| **Core/**  **Non-core** | **Element name** | **Values** | **Commentary** | **Implementation notes** |
| --- | --- | --- | --- | --- |
| Core and  Non-core | NEOADJUVANT THERAPY | Single selection value list:  • Information not provided  • Not administered  • Administered, specify type  Non-core: Multi selection value list  (select all that apply):   * Chemotherapy * Radiotherapy * Targeted therapy, specify if available * Immunotherapy, specify if available | The dataset has been developed for the reporting of resection and biopsy specimens of the nasopharynx and oropharynx. The protocol applies to all invasive carcinomas of the nasopharynx and oropharynx including the base of tongue, tonsils, soft palate, posterior wall, and uvula. Lymphomas and sarcomas are not included. Neck dissections and nodal excisions are dealt with in a separate dataset, and this dataset should be used in conjunction, where applicable.  When a biopsy specimen is all that is received, elements specific to the biopsy should be reported and the remaining items that are applicable to surgically resected tumours omitted. For carcinomas of the oropharynx, there is no allowance for a single tumour that is “multifocal”. Although multiple synchronous and metachronous primary oropharyngeal squamous cell carcinomas are uncommon and are usually of the same high risk human papillomavirus (HPV) type, there is no data to suggest that they are not simply separate primary tumours.1 Thus, for oropharyngeal carcinomas, each distinct focus should be considered a separate primary tumour, and should receive its own separate dataset. However, for nasopharyngeal tumours, even if the tumour appears to be multifocal clinically and pathologically, these are regarded and treated as a single primary.2-4  **References**  1 Caley A, Evans M, Powell N, Paleri V, Tomkinson A, Urbano TG, Jay A, Robinson M and Thavaraj S (2015). Multicentric human papillomavirus-associated head and neck squamous cell carcinoma. Head Neck 37(2):202-208.  2 Kwong DL, Nicholls J, Wei WI, Chua DT, Sham JS, Yuen PW, Cheng AC, Yau CC, Kwong PW and Choy DT (2001). Correlation of endoscopic and histologic findings before and after treatment for nasopharyngeal carcinoma. Head Neck 23(1):34-41.  3 King AD and Bhatia KS (2010). Magnetic resonance imaging staging of nasopharyngeal carcinoma in the head and neck. World J Radiol 2(5):159-165.  4 Bagri PK, Singhal MK, Singh D, Kapoor A, Jakhar SL, Sharma N, Beniwal S, Kumar HS, Sharma A and Bardia MR (2014). Diagnosis of post-radiotherapy local failures in nasopharyngeal carcinoma: a prospective institutional study. Iran J Cancer Prev 7(1):35-39. |  |
| Core | OPERATIVE PROCEDURE | Multi selection value list (select all that apply):  • Not specified  OR  • Resection, specify   * Transoral laser microsurgical resection * Transoral robotic surgical resection * Other, specify   • Biopsy (excisional, incisional), specify  • Neck (lymph node) dissection\*, specify  • Other, specify | **Oropharynx**  Many oropharyngeal carcinomas are treated non-surgically so that guidance relating to small biopsies is most appropriate for these tumours.1  Open surgical resections have become less common. Transoral approaches such as transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) that are less morbid and have shown promising oncologic outcomes and are utilized, particularly for small, early carcinomas, both HPV positive and negative.2,3 Resection specimens of carcinomas from this area should be carefully oriented by the surgeon so that surgically important resection margins can be appropriately sampled and reported.  **Nasopharynx**  The vast majority of nasopharyngeal carcinomas are treated non-surgically so that guidance relating to small biopsies is most appropriate for these tumours.4 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.  **References**  1 Lui VW and Grandis JR (2012). Primary chemotherapy and radiation as a treatment strategy for HPV-positive oropharyngeal cancer. *Head Neck Pathol* 6 Suppl 1:S91-97.  2 Wilkie MD, Upile NS, Lau AS, Williams SP, Sheard J, Helliwell TR, Robinson M, Rodrigues J, Beemireddy K, Lewis-Jones H, Hanlon R, Husband D, Shenoy A, Roland NJ, Jackson SR, Bekiroglu F, Tandon S, Lancaster J and Jones TM (2016). Transoral laser microsurgery for oropharyngeal squamous cell carcinoma: A paradigm shift in therapeutic approach. *Head Neck* 38(8):1263-1270.  3 Holsinger FC and Ferris RL (2015). Transoral Endoscopic Head and Neck Surgery and Its Role Within the Multidisciplinary Treatment Paradigm of Oropharynx Cancer: Robotics, Lasers, and Clinical Trials. *J Clin Oncol* 33(29):3285-3292.  4 Wei WI and Sham JS (2005). Nasopharyngeal carcinoma. *Lancet* 365(9476):2041-2054. | \*If a neck dissection is submitted, then a separate dataset is used to record the information. |
| Core | SPECIMENS SUBMITTED | •Multi selection value list (select all that apply):  • Not specified  OR  • 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 | **Oropharynx (Figure 1)**  The oropharynx is the portion of the continuity of the pharynx extending from the plane of the superior surface of the soft palate to the plane of the superior surface of the hyoid bone or floor of the vallecula.1 The contents of the oropharynx include:  - soft palate  - palatine tonsils  - anterior and posterior tonsillar pillars  - tonsillar fossa  - uvula  - base of tongue (lingual tonsil)  - vallecula  - posterior oropharyngeal wall  - lateral oropharyngeal wall.  **Nasopharynx (see Figure 1)**  The nasopharynx is the superior portion of the pharynx and is situated behind the nasal cavity and above the soft palate; it begins anteriorly at the posterior choana and extends along the plane of the airway to the level of the free border of the soft palate.1 The contents of the nasopharynx include:  - nasopharyngeal tonsils (adenoids) which lie along the posterior and lateral aspect of the nasopharynx  - orifices of the Eustachian tubes which lie along the lateral aspects of the nasopharyngeal wall  - fossa of Rosenmüller.  **Waldeyer’s ring**  Waldeyer’s ring is formed by a ring or group of extranodal lymphoid tissues at the upper end of the pharynx and consists of the:  - palatine tonsils  - pharyngeal tonsil (adenoids)  - base of tongue/lingual tonsil  - adjacent submucosal lymphatic tissues.  The oropharynx is clearly delineated from the nasopharynx by the soft palate. The inferior portion of the soft palate is oropharyngeal and the superior portion nasopharyngeal. Posteriorly, the nasopharynx extends from the level of the free edge of the soft palate to the skull base.  **References**  1 Patel S and Shah JP (2009). Pharynx. In: *AJCC Cancer Staging Manual 7th Edition*, Edge SB, Byrd DR, Carducci MA, Compton CA (eds), Springer, New York, 41-56. | . |
| Core | TUMOUR SITE | Multi selection value list (select all that apply):  • Cannot be assessed  OR  • Oropharynx   * Left * Right * Midline * Laterality not specified * Palatine tonsil * Base of tongue/lingual tonsil * Soft palate * Uvula * Pharyngeal wall (posterior) * Pharyngeal wall (lateral) * Other, specify   • Nasopharynx   * Left * Right * Midline * Laterality not specified * Nasopharyngeal tonsils (adenoids) * Fossa of Rosenmüller * Lateral wall * Other, specify   • Other, specify including laterality | Tumour 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. |  |
| Core and Non-core | TUMOUR DIMENSIONS | Numeric:  • Maximum tumour dimension (largest tumour) \_\_\_ mm  • Non-core: Additional dimensions (largest tumour)  \_\_\_ mm x \_\_\_ mm  • Cannot be assessed, specify | 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.1 Tumour size is also important in salvage nasopharyngectomy specimens as a correlate to prognosis after surgery.2,3  **References**  1 Haughey BH, Hinni ML, Salassa JR, Hayden RE, Grant DG, Rich JT, Milov S, Lewis JS, Jr. and Krishna M (2011). Transoral laser microsurgery as primary treatment for advanced-stage oropharyngeal cancer: a United States multicenter study. *Head Neck* 33(12):1683-1694.  2 Chan JY and Wei WI (2016). Impact of resection margin status on outcome after salvage nasopharyngectomy for recurrent nasopharyngeal carcinoma. *Head Neck* 38 Suppl 1:E594-599.  3 Chan JY, To VS, Chow VL, Wong ST and Wei WI (2014). Multivariate analysis of prognostic factors for salvage nasopharyngectomy via the maxillary swing approach. *Head Neck* 36(7):1013-1017. |  |
| Core | HISTOLOGICAL TUMOUR TYPE | Multi selection value list (select all that apply):  • **Salivary gland carcinoma**, specify type  • **Neuroendocrine carcinoma**, specify type  • Other, specify type  **Carcinomas of the oropharynx**  • Squamous cell carcinoma, conventional  Single selection value list:   * Keratinizing * Nonkeratinizing * Nonkeratinizing with maturation (“partially keratinizing”)   • Acantholytic squamous cell carcinoma  • Adenosquamous carcinoma  • Basaloid squamous cell carcinoma  • Papillary squamous cell carcinoma  • Spindle cell carcinoma  • Verrucous carcinoma  • Lymphoepithelial carcinoma  **Carcinomas of the nasopharynx**  • Nonkeratinizing squamous cell carcinoma  Single selection value list:   * Differentiated * Undifferentiated (lymphoepithelial)   • Keratinizing squamous cell carcinoma  • Basaloid squamous cell carcinoma  • Nasopharyngeal papillary adenocarcinoma  • Cannot be assessed, specify | The latest World Health Organization (WHO) classification of carcinomas of the oropharynx1 has simplified the nomenclature of oropharyngeal squamous cell carcinoma to HPV-positive (p16 positivity an acceptable surrogate marker) and HPV-negative (p16 negativity an acceptable surrogate marker), removing further histologic typing. This is because for HPV/p16 positive squamous cell carcinomas, histologic subtype (nonkeratinizing, basaloid, papillary, etc) does not appear to further segregate outcomes in any meaningful or reproducible way. However, even if HPV/p16 status is known, the histologic type can still be useful for pathology practice (comparison to possible new primaries, for frozen sections, and for comparison with possible metastases that may subsequently occur). In this dataset we recommend recording histological type and viral status as separate data items.  For nasopharyngeal carcinomas, the WHO classification2 still refers to them by histologic type. However, Epstein-Barr Virus (EBV) status should be assessed and reported as well, if possible.  Salivary gland carcinomas are typed based on the recent WHO classification, and matching the International Collaboration on Cancer Reporting (ICCR) *Carcinomas of the major salivary glands* dataset,3 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.4,5 Refer to the ICCR *Carcinomas of the major salivary glands* dataset3 for more details.  For neuroendocrine carcinomas, there is a paucity of data regarding stage variables and outcome, but histologic typing provides strong and useful information for treatment and prognosis.  **WHO classification of tumours of the nasopharynxa6**   | **Descriptor** | **ICD-O codes** | | --- | --- | | **Nasopharyngeal carcinoma** |  | | Nonkeratinizing squamous cell carcinoma | 8072/3 | | Keratinizing squamous cell carcinoma | 8071/3 | | Basaloid squamous cell carcinoma | 8083/3 | | Nasopharyngeal papillary adenocarcinoma (low grade) | 8260/3 | | **Salivary gland tumours** |  | | Adenoid cystic carcinoma | 8200/3 | | Salivary gland anlage tumour |  |   a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.  © WHO/International Agency for Research on Cancer (IARC). Reproduced with permission  **WHO classification of tumours of the oropharynx (base of tongue, tonsils, adenoids)a7**   | **Descriptor** | **ICD-O codes** | | --- | --- | | **Squamous cell carcinoma** |  | | Squamous cell carcinoma, HPV-positive | 8085/3\* | | Squamous cell carcinoma, HPV-negative | 8086/3\* | | **Salivary gland tumours** |  | | Pleomorphic adenoma | 8940/0 | | Adenoid cystic carcinoma | 8200/3 | | Polymorphous adenocarcinoma | 8525/3 | | **Haematolymphoid tumours** |  | | Hodgkin lymphoma, nodular lymphocyte predominant | 9659/3 | | Classical Hodgkin lymphoma |  | | Nodular sclerosis classical Hodgkin lymphoma | 9663/3 | | Mixed cellularity classical Hodgkin lymphoma | 9652/3 | | Lymphocyte-rich classical Hodgkin lymphoma | 9651/3 | | Lymphocyte-depleted classical Hodgkin lymphoma | 9653/3 | | Burkitt lymphoma | 9687/3 | | Follicular lymphoma | 9690/3 | | Mantle cell lymphoma | 9673/3 | | T-lymphoblastic leukaemia/lymphoma | 9837/3 | | Follicular dendritic cell sarcoma | 9758/3 |   a The morphology codes are from the International Classification of Diseases for Oncology (ICD-O). Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour; /2 for carcinoma in situ and grade III intraepithelial neoplasia; and /3 for malignant tumours.  © WHO/IARC. Reproduced with permission  **References**  1 Westra WH, Boy S, El-Mofty SK, Gillison M, Schwartz MR, Syrjanen S, Yarbrough WG (2017). Squamous cell carcinoma, HPV-positive. pp 136-138. In: *WHO Classification of Head and Neck Tumours. (4th edition)*. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ (eds). IARC, Lyon, France.  2 Chan JKC, Pilch PZ, Kuo TT, Wenig BM, Lee AWM (2005). WHO histological classification of tumours of the nasopharynx. pp 82-84. In: *WHO Classification of Tumours. Pathology and Genetics of Head and Neck Tumours (3rd edition)*. Barnes L, Eveson JW, Reichart P, Sidransky D (eds). IARC, Paris, France.  3 ICCR (International Collaboration on Cancer Reporting) (2018). *Carcinomas of the major salivary glands Histopathology Reporting Guide.* Available at:http://www.iccr-cancer.org/datasets/published-datasets/head-neck (Accessed 13th September 2018).  4 Olarte LS and Megwalu UC (2014). The Impact of Demographic and Socioeconomic Factors on Major Salivary Gland Cancer Survival. *Otolaryngol Head Neck Surg* 150(6):991-998.  5 Baddour HM, Jr., Fedewa SA and Chen AY (2016). Five- and 10-Year Cause-Specific Survival Rates in Carcinoma of the Minor Salivary Gland. *JAMA Otolaryngol Head Neck Surg* 142(1):67-73.  6 Petersson BF, Bell D, El-Mofty SK, Gillison M, Lewis JS, Nadal A, Nicolai P and Wenig BM (2017). Nasopharyngeal carcinoma. pp 65-70. In: *WHO Classification of Head and Neck Tumours (4th Edition)*. El-Naggar AK, Chan JKC, Grandis JR, Takata T and Slootweg PJ (eds). IARC, Lyon, France.  7 Barnes L, Eveson JW, Reichart P, Sidransky D (eds) (2005). *WHO Classification of Tumours. Pathology and Genetics of Head and Neck Tumours (3rd edition).* IARC, Paris, France. | Value list from the WHO Classification of Head and Neck Tumours (2017).  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). |
| Core | HISTOLOGICAL TUMOUR GRADE | Single selection value list:  • Not applicable  • GX: Cannot be assessed  • G1: Well differentiated  • G2: Moderately differentiated  • G3: Poorly differentiated  • Other, specify  • Cannot be assessed, specify | Only applicable for conventional, Epstein-Barr Virus (EBV) negative nasopharyngeal carcinomas and for human papillomavirus (HPV) negative oropharyngeal and nasopharyngeal carcinomas and for carcinomas where the viral status cannot be determined. If the tumour is post-treatment, grading is not applicable since there are no studies establishing its significance.  For virus-related oropharyngeal and nasopharyngeal squamous cell carcinomas, formal grading is not applicable. HPV-positive oropharyngeal carcinomas and EBV-related nasopharyngeal carcinomas are prognostically favourable relative to the virus negative ones, yet appear poorly differentiated morphologically due to their lymphoepithelial or nonkeratinizing morphology.1,2  For the virus negative squamous cell carcinomas (“conventional” tumours) in both the oropharynx and nasopharynx, grading is based on the degree of resemblance to the normal epithelium and follows the descriptions in the WHO classification. This is identical to conventional squamous cell carcinomas at other head and neck anatomic subsites. Specific variants of squamous cell carcinoma such as spindle cell, verrucous, basaloid, papillary, and adenosquamous have intrinsic biological behaviours and currently do not require grading.  **References**  1 Ke K, Wang H, Fu S, Zhang Z, Duan L, Liu D and Ye J (2014). Epstein-Barr virus-encoded RNAs as a survival predictor in nasopharyngeal carcinoma. *Chin Med J (Engl)* 127(2):294-299.  2 Heath S, Willis V, Allan K, Purdie K, Harwood C, Shields P, Simcock R, Williams T and Gilbert DC (2012). Clinically significant human papilloma virus in squamous cell carcinoma of the head and neck in UK practice. *Clin Oncol (R Coll Radiol)* 24(1):e18-23. |  |
| Non-core | DEPTH OF INVASION | Numeric/Single selection value list:  • \_\_\_ mm  • Not applicable  • Cannot be assessed, specify | Depth of invasion is less well established as a staging and prognostic parameter for oropharyngeal tumours than for oral cavity carcinomas. The maximum depth of invasion should be recorded in millimetres from the normal surface epithelium to the deepest point of tumour invasion, but *only* for those tumours clearly arising from the surface epithelium. This does *not* apply for those arising submucosally from the tonsillar crypt epithelium which lack landmarks from which to measure “depth”. For surface tumours, if the tumour is ulcerated, then the reconstructed surface should be used. Note that depth of invasion, defined in this way, is not the same as tumour thickness (measured from surface of tumour to deepest invasion) which will be larger than depth of invasion in exophytic tumours and smaller in ulcerated tumours.1 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.1-9 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.10,11  **References**  1 Huang SH, Hwang D, Lockwood G, Goldstein DP and O'Sullivan B (2009). Predictive value of tumor thickness for cervical lymph-node involvement in squamous cell carcinoma of the oral cavity: a meta-analysis of reported studies. *Cancer* 115(7):1489-1497.  2 Woolgar JA (2006). Histopathological prognosticators in oral and oropharyngeal squamous cell carcinoma. *Oral Oncol* 42(3):229-239.  3 Gonzalez-Moles MA, Esteban F, Rodriguez-Archilla A, Ruiz-Avila I and Gonzalez-Moles S (2002). Importance of tumour thickness measurement in prognosis of tongue cancer. *Oral Oncol* 38(4):394-397.  4 O-charoenrat P, Pillai G, Patel S, Fisher C, Archer D, Eccles S and Rhys-Evans P (2003). Tumour thickness predicts cervical nodal metastases and survival in early oral tongue cancer. *Oral Oncol* 39(4):386-390.  5 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.  6 Quaedvlieg PJ, Creytens DH, Epping GG, Peutz-Kootstra CJ, Nieman FH, Thissen MR and Krekels GA (2006). Histopathological characteristics of metastasizing squamous cell carcinoma of the skin and lips. *Histopathology* 49(3):256-264.  7 Pentenero M, Gandolfo S and Carrozzo M (2005). Importance of tumor thickness and depth of invasion in nodal involvement and prognosis of oral squamous cell carcinoma: a review of the literature. *Head Neck* 27(12):1080-1091.  8 Sparano A, Weinstein G, Chalian A, Yodul M and Weber R (2004). Multivariate predictors of occult neck metastasis in early oral tongue cancer. *Otolaryngol Head Neck Surg* 131(4):472-476.  9 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.  10 Chan JY, To VS, Chow VL, Wong ST and Wei WI (2014). Multivariate analysis of prognostic factors for salvage nasopharyngectomy via the maxillary swing approach. *Head Neck* 36(7):1013-1017.  11 Chan JY and Wei WI (2016). Impact of resection margin status on outcome after salvage nasopharyngectomy for recurrent nasopharyngeal carcinoma. *Head Neck* 38 Suppl 1:E594-599. |  |
| Core | PERINEURAL INVASION | Single selection value list:  • Not identified  • Present  • Cannot be assessed, specify | Traditionally, the presence of perineural invasion (neurotropism) is an important predictor of poor  prognosis in head and neck cancer of virtually all sites.1 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.2 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.3-5 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.6-8 There are no data on perineural invasion for nasopharyngeal carcinomas so it is considered “not applicable” for these tumours.  **References**  1 Smith BD (2009). Prognostic factors in patients with head and neck cancer. In: *Head and Neck Cancer: A Multidisciplinary Approach*. Harrison LB, Sessions RB, Hong WK (eds). Lippincott Williams and Wilkins, Philadelphia, USA.  2 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.  3 Sinha P, Kallogjeri D, Gay H, Thorstad WL, Lewis JS, Jr., Chernock R, Nussenbaum B and Haughey BH (2015). High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer. *Oral Oncol* 51(5):514-520.  4 Haughey BH and Sinha P (2012). Prognostic factors and survival unique to surgically treated p16+ oropharyngeal cancer. *Laryngoscope* 122 Suppl 2:S13-33.  5 de Almeida JR, Li R, Magnuson JS, Smith RV, Moore E, Lawson G, Remacle M, Ganly I, Kraus DH, Teng MS, Miles BA, White H, Duvvuri U, Ferris RL, Mehta V, Kiyosaki K, Damrose EJ, Wang SJ, Kupferman ME, Koh YW, Genden EM and Holsinger FC (2015). Oncologic Outcomes After Transoral Robotic Surgery: A Multi-institutional Study. *JAMA Otolaryngol Head Neck Surg* 141(12):1043-1051.  6 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.  7 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.  8 Amin MB, Edge S, 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, Meyer LR (eds) (2017). *AJCC Cancer Staging Manual 8th ed.* Springer, New York. | Not applicable for nasopharynx. |
| Core | LYMPHOVASCULAR INVASION | Single selection value list:  • Not identified  • Present  • Cannot be assessed, specify | 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.1-5 The presence of lymphovascular invasion may impact decisions on therapy. If it is the only risk factor present, then by American Society for Radiation Oncology (ASTRO) guidelines it may be used to advise post-operative radiation after careful discussion of patient preference.6  **References**  1 Sinha P, Kallogjeri D, Gay H, Thorstad WL, Lewis JS, Jr., Chernock R, Nussenbaum B and Haughey BH (2015). High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer. *Oral Oncol* 51(5):514-520.  2 Haughey BH and Sinha P (2012). Prognostic factors and survival unique to surgically treated p16+ oropharyngeal cancer. *Laryngoscope* 122 Suppl 2:S13-33.  3 de Almeida JR, Li R, Magnuson JS, Smith RV, Moore E, Lawson G, Remacle M, Ganly I, Kraus DH, Teng MS, Miles BA, White H, Duvvuri U, Ferris RL, Mehta V, Kiyosaki K, Damrose EJ, Wang SJ, Kupferman ME, Koh YW, Genden EM and Holsinger FC (2015). Oncologic Outcomes After Transoral Robotic Surgery: A Multi-institutional Study. *JAMA Otolaryngol Head Neck Surg* 141(12):1043-1051.  4 Rahima B, Shingaki S, Nagata M and Saito C (2004). Prognostic significance of perineural invasion in oral and oropharyngeal carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 97(4):423-431.  5 Iyer NG, Dogan S, Palmer F, Rahmati R, Nixon IJ, Lee N, Patel SG, Shah JP and Ganly I (2015). Detailed Analysis of Clinicopathologic Factors Demonstrate Distinct Difference in Outcome and Prognostic Factors Between Surgically Treated HPV-Positive and Negative Oropharyngeal Cancer. *Ann Surg Oncol* 22(13):4411-4421.  6 Amin MB, Edge S, 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, Meyer LR (eds) (2017). *AJCC Cancer Staging Manual 8th ed.* Springer, New York. | Not applicable for nasopharynx. |
| Core | MARGIN STATUS | Single selection value list/text/numeric:  Invasive carcinoma\*\*  • 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\*\*\***  • 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 | 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.1-5 The definition of a positive margin is controversial.6,7 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).6 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,6,8,9 but the definition of a “close” margin is not standardized as the effective cut-off varies between studies and between anatomic subsites. Thus distance of tumour from the nearest margin should be recorded when it can be measured. Distance may not be feasible to report if separate margin specimens are submitted in addition to the main specimen. In this instance, state that margins are negative, but do not provide a distance. Distance from margins essentially cannot be ascertained in transoral laser microsurgery (TLM), but may not be of the same significance as for en-bloc resections or transoral robotic surgery (TORS) specimens.  Because of the uncertainty and difficulty (if not impossibility) of telling in situ from invasive (“metastasis-capable”) squamous cell carcinoma in crypt-derived tumours of the oropharynx and nasopharynx, the reporting is simplified here just as “distance of closest carcinoma” to the margin, without reference to invasive or in situ.  Reporting of surgical margins for non-squamous carcinomas should follow those used for such tumours at all head and neck subsites.  **References**  1 Sinha P, Kallogjeri D, Gay H, Thorstad WL, Lewis JS, Jr., Chernock R, Nussenbaum B and Haughey BH (2015). High metastatic node number, not extracapsular spread or N-classification is a node-related prognosticator in transorally-resected, neck-dissected p16-positive oropharynx cancer. *Oral Oncol* 51(5):514-520.  2 Haughey BH and Sinha P (2012). 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Surgical margins in head and neck squamous cell carcinoma: what is 'close'? *Eur Arch Otorhinolaryngol* 270(10):2603-2609.  9 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. | \*\* There is no clear morphologic distinction between invasive and in situ carcinoma for HPV-positive oropharyngeal and EBV-positive nasopharyngeal carcinomas, so all carcinoma at margin should be included in evaluation simply as “involved by carcinoma”.  \*\*\* Only applicable for HPV-negative oropharyngeal and EBV-negative nasopharyngeal tumours and for tonsillar surface disease. High-grade dysplasia is synonymous with moderate/severe dysplasia. |
| Non-core | COEXISTENT PATHOLOGY | Multi selection value list (select all that apply):  • None identified  OR  • Dysplasia^  Single selection value list:   * Mild * Moderate * Severe * Focal * Multifocal * Discontinuous with the primary site   • Carcinoma in situ  Single selection value list:   * Focal * Multifocal * Discontinuous with the primary site   • Other, specify | 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. | ^ Applicable for oropharyngeal surface mucosal disease only; not for tonsillar crypt epithelium. |
| Core and  Non-core | ANCILLARY STUDIES | Single selection value list:  **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   Non-core   * High risk HPV specific testing   Single selection value list:  • DNA PCR   * Not identified * Present   • DNA in situ hybridization   * Not identified * Present   • E6/E7 mRNA in situ hybridization   * Not identified * Present   • E6/E7 mRNA RTPCR   * Not identified * Present   **Viral testing/Viral tumour markers**  NASOPHARYNX  • Not performed/unknown  • Performed   * EBV (EBER) in situ hybridization – Positive * EBV (EBER) in situ hybridization – Negative   Non-Core  **Other ancillary studies**  • Not performed  • Performed, specify | In resource-limited practices (or when only extremely limited biopsy samples are available that preclude further testing etc.) where p16/HPV (oropharynx) or Epstein-Barr Virus (EBV) (nasopharynx) testing cannot be performed, staging and treatment of patients will be inherently different.1 The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) recommend that oropharyngeal squamous cell carcinomas that cannot be tested for p16/HPV be regarded and treated as HPV-negative. This recommendation should be followed for the completion of the ICCR dataset.  Given that most HPV-related oropharyngeal squamous cell carcinomas are nonkeratinizing morphologically, arise deep in the tonsillar parenchyma, have cystic nodal metastases, and may have particular clinical features such as arising in non-smokers who are younger than typical head and neck squamous cell carcinomas, certain patients can be strongly suspected as having HPV-related tumours. In particular, nonkeratinizing histologic morphology, present in 50-60% of oropharyngeal squamous cell carcinoma, correlates very well with positive HPV status.2 However, prediction of HPV status by such surrogate marker and clinical grounds is less reliable than direct p16/HPV testing.3 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.4,5 A smaller subset of nasopharyngeal carcinomas is related to transcriptionally active high risk HPV.  HPV-positive oropharyngeal carcinoma represents a unique squamous cell carcinoma type with proven more favourable prognosis than for HPV-negative tumours.6 Staging of these patients is now different than for HPV-negative tumours and treatment differences are emerging.  There are many methods for testing HPV status with p16 immunohistochemistry emerging as a simple, thoroughly validated prognostic marker in oropharyngeal squamous cell carcinoma (SCC).7 The most commonly used criterion for positivity as a surrogate marker moderate to intense nuclear and cytoplasmic staining in 70% or more of the tumour cells, which is the recommended cutoff for these guidelines,8 with the caveat that the correlation with HPV status is not 100%.9,10 The combination of p16 immunohistochemistry with nonkeratinizing morphology is very strongly associated with transcriptionally-active high risk HPV in the oropharynx.2 HPV specific tests include in situ hybridization for DNA, PCR for HPV-DNA, RT-PCR for HPV-mRNA, and in situ hybridization for mRNA. There is no consensus on the best methodology for HPV testing but the World Health Organization (WHO), AJCC, UICC, and a College of American Pathologists Expert Panel have all recommended p16 immunohistochemistry. Additional HPV-specific testing is performed at the discretion of the pathologist.  The new WHO Blue Book terms squamous cell carcinomas of the oropharynx simply as HPV-positive or HPV-negative.11,12 However, they specifically note that p16 immunohistochemistry alone (with appropriate criteria for a positive versus negative test) is a suitable surrogate marker. They recommend the terminology HPV-positive even if only p16 is performed.  EBV is associated with the nonkeratinizing types of nasopharyngeal carcinomas in the vast majority of patients. The most reliable detection method for EBV is in situ hybridization for EBV encoded early RNA (EBER) present in cells latently infected by EBV, and is recommended because it is a modestly strong favourable prognostic marker and because it is confirmation of the tumour having a nasopharyngeal association.13 A subset of patients with nasopharyngeal carcinoma are related to transcriptionally-active high risk HPV.14-16 Most of these tumours are described as nonkeratinizing differentiated using the WHO terminology. They are EBV (EBER) negative and p16 positive. Testing for HPV/p16 in EBV negative nonkeratinizing carcinomas, however, is at the discretion of the local practice. It may be indicated in routine clinical practice to help alert the clinician that this may be an oropharyngeal primary tumour that is secondarily involving the nasopharynx and not because the HPV is of proven prognostic benefit in such tumours.14-16  **References**  1 Chan MW, Yu E, Bartlett E, O'Sullivan B. et al (2017). Morphologic and topographic radiologic features of human 2 papillomavirus-related and unrelated oropharyngeal carcinoma. *Head Neck* 39(8):1524-1534.  2 Gondim DD, Haynes W, Wang X, Chernock RD, El-Mofty SK and Lewis JS, Jr. (2016). Histologic Typing in Oropharyngeal Squamous Cell Carcinoma: A 4-Year Prospective Practice Study With p16 and High-Risk HPV mRNA Testing Correlation. *Am J Surg Pathol* 40(8):1117-1124.  3 D'Souza G, Zhang HH, D'Souza WD, Meyer RR and Gillison ML (2010). 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| Core | PATHOLOGICAL STAGING (UICC TNM 8th edition)  TNM descriptors | Choose if applicable:  • m - multiple primary tumours  • r - recurrent  • y - post-therapy | This protocol recommends the T-classification schemes published by the Union for International Cancer Control (UICC) and the 8th edition of the American Joint Committee on Cancer (AJCC) for the pharynx.1,2 It is quite noteworthy that the oropharyngeal carcinomas staging has been modified significantly from past systems, as the identification of HPV-positive oropharyngeal squamous cell carcinoma (SCC) as a specific subgroup means that the older versions ineffectively stratify outcomes.3  By convention, the designation “T” refers to a primary tumour that has not been previously treated. The symbol “p” refers to the pathologic classification of the stage, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumour adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. There is no pathologic M0 category as this designation requires clinical evaluation and imaging. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.  Pathological staging is usually performed after surgical resection of the primary tumour and depends on documentation of the anatomic extent of disease, whether or not the primary tumour has been completely removed. If a biopsied tumour is not resected for any reason (e.g. when technically unfeasible) and if the highest T and N categories or the M1 category of the tumour can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer, and thus this information provided.  For identification of special cases of TNM or pTNM classifications, “y” and “r” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.  The “y” prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e. neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumour actually present at the time of that examination. The “y” categorization is not an estimate of tumour prior to multimodality therapy (i.e. before initiation of neoadjuvant therapy).  The “r” prefix indicates a recurrent tumour when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.  **References**  1 Patel S and Shah JP (2009). Pharynx. pp 41-56. In: *AJCC Cancer Staging Manual 7th Edition*, Edge SB, Byrd DR, Carducci MA, Compton CA (eds). Springer, New York.  2 Sobin L, Gospodarowicz M, Wittekind C and International Union against Cancer (eds) (2009). *TNM Classification of Malignant Tumours (7th edition)*. Wiley-Blackwell, Chichester, UK and Hoboken, New Jersey.  3 Dahlstrom KR, Calzada G, Hanby JD, Garden AS, Glisson BS, Li G, Roberts DB, Weber RS and Sturgis EM (2013). An evolution in demographics, treatment, and outcomes of oropharyngeal cancer at a major cancer center: a staging system in need of repair. *Cancer* 119(1):81-89. | Note that permission to publish the TNM cancer staging tables may be needed in your implementation. It is advisable to check.  Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2017, Publisher Wiley-Blackwell. |
| Core | Primary tumour (pT) | Single selection value list:  **p16 Positive oropharynx**  • T0 No evidence of primary tumour, but p16 positive cervical node(s) involved  • T1 Tumour 2 cm or less in greatest dimension  • T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension  • T3 Tumour more than 4 cm in greatest dimension or extension to lingual surface of epiglottis  • T4 Tumour invades any of the following: larynx^^, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, mandible^^, lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery  **p16 Negative oropharynx**  • Tis Carcinoma in situ  • T1 Tumour 2 cm or less in greatest dimension  • T2 Tumour more than 2 cm but not more than 4 cm in greatest dimension  • T3 Tumour more than 4 cm in greatest dimension or extension to lingual surface of epiglottis  • T4a Moderately advanced local disease  Tumour invades any of the following: larynx^^, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, or mandible  • T4b Very advanced local disease  Tumour invades any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery  **Nasopharynx**  • T0 No evidence of primary tumour, but EBV-positive cervical node(s) involved  • T1 Tumour confined to the nasopharynx, or extends to oropharynx and/or nasal cavity without parapharyngeal involvement  • T2 Tumour with extension to parapharyngeal space and/or infiltration of the medial pterygoid, lateral pterygoid, and/or prevertebral muscles  • T3 Tumour invades bony structures of skull base cervical vertebra, pterygoid structures, and/or paranasal sinuses  • T4 Tumour with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or infiltration beyond the lateral surface of the lateral pterygoid muscle |  | If a lymph node/neck dissection is submitted, then a separate dataset is to be completed for the corresponding neck nodal disease specimen(s).  ^^ Mucosal extension to lingual surface of epiglottis from primary tumours of the base of the tongue and vallecula does not constitute invasion of the larynx. |

**Figures**

Figure 1. Normal anatomy of the pharynx

