: >10 mitoses/2mm2 and >20% Ki-67 proliferation index.5,6 Further, NECs are separated into small cell NEC and large cell NEC, showing tumour necrosis, >10 mitoses/2 mm2 and >20% Ki-67 proliferation index,5,7-9 with universal Rb1 loss and common p53 overexpression.10 Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNEN) usually consist of a poorly differentiated NEC component and a SCC or adenocarcinoma component. Immunohistochemically confirmed and morphologically distinct tumour components should be recognised and reported irrespective of their extent.For salivary-type tumour arising from mucosal glands, please refer to the International Collaboration on Cancer Reporting (ICCR) Carcinomas of the major salivary glands dataset for descriptors and ICD-O codes.11**Table 1 (See end of the document for Table)****References** 1 WHO Classification of Tumours Editorial Board (2024). *Head and Neck Tumours, WHO Classification of Tumours, 5th Edition, Volume 10.* IARC Press, Lyon.2 Wenig BM (2002). Squamous cell carcinoma of the upper aerodigestive tract: precursors and problematic variants. *Mod Pathol* 15(3):229-254.3 Chute DJ and Stelow EB (2010). Cytology of head and neck squamous cell carcinoma variants. *Diagn Cytopathol* 38(1):65-80.4 Lopez F, Williams MD, Cardesa A, Hunt JL, Strojan P, Rinaldo A, Nixon IJ, Rodrigo JP, Saba NF, Mendenhall WM, Quer M, Suarez C and Ferlito A (2017). How phenotype guides management of non-conventional squamous cell carcinomas of the larynx? *Eur Arch Otorhinolaryngol*. 274(7):2709-2726.5 Bal M, Sharma A, Rane SU, Mittal N, Chaukar D, Prabhash K and Patil A (2022). Neuroendocrine Neoplasms of the Larynx: A Clinicopathologic Analysis of 27 Neuroendocrine Tumors and Neuroendocrine Carcinomas. *Head Neck Pathol* 16(2):375-387.6 Asa SL, Arkun K, Tischler AS, Qamar A, Deng FM, Perez-Ordonez B, Weinreb I, Bishop JA, Wenig BM and Mete O (2021). Middle Ear "Adenoma": a Neuroendocrine Tumor with Predominant L Cell Differentiation. *Endocr Pathol* 32(4):433-441.7 Rivero A and Liang J (2016). Sinonasal small cell neuroendocrine carcinoma: a systematic review of 80 patients. *Int Forum Allergy Rhinol* 6(7):744-751.8 Kuan EC, Alonso JE, Tajudeen BA, Arshi A, Mallen-St Clair J and St John MA (2017). Small cell carcinoma of the head and neck: A comparative study by primary site based on population data. *Laryngoscope* 127(8):1785-1790.9 van der Laan TP, Iepsma R, Witjes MJ, van der Laan BF, Plaat BE and Halmos GB (2016). Meta-analysis of 701 published cases of sinonasal neuroendocrine carcinoma: The importance of differentiation grade in determining treatment strategy. *Oral Oncol* 63:1-9.10 Uccella S, La Rosa S, Metovic J, Marchiori D, Scoazec JY, Volante M, Mete O and Papotti M (2021). Genomics of High-Grade Neuroendocrine Neoplasms: Well-Differentiated Neuroendocrine Tumor with High-Grade Features (G3 NET) and Neuroendocrine Carcinomas (NEC) of Various Anatomic Sites. *Endocr Pathol* 32(1):192-210.11 International Collaboration on Cancer Reporting (2024). *Carcinomas of the major salivary glands Histopathology Reporting Guide. 2nd edition*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/head-neck/salivary-glands/ (Accessed 31st July 2024).12 Fritz A, Percy C, Jack A,  Shanmugaratnam K, Sobin L, Parkin DM  and Whelan S (eds) (2020). *International Classification of Diseases for Oncology, Third edition, Second revision ICD-O-3.2*. Available from: http://www.iacr.com.fr/index.php?option=com\_content&view=category&layout=blog&id=100&Itemid=577 (Accessed 16th March 2024).  | Value list based on the WHOClassification of Head and Neck Tumours (2024).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 for Research on Cancer (IARC).c For histological type of salivary gland-type carcinomas, refer to theCarcinomas of the major salivary glands dataset. |
| Core | HISTOLOGICAL TUMOUR GRADEd | * Grade 1, well differentiated, low grade
* Grade 2, moderately differentiated, intermediate grade
* Grade 3, poorly differentiated, high grade
* Undifferentiated
* High grade transformation

Grading system used, *specify* * Cannot be assessed, *specify*
 | Although human papillomavirus (HPV)-associated carcinomas arising in the oropharynx are not graded (see ICCR Carcinomas of the oropharynx and nasopharynx dataset1), there is insufficient evidence to justify this approach in the hypopharynx and larynx. The recommendation is that HPV assessment should not be performed except for basaloid, lymphoepithelial, and papillary carcinomas. The conventional grading system for classical SCC should be used for all tumours at these sites.2,3-8Grading is based on the degree of resemblance of the carcinoma to the normal epithelium and follows the descriptions in the WHO Classification.2 The most aggressive area is graded as well, moderately, or poorly differentiated. This system is widely used and prognostically useful, even though it suffers from inter-observer variability and sampling problems. While most SCCs will be well or moderately differentiated, it is important for prognostication to separate tumours based on differentiation. Where a tumour has a varied appearance, then the highest grade (poorest differentiation) is recorded as a core data item, while the predominant pattern may be recorded as non-core data.Squamous cell carcinoma (SCC) subtypes (such as verrucous, basaloid, adenosquamous and spindle cell) are considered to have intrinsic biological potential and are not graded. Still, several grading systems for each tumour type are available, with differing merits, and as such, recording which system has been applied is more clinically meaningfully (use ‘specify’ to state the system used), with the ICCR deferring to the WHO Classification current edition for grading guidance and preference.2For the grading of salivary-type tumour arising from mucosal glands, please refer to the ICCR Carcinomas of the major salivary glands dataset for descriptors.9**References** 1 International Collaboration on Cancer Reporting (2024). *Carcinomas of the oropharynx and nasopharynx Histopathology Reporting Guide. 2nd edition*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/head-neck/nasopharynx/ (Accessed 31st July 2024).2 WHO Classification of Tumours Editorial Board (2024). *Head and Neck Tumours, WHO Classification of Tumours, 5th Edition, Volume 10*. IARC Press, Lyon.3 Jakobsson PA, Eneroth CM, Killander D, Moberger G and Martensson B (1973). Histologic classification and grading of malignancy in carcinoma of the larynx. *Acta Radiol Ther Phys Biol* 12(1):1-8.4 Roland NJ, Caslin AW, Nash J and Stell PM (1992). Value of grading squamous cell carcinoma of the head and neck. *Head Neck* 14(3):224-229.5 Kearsley JH and Thomas S (1993). Prognostic markers in cancers of the head and neck region. *Anticancer Drugs* 4(4):419-429.6 Snow GB, Annyas AA, van Slooten EA, Bartelink H and Hart AA (1982). Prognostic factors of neck node metastasis. *Clin Otolaryngol Allied Sci* 7(3):185-192.7 Henson DE (1988). The histological grading of neoplasms. *Arch Pathol Lab Med* 112(11):1091-1096.8 Sethi S, Lu M, Kapke A, Benninger MS and Worsham MJ (2009). Patient and tumor factors at diagnosis in a multi-ethnic primary head and neck squamous cell carcinoma cohort. *J Surg Oncol* 99(2):104-108.9 International Collaboration on Cancer Reporting (2024). *Carcinomas of the major salivary glands Histopathology Reporting Guide. 2nd edition*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/head-neck/salivary-glands/ (Accessed 31st July 2024).  | Applicable to conventional squamous cell carcinoma and minor salivary gland tumours only.d Neuroendocrine neoplasms are graded as part of the tumourclassification (see Histological Tumour Type).  |
| Non-core | PATTERN OF INVASIVE FRONT | * Cohesive
* Non-cohesive

**Tumour budding**  Number of buds per 0.785 mm2* <5 buds
* ≥5 buds
 | The pattern of invasion at the invasive tumour front is of proven prognostic value for oral and oropharyngeal carcinomas,and there is evidence that a similar approach may be of value to predict nodal metastasis for hypopharyngeal and laryngeal carcinomas too.1-4 The invasive tumour front may show cohesive or non-cohesive patterns. Cohesive invasion pattern consists of broad sheets of tumour cells or nests with >15 tumour cells. Non-cohesive invasion pattern is characterised by narrow strands and small groups of ≤15 tumour cells and single tumour cells. Additionally, tumour budding has emerged as a promising biomarker in various carcinomas, with early evidence suggesting that it is an independent adverse prognostic factor in carcinoma of the larynx and hypopharynx.5-11Tumour budding is defined as single tumour cells or clusters of up to four tumour cells at the invasive tumour front. There is no consensus yet how it should be assessed and graded in laryngeal and hypopharyngeal carcinomas. It has been recommended to count the number of buds on hematoxylin and eosin (H&E) slides in areas showing maximal budding, in a single x20 high power field (HPF).5,6,11 Depending on the eyepiece field diameter of the microscope, the number of buds may need to be normalised to represent the number for a field of 0.785 mm2 (objective lens 20x with eyepiece diameter of 20 mm). For risk stratification in SCC of the head and neck, a cutoff point of 5 buds (low risk <5 buds versus high risk ≥5 buds) has been used in the majority of the published studies.6,11**References** 1 Jakobsson PA, Eneroth CM, Killander D, Moberger G and Martensson B (1973). Histologic classification and grading of malignancy in carcinoma of the larynx. *Acta Radiol Ther Phys Biol* 12(1):1-8.2 Brandwein-Gensler M, Smith RV, Wang B, Penner C, Theilken A, Broughel D, Schiff B, Owen RP, Smith J, Sarta C, Hebert T, Nason R, Ramer M, DeLacure M, Hirsch D, Myssiorek D, Heller K, Prystowsky M, Schlecht NF and Negassa A (2010). Validation of the histologic risk model in a new cohort of patients with head and neck squamous cell carcinoma. *Am J Surg Pathol* 34(5):676-688.3 Bryne M, Jenssen N and Boysen M (1995). Histological grading in the deep invasive front of T1 and T2 glottic squamous cell carcinomas has high prognostic value. *Virchows Arch* 427(3):277-281.4 Yilmaz T, Hoşal AS, Gedikoğlu G and Kaya S (1999). Prognostic significance of histopathological parameters in cancer of the larynx. *Eur Arch Otorhinolaryngol* 256(3):139-144.5 Boxberg M, Kuhn PH, Reiser M, Erb A, Steiger K, Pickhard A, Straßen U, Koob I, Kolk A, Warth A, Jesinghaus M and Weichert W (2019). Tumor Budding and Cell Nest Size Are Highly Prognostic in Laryngeal and Hypopharyngeal Squamous Cell Carcinoma: Further Evidence for a Unified Histopathologic Grading System for Squamous Cell Carcinomas of the Upper Aerodigestive Tract. *Am J Surg Pathol* 43(3):303-313.6 Mäkitie AA, Almangush A, Rodrigo JP, Ferlito A and Leivo I (2019). Hallmarks of cancer: Tumor budding as a sign of invasion and metastasis in head and neck cancer. *Head Neck* 41(10):3712-3718.7 Öztürk Ç, Paşaoğlu HE, Emre F, Ege T and Tetikkurt Ü S (2022). High tumor budding activity may predict poor prognosis in laryngeal squamous cell carcinomas. *Indian J Pathol Microbiol* 65(2):280-287.8 Stögbauer F, Beck S, Ourailidis I, Hess J, Poremba C, Lauterbach M, Wollenberg B, Buchberger AMS, Jesinghaus M, Schirmacher P, Stenzinger A, Weichert W, Boxberg M and Budczies J (2023). Tumour budding-based grading as independent prognostic biomarker in HPV-positive and HPV-negative head and neck cancer. *Br J Cancer* 128(12):2295-2306.9 Karpathiou G, Vieville M, Gavid M, Camy F, Dumollard JM, Magné N, Froudarakis M, Prades JM and Peoc'h M (2019). Prognostic significance of tumor budding, tumor-stroma ratio, cell nests size, and stroma type in laryngeal and pharyngeal squamous cell carcinomas. *Head Neck* 41(6):1918-1927.10 Sarioglu S, Acara C, Akman FC, Dag N, Ecevit C, Ikiz AO, Cetinayak OH and Ada E (2010). Tumor budding as a prognostic marker in laryngeal carcinoma. *Pathol Res Pract* 206(2):88-92.11 Chiesa-Estomba CM, Thompson L, Agaimy A, Zidar N, Simpson RHW, Franchi A, Rodrigo JP, Mäkitie AA, Almangush A, Leivo I and Ferlito A (2023). Predictive value of tumor budding in head and neck squamous cell carcinoma: an update. *Virchows Arch* 483(4):441-449.  | Applicable to resection specimens only. |
| Core | EXTENT OF INVASION | **Larynx*** Not identified
* Present (select all that apply)

 Clinical observation Histologic  and/or imaging  * Mucosa involvement
* Paraglottic space involvement
* Pre-epiglottic space involvement
* Inner cortex of cartilage
* Full thickness invasion of cartilage
* Soft tissues of neck, thyroid, prevertebral space, carotid artery or mediastinal

structures involvement* Other, *specify*
* Cannot be assessed, *specify*

**Hypopharynx*** Not identified
* Present (select all that apply)

 Clinical observation Histologic  and/or imaging * Limited to wall of hypopharynx
* Extends outside wall of hypopharynx
* Other, *specify*
* Cannot be assessed, *specify*
 | In the larynx, the invasion of tissue compartments deep to the mucosa is important for staging. The important tissues for staging purposes are the paraglottic space, the pre-epiglottic space and the thyroid and cricoid cartilages. One of the points of distinction between T3 and T4a carcinomas is whether cartilage invasion involves the inner cortex (partial) or outer cortex (full thickness). Further, involvement of the adjacent soft tissues, oesophagus, trachea, encasement of the carotid artery, and/or involvement of the mediastinum, are seen in advanced disease and are prognostically significant.1-4 In the hypopharnyx, the extent of invasion is important, too. The involvement oesophagus, thyroid/cricoid cartilage, hyoid bone, thyroid gland, central compartment soft tissue (prelaryngeal strap muscle, subcutanous fat), prevertebral fascia, carotid structures and mediastinal structures are important for staging and prognostically significant.3**References** 1 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control.* *TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.2 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.3 WHO Classification of Tumours Editorial Board (2024). *Head and Neck Tumours, WHO Classification of Tumours, 5th Edition, Volume 10.* IARC Press, Lyon. 4 Alkureishi LW, Ross GL, Shoaib T, Soutar DS, Robertson AG, Sorensen JA, Thomsen J, Krogdahl A, Alvarez J, Barbier L, Santamaria J, Poli T, Sesenna E, Kovacs AF, Grunwald F, Barzan L, Sulfaro S and Alberti F (2008). Does tumor depth affect nodal upstaging in squamous cell carcinoma of the head and neck? *Laryngoscope* 118(4):629-634.  |  |
| Core | LYMPHOVASCULAR INVASION | * Not identified
* Present
* Indeterminate, *specify reason*
 | Reports on the prognostic value of lymphovascular invasion in laryngeal and hypopharyngeal carcinomas are variable, but some studies suggest that it is an independent indicator of poor outcome.1-5 The consensus of the Dataset Authoring Committee was that lymphovascular invasion should be a core element.Lymphovascular invasion is recognised by the presence of tumour cells within an endothelial-lined space and should be distinguished from retraction artefact. Small vessel invasion includes invasion of the lymphatics, capillaries or post-capillary venules. As it is often difficult to distinguish among the types of small vessels, their invasion by tumour cells is reported as lymphovascular invasion. Recognition of lymphovascular invasion may be difficult and subjective and can be improved by using immunohistochemistry (e.g., D2-40, CD61) and histochemical stains (e.g., elastic staining to identify venous elastic lamina) but this is not recommended in routine work. Specifically, CD61 is a marker of activation of the fibrinogen cascade, and its presence in a linear fashion on platelets in a space confirms fibrin is present, and thus genuine vascular/endothelial destruction.6Cases that are still equivocal after taking additional steps may be reported as ‘indeterminate’ for lymphovascular invasion, but this designation should be sparingly used and it is useful to provide the reason in a comment in the report.**References** 1 Suzuki M, Suzuki T, Asai M, Ichimura K, Nibu K, Sugasawa M and Kaga K (2007). Clinicopathological factors related to cervical lymph node metastasis in a patient with carcinoma of the oral floor. *Acta Otolaryngol Suppl*(559):129-135.2 Poleksic S and Kalwaic HJ (1978). Prognostic value of vascular invasion in squamous cell carcinoma of the head and neck. *Plast Reconstr Surg* 61(2):234-240.3 Fletcher KT, Gal TJ, Ebelhar AJ, Valentino J, Brill YM, Dressler EV and Aouad RK (2017). Prognostic indicators and survival in salvage surgery for laryngeal cancer. *Head Neck* 39(10):2021-2026.4 Scharpf J, Ward M, Adelstein D, Koyfman S and Li M (2018). Elucidation of salvage laryngectomy pathologic and clinical variables to guide further treatment intensification investigation. *Laryngoscope* 128(4):823-830.5 Tsai MH, Chuang HC, Lin YT, Huang TL, Fang FM, Lu H and Chien CY (2021). Survival Outcomes and Predictors for Patients who Failed Chemoradiotherapy/Radiotherapy and Underwent Salvage Total Laryngectomy. *Int J Environ Res Public Health* 18(2):371.6 Cracolici V, Parilla M, Henriksen KJ and Cipriani NA (2020). An Evaluation of CD61 Immunohistochemistry in Identification of Vascular Invasion in Follicular Thyroid Neoplasms. *Head Neck Pathol* 14(2):399-405.  |  |
| Core | PERINEURAL INVASION | * Not identified
* Present
* Indeterminate, *specify reason*
 | The presence or absence of perineural invasion should be recorded, regardless of the size of the nerve. Invasion of the perineural plane is a predictor of local recurrence and nodal metastasis and may prompt consideration of adjuvant chemoradiotherapy.1-10 The perineural plane is a potential space between the bundles of axons and the perineurium; the presence of carcinoma around a nerve (external to the perineurium) is not regarded as perineural invasion. There is currently insufficient evidence to separate it into extratumoural and intratumoural invasion though some studies suggest that extratumoural perineural invasion is more important.2 For this dataset, either intratumoural or extratumoural invasion is regarded as a positive finding.**References** 1 Fagan JJ, Collins B, Barnes L, D'Amico F, Myers EN and Johnson JT (1998). Perineural invasion in squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg* 124(6):637-640.2 Miller ME, Palla B, Chen Q, Elashoff DA, Abemayor E, St John MA and Lai CK (2012). A novel classification system for perineural invasion in noncutaneous head and neck squamous cell carcinoma: histologic subcategories and patient outcomes. *Am J Otolaryngol* 33(2):212-215.3 Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, Kish JA, Kim HE, Cmelak AJ, Rotman M, Machtay M, Ensley JF, Chao KS, Schultz CJ, Lee N and Fu KK (2004). Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 350(19):1937-1944.4 Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefebvre JL, Greiner RH, Giralt J, Maingon P, Rolland F, Bolla M, Cognetti F, Bourhis J, Kirkpatrick A and van Glabbeke M (2004). Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 350(19):1945-1952.5 Strojan P, Ferlito A, Langendijk JA and Silver CE (2012). Indications for radiotherapy after neck dissection. *Head Neck* 34(1):113-119.6 Sethi S, Lu M, Kapke A, Benninger MS and Worsham MJ (2009). Patient and tumor factors at diagnosis in a multi-ethnic primary head and neck squamous cell carcinoma cohort. *J Surg Oncol* 99(2):104-108.7 Brandwein-Gensler M, Smith RV, Wang B, Penner C, Theilken A, Broughel D, Schiff B, Owen RP, Smith J, Sarta C, Hebert T, Nason R, Ramer M, DeLacure M, Hirsch D, Myssiorek D, Heller K, Prystowsky M, Schlecht NF and Negassa A (2010). Validation of the histologic risk model in a new cohort of patients with head and neck squamous cell carcinoma. *Am J Surg Pathol* 34(5):676-688.8 Fletcher KT, Gal TJ, Ebelhar AJ, Valentino J, Brill YM, Dressler EV and Aouad RK (2017). Prognostic indicators and survival in salvage surgery for laryngeal cancer. *Head Neck* 39(10):2021-2026.9 Zhu X, Duan F, Zhu Y, Shi X, Sun S, Cheng Y and Chen X (2021). Perineural Invasion as a Prognostic Factor in Laryngeal Squamous Cell Cancer: A Matched-Pair Survival Analysis. *Cancer Invest* 39(9):734-740.10 Shin HI, Bang JI, Kim GJ, Sun DI and Kim SY (2023). Perineural Invasion Predicts Local Recurrence and Poor Survival in Laryngeal Cancer. *J Clin Med* 12(2):449.  |  |
| Core  | MARGIN STATUS | **Invasive carcinoma*** Not involved

 Distance of tumour from  closest margin \_\_\_ mm* Distance not assessable

 Specify closest margin(s), if  possible * Involved

 Specify margin(s), if possible* Cannot be assessed, *specify*

**Carcinoma in situ/high grade dysplasiae*** Not applicable
* Not involved

 Distance of carcinoma in situ/high grade dysplasia from closest margin \_\_\_ mm* Distance not assessable

 Specify closest margin(s), if  possible * Involved

 Specify margin(s), if possible* Cannot be assessed, *specify*
 | A positive margin is usually defined by the presence of an invasive carcinoma or carcinoma in situ at margins. It is recommended that the distance from in situ or invasive carcinoma to the closest margin is measured and reported in mm, if assessable. Margin status is a predictor of local recurrence and may require consideration of adjuvant therapy.1-7The definition of a ‘close margin’ varies between published series, typically being regarded as between 3 and 5 mm.8 For laser resections of glottic carcinomas even 1 mm may be adequate due to the thermal damage and shrinkage of tissue at the margin.1,8-11**References** 1 Hinni ML, Ferlito A, Brandwein-Gensler MS, Takes RP, Silver CE, Westra WH, Seethala RR, Rodrigo JP, Corry J, Bradford CR, Hunt JL, Strojan P, Devaney KO, Gnepp DR, Hartl DM, Kowalski LP, Rinaldo A and Barnes L (2013). Surgical margins in head and neck cancer: a contemporary review. *Head Neck* 35(9):1362-1370.2 Slootweg PJ, Hordijk GJ and Schade Y et al (2002). Treatment failure and margin status in head and neck cancer. A critical view on the the potential value of molecular pathology. *Oral Oncol* 38:500-503.3 Laskar SG, Agarwal JP, Srinivas C and Dinshaw KA (2006). Radiotherapeutic management of locally advanced head and neck cancer. *Expert Rev Anticancer Ther* 6(3):405-417.4 Bradley PJ, MacLennan K, Brakenhoff RH and Leemans CR (2007). Status of primary tumour surgical margins in squamous head and neck cancer: prognostic implications. *Curr Opin Otolaryngol Head Neck Surg* 15(2):74-81.5 Langendijk JA, Ferlito A, Takes RP, Rodrigo JP, Suarez C, Strojan P, Haigentz M, Jr. and Rinaldo A (2010). Postoperative strategies after primary surgery for squamous cell carcinoma of the head and neck. *Oral Oncol* 46(8):577-585.6 Hamman J, Howe CL, Borgstrom M, Baker A, Wang SJ and Bearelly S (2022). Impact of Close Margins in Head and Neck Mucosal Squamous Cell Carcinoma: A Systematic Review. *Laryngoscope* 132(2):307-321.7 Sunkara PR, Graff JT and Cramer JD (2023). Association of Surgical Margin Distance With Survival in Patients With Resected Head and Neck Squamous Cell Carcinoma: A Secondary Analysis of a Randomized Clinical Trial. *JAMA Otolaryngol Head Neck Surg* 149(4):317-326.8 Alicandri-Ciufelli M, Bonali M, Piccinini A, Marra L, Ghidini A, Cunsolo EM, Maiorana A, Presutti L and Conte PF (2013). Surgical margins in head and neck squamous cell carcinoma: what is 'close'? *Eur Arch Otorhinolaryngol* 270(10):2603-2609.9 Ansarin M, Santoro L, Cattaneo A, Massaro MA, Calabrese L, Giugliano G, Maffini F, Ostuni A and Chiesa F (2009). Laser surgery for early glottic cancer: impact of margin status on local control and organ preservation. *Arch Otolaryngol Head Neck Surg* 135(4):385-390.10 Singh A, Qayyumi B and Chaturvedi P (2020). An Update on Surgical Margins in the Head Neck Squamous Cell Carcinoma: Assessment, Clinical Outcome, and Future Directions. *Curr Oncol Rep* 22(8):82.11 Mariani C, Carta F, Bontempi M, Marrosu V, Tatti M, Pinto V, Gerosa C and Puxeddu R (2023). Management and Oncologic Outcomes of Close and Positive Margins after Transoral CO(2) Laser Microsurgery for Early Glottic Carcinoma. *Cancers (Basel)* 15(5):1490.  | e High grade dysplasia is synonymous with moderate/severe dysplasia. |
| Non-core | COEXISTENT PATHOLOGY | * None identified
* Necrotising sialometaplasia
* Infection, *specify*
* Dysplasia, *specify*
* Hyperplasia, *specify*
* Other, *specify*
 | This is a non-core element to provide the pathologist with the flexibility to record any other diseases that have potential impact on clinical management, such as infections, necrotising sialometaplasia, dysplasia, hyperplasia. |  |
| Core and Non-core | ANCILLARY STUDIES | * Not performed
* Performed

 **Neuroendocrine neoplasms**  (select all that apply)* Not applicable
* Neuroendocrine markers, *specify*
* Cytokeratin(s), *specify*
* Ki-67 proliferation index

\_\_\_ %* Rb
* Retained
* Deficient
* p53
* Abnormal, *specify*
* Other, *record test(s), methodology and results*

 **Squamous cell carcinoma and**  **subtypes** *Record test(s), methodology*  *and results* **Representative blocks for ancillary studies**, *specify those blocks best representing tumour and/or normal tissue for further study* | For neuroendocrine neoplasms core elements are neuroendocrine markers, epithelial markers, and Ki-67 proliferation index. The diagnosis of neuroendocrine neoplasms (specifically NET and NEC) must be confirmed immunohistochemically, with positive reaction for neuroendocrine markers (synaptophysin, chromogranin, INSM1) and for epithelial markers (pancytokeratin, cytokeratin). Furthermore, a proliferation index as determined by Ki-67 immunohistochemical analysis is recommended for grading all NETs, helping to confirm NECs, and p53 and Rb1 may be helpful in the distinction between NET and NEC, especially G3 NET from NEC.1,2,3 The majority of SCC are diagnosed on the basis of morphology. Immunohistochemistry must be used only in case of poorly differentiated SCC to confirm the diagnosis (e.g., p40, CK 5/6, p63). If necessary, other malignant tumours such as melanoma and lymphomas must be excluded by the use of the appropriate immunohistochemistry. Special stains for mucin and FISH for MAML2 rearrangement may help to diagnose mucoepidermoid carcinoma.The literature recognises that a very few HPV-associated carcinomas may occur in the hypopharynx and larynx, but prognostic relevance is uncertain.4 There is some evidence suggesting that HPV-associated hypopharyngeal and laryngeal carcinoma may have a better prognosis.5-7 HPV testing may be performed, particularly in cases with basaloid, papillary, lymphoepithelial or warty morphology.5,8,9 p16INK4a immunohistochemistry as a surrogate marker for HPV-associated carcinoma may be less reliable in the larynx than in the oropharynx.10Programmed cell death-ligand 1 (PD-L1) expression has been used as predictive biomarker for checkpoint inhibitor therapy since the anti-programmed cell death-1 receptor (PD-1) antibodies, nivolumab and pembrolizumab, have been approved for the treatment of patients with recurrent and/or unresectable metastatic head and neck SCC.11,12 It is currently advised to use antibody 22C3 and to calculate a combined positive score (CPS), defined as the number of PD-L1-positive cells (tumour cells, lymphocytes, and macrophages) divided by the total number of tumour cells × 100. PD-L1 expression is associated with an increased objective response rates in patients with CPS ≥1, with a better response with CPS ≥20.13,14 However, the lack of response in some PD-L1 positive patients clearly indicates that other factors are involved in the resistance to treatment with check-point inhibitors.15 **References** 1 Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, Busam KJ, de Krijger RR, Dietel M, El-Naggar AK, Fernandez-Cuesta L, Klöppel G, McCluggage WG, Moch H, Ohgaki H, Rakha EA, Reed NS, Rous BA, Sasano H, Scarpa A, Scoazec JY, Travis WD, Tallini G, Trouillas J, van Krieken JH and Cree IA (2018). A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. *Mod Pathol* 31(12):1770-1786.2 Asa SL, Arkun K, Tischler AS, Qamar A, Deng FM, Perez-Ordonez B, Weinreb I, Bishop JA, Wenig BM and Mete O (2021). 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HPV Positive Status Is a Favorable Prognostic Factor in Non-Nasopharyngeal Head and Neck Squamous Cell Carcinoma Patients: A Retrospective Study From the Surveillance, Epidemiology, and End Results Database. *Front Oncol* 11:688615.8 WHO Classification of Tumours Editorial Board (2024). *Head and Neck Tumours, WHO Classification of Tumours, 5th Edition, Volume 10.* IARC Press, Lyon.9 Acuña G, Gomà M, Temprana-Salvador J, Garcia-Bragado F, Alós L, Ordi J, Cardesa A and Nadal A (2019). Human papillomavirus in laryngeal and hypopharyngeal lymphoepithelial carcinoma. *Mod Pathol* 32(5):621-626.10 Mena M, Wang X, Tous S, Quiros B, Clavero O, Alejo M, Morey F, Taberna M, Leon Vintro X, Lloveras Rubio B, Alos L, Mehanna H, Quint W, Pawlita M, Tommasino M, Pavón MA, Muñoz N, De Sanjose S, Bosch FX, Alemany L, On Behalf Of The Ico International Hpv In H and Neck Cancer Study G (2022). 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Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *Lancet* 393(10167):156-167.13 Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, Heath K, McClanahan T, Lunceford J, Gause C, Cheng JD and Chow LQ (2016). Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. *Lancet Oncol* 17(7):956-965.14 Burtness B, Harrington KJ, Greil R, Soulières D, Tahara M, de Castro G, Jr., Psyrri A, Basté N, Neupane P, Bratland Å, Fuereder T, Hughes BGM, Mesía R, Ngamphaiboon N, Rordorf T, Wan Ishak WZ, Hong RL, González Mendoza R, Roy A, Zhang Y, Gumuscu B, Cheng JD, Jin F and Rischin D (2019). Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *Lancet* 394(10212):1915-1928.15 Litchfield K, Reading JL, Puttick C, Thakkar K, Abbosh C, Bentham R, Watkins TBK, Rosenthal R, Biswas D, Rowan A, Lim E, Al Bakir M, Turati V, Guerra-Assunção JA, Conde L, Furness AJS, Saini SK, Hadrup SR, Herrero J, Lee SH, Van Loo P, Enver T, Larkin J, Hellmann MD, Turajlic S, Quezada SA, McGranahan N and Swanton C (2021). Meta-analysis of tumor- and T cell-intrinsic mechanisms of sensitization to checkpoint inhibition. *Cell* 184(3):596-614.e514.  |  |
| Core | PATHOLOGICAL STAGING(UICC TNM 8**th** edition)f | **TNM Descriptors** (only if applicable) (select all that apply)* m - multiple primary tumours
* r - recurrent
* y - during or following multimodality therapy

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

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

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

Primary tumour: Hypopharynxg* T1 Tumour limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
* T2 Tumour invades more than one subsite of hypopharynx or an adj acent site, or measures more than 2 cm but not more than 4 cm in greatest dimension, without fixation of hemilarynx
* T3 Tumour more than 4cm in greatest dimension, or with fixation of hemilarynx or extension to oesophageal mucosa
* T4a Tumour invades any of the following: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartment soft tissueh
* T4b Tumour invades prevertebral fascia, encases carotid artery, or invades mediastinal structures
 | By UICC/American Joint Committee on Cancer (AJCC) convention,1,2 the designation ‘T’ refers to a primary tumour that has not been previously treated. The symbol ‘p’ refers to the pathologic classification of the stage, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumour adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. There is no pathologic M0 category as this designation requires clinical evaluation and imaging. Clinical classification (cTNM) is usually carried out by the evaluating clinician before treatment during initial evaluation of the patient or when pathologic classification is not possible.Pathological staging is usually performed after surgical resection of the primary tumour and depends on documentation of the anatomic extent of disease, whether or not the primary tumour has been completely removed. If a biopsied tumour is not resected for any reason (e.g., when technically unfeasible) and if the highest T and N categories or the M1 category of the tumour can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied even though total removal of the primary cancer was not performed. **UICC TNM 81**Primary Tumour: SubglottisNote that the UICC and AJCC staging differs for T3/T4a subglottic carcinomas.1,2 In the AJCC system, T3 carcinomas include those limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage.2LarynxNormal (T1) or impaired (T2) vocal cord mobility and vocal cord fixation (T3) may only be determined clinically.**TNM Descriptors**For identification of special cases of TNM or pTNM classifications, the ‘m’ suffix and ‘y’ and ‘r’ prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.The ‘m’ suffix indicates the presence of multiple primary tumours in a single site and is recorded in parentheses: pT(m)NM.The ‘y’ prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a ‘y’ prefix. The ycTNM or ypTNM categorises the extent of tumour actually present at the time of that examination. The ‘y’ categorisation is not an estimate of tumour prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy).The ‘r’ prefix indicates a recurrent tumour when staged after a documented disease-free interval, and is identified by the ‘r’ prefix: rTNM.For the pN classification of regional lymph nodes, see ICCR Nodal excisions and neck dissection specimens dataset.3Reporting of pathological staging categories (pT, pN, pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM8 and AJCC TNM8,1,2 the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.Pathological staging should not be reported if the submitted specimen is insufficient for definitive staging, especially with biopsy samples (core needle, incisional or excisional). Staging is based on the submitted resection, and even if there is grossly residual disease or there is tumour at the margin, pT staging should only be reported on findings in the resection specimen and/or at operation.1,2The reference document TNM Supplement: A commentary on uniform use, 5th Edition (C Wittekind et al. editors) may be of assistance when staging.4**References** 1 Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control.* *TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.2 Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM and Meyer LR (eds) (2017). *AJCC Cancer Staging Manual. 8th ed.*, Springer, New York.3 International Collaboration on Cancer Reporting (2024). *Nodal Excisions and Neck Dissection Specimens for Head & Neck Tumours Histopathology Reporting Guide. 2nd edition*. Available from: https://www.iccr-cancer.org/datasets/published-datasets/head-neck/nodal-excisions/ (Accessed 31st July 2024).4 Wittekind C, Brierley JD, van Eycken AL and van Eycken E (eds) (2019). *TNM Supplement: A Commentary on Uniform Use, 5th Edition,* Wiley, USA. | Note that permission to publish the TNM cancer staging tables may be needed in your implementation. It is advisable to check.f Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (incorporating any errata published up until 12th July 2024).g Note that the results of neck (lymph node) dissection are derived from a separate dataset.h Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat. |

**Figures**



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

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

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**Tables**

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

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

a These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).12 Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade Ill intraepithelial neoplasia; /3 for malignant tumours, primary site; and /6 for malignant tumours, metastatic site. Behaviour code /6 is not generally used by cancer registries.

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

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1 WHO Classification of Tumours Editorial Board (2024). *Head and Neck Tumours, WHO Classification of Tumours, 5th Edition, Volume 10.* IARC Press, Lyon.

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