# Standaardrapport orofarynx

Conclusie

**Neoadjuvante therapie:** Kies een optie.

**Tumorlokalisatie:** Kies een optie.

 *Indien andere, specificeer:*

**Lateraliteit**: Kies een optie.

**Focaliteit:** Kies een optie.

 *Indien multifocaal, specificeer aantal foci:*

 *Indien niet beoordeeld kan worden, specificeer:*

**Tumorafmetingen**: Kies een optie.

 Maximale tumordimensie (in mm):

 *Indien niet bepaald kan worden, specificeer:*

**Histologisch tumortype[[1]](#footnote-1):** Kies een optie.

 *Indien van toepassing, specificeer type:*

**HPV-typering**: Kies een optie.

 *Indien uitgevoerd, specificeer methode:* Kies een optie.

**Differentiatiegraad:** Kies een optie.

*Indien niet beoordeeld kan worden, specificeer:*

**Lokale uitbreiding**: Kies een optie.

*Indien lokale uitbreiding werd aangetoond, specificeer locatie:*

*Indien lokale uitbreiding niet beoordeeld kan worden, specificeer:*

**Lymfovasculaire invasie**: Kies een optie.

 *Indien onderscheid tussen lymfevat- en bloedvatinvasie mogelijk, specificeer:* Kies een optie.

*Indien niet met zekerheid te bepalen, specificeer:*

**Perineurale invasie[[2]](#footnote-2)**: Kies een optie.

*Indien niet met zekerheid te bepalen, specificeer:*

**Definitieve minimale tumorvrije marge invasief carcinoom**

**(incl. eventuele naresecties en vriescoupes)[[3]](#footnote-3):** Kies een optie.

Definitieve minimale tumorvrije marge (in mm):

Specificeer dichtstbijzijnde snedevlak, indien mogelijk:

*Indien niet beoordeeld kan worden, specificeer:*

**Definitieve minimale vrije marge ernstige dysplasie/in situ carcinoom**

**(incl. eventuele naresecties en vriescoupes)[[4]](#footnote-4):** Kies een optie.

Definitieve minimale vrije marge (in mm):

Specificeer dichtstbijzijnde snedevlak, indien mogelijk:

*Indien niet beoordeeld kan worden, specificeer:*

**pTNM classificatie (UICC TNM 8e editie met errata)[[5]](#footnote-5):** **pT**

Kies de classificatie die van toepassing is:

*Orofarynx, p16-positief:* Kies een optie.

*Orofarynx, p16-negatief:* Kies een optie.

Voorvoegsels:

m (multipele primaire tumoren): Kies een optie.

r (recidief): Kies een optie.

y (na neoadjuvante therapie): Kies een optie.

Scope

Primaire resectie- en biopsiestalen van primaire carcinomen (inclusief van kleine speekselklieren) van de orofarynx, met inbegrip van de tongbasis, amandelen, fossa tonsillaris, amandelpijlers, zacht gehemelte, achterste en laterale wanden en uvula.

Opmerkingen

* Als een biopsie het enige staal is dat werd ontvangen moeten variabelen die specifiek zijn voor de biopsie worden gerapporteerd, aangezien variabelen die van toepassing zijn op chirurgisch verwijderde tumoren niet op betrouwbare wijze kunnen worden ingevuld.
* Voor resecties van recidieven kan de dataset pragmatisch worden gebruikt, hoewel sommige variabelen mogelijk niet toepasbaar of te beoordelen zijn.
* Mucosaal melanoom, lymfomen en sarcomen worden in aparte datasets behandeld.
* Neuro-endocriene neoplasmen worden in een aparte dataset behandeld.
* Halsdissecties en klierexcisies worden behandeld in een aparte dataset. Deze dataset moet, indien van toepassing, in combinatie worden gebruikt.
* Voor orofaryngeale carcinomen moet elke afzonderlijke focus worden beschouwd als een afzonderlijke primaire tumor en moet deze zijn eigen afzonderlijke dataset krijgen.

Dataset gebaseerd op

Chernock RD, Badoual C, Faquin WC, Hernandez-Prera J, Iyer NG, Katabi N, O’Sullivan B, Robinson M, Willems S, Helliwell T, Thompson LDR, (2024). *Carcinomas of the Oropharynx and Nasopharynx Histopathology Reporting Guide. 2nd edition*. International Collaboration on Cancer Reporting; Sydney, Australia. ISBN: 978-1-922324-47-4.

Bijkomende informatie[[6]](#footnote-6)

**Note 1 – Tumour site**

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

**Note 2 – Tumour dimensions**

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

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

**Note 3 – Histological tumour type**

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

The latest WHO Classification of carcinomas of the oropharynx7 has simplified the nomenclature of oropharyngeal SCC to HPV-associated (p16 positivity is an acceptable surrogate marker) and HPV- independent (p16 negativity is an acceptable surrogate marker), removing further histologic typing. Specifically, HPV-associated is the term applied even if only p16 is performed. This is because for HPV- associated SCCs, histologic subtype (non-keratinising, basaloid, papillary, etc.) does not appear to further segregate outcomes in any meaningful or reproducible way. However, even if the HPV status is known, the histologic type can still be useful for pathology practice (comparison to possible new primaries, for frozen sections, and for comparison with possible metastases that may subsequently occur). In this ICCR dataset we recommend recording histological type and viral status as separate data items.

For nasopharyngeal carcinomas, the WHO Classification7 still refers to them by histologic type. However, Epstein-Barr virus (EBV) status (generally by EBER in situ hybridisation) should be assessed and reported as well, if possible.

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

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

## Table 1: World Health Organization classification of tumours of the oropharynx.7

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

a These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).33 Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour;

/2 for carcinoma in situ and grade 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.

© World Health Organization/International Agency for Research on Cancer. Reproduced with permission.

## Table 2: World Health Organization classification of tumours of the nasopharynx.7

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

a These morphology codes are from the International Classification of Diseases for Oncology, third edition, second revision (ICD-0-3.2).33 Behaviour is coded /0 for benign tumours; /1 for unspecified, borderline, or uncertain behaviour;

/2 for carcinoma in situ and grade 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.

© World Health Organization/International Agency for Research on Cancer. Reproduced with permission.

**Note 4 – Histological tumour grade**

Histological tumour grade is only applicable for conventional, EBV-negative nasopharyngeal carcinomas and for HPV-independent oropharyngeal and nasopharyngeal carcinomas and for carcinomas where the viral status cannot be determined. If the tumour is post-treatment, grading is not applicable since there are no studies establishing its significance. The ‘other’ category should be selected for salivary carcinomas and neuroendocrine neoplasms. Salivary carcinomas should be graded according to grading systems for individual tumour types, when applicable (refer to the ICCR Carcinomas of the major salivary glands dataset for details25). Neuroendocrine neoplasms should be graded as per the ICCR Carcinomas of the hypopharynx, larynx and trachea dataset.34

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

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

Neuroendocrine neoplasms, as newly defined,7 include paraganglioma/pheochromocytoma, NETs, and NECs. NETs are separated into grades (1, 2, and 3) based on mitotic rate: grade 1: <2 mitoses/2 millimetres (mm)2; grade 2: ≥2-10 mitoses/2 mm2; grade 3: ≥11 mitoses/2 mm2. Ki-67 proliferation indices should be reported, but criteria for grading based on Ki-67 are not yet fully developed for each of the anatomic sites in the head and neck. Grade 1 tumours generally have a Ki-67 proliferation index of < 2%, grade 2 of 2-20% and grade 3

>20%.31,40 NECs are separated into small cell and large cell categories, showing tumour necrosis, >10 mitoses/2 mm2 and >20% Ki-67 proliferation index,31,41-43 with universal Rb1 loss and common p53 overexpression.44 At present, the site, tumour category, and grade should be reported, with additional advances in this field incorporated when validated further.

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

**Note 5 – Ancillary studies**

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

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

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

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

There are many methods for testing HPV status. p16 immunohistochemistry is a simple validated HPV surrogate and prognostic marker in oropharyngeal SCC.77 The most commonly used criterion for positivity as a surrogate marker is: moderate to intense, block-like, nuclear and cytoplasmic staining in ≥70% of the tumour cells,78 with the caveat that the correlation with HPV status is not 100%.79,80 The combination of p16 immunohistochemistry with non-keratinising morphology is very strongly associated with transcriptionally-active high-risk HPV in the oropharynx. Even so, a small minority of patients will be misclassified.72,81,82 Emerging evidence indicates that p16/HPV discordant tumours are associated with reduced survival compared to double positive tumours.81-84 Furthermore, the p16/HPV discordant population may be significantly larger in low HPV prevalence geographic regions.85 HPV specific tests include in situ hybridisation for DNA, PCR for HPV-DNA, RT-PCR for HPV-mRNA, and in situ hybridisation for mRNA. There is no consensus on the best methodology for HPV testing but the WHO, UICC, AJCC, and the College of American Pathologists have all recommended p16 immunohistochemistry.7,18,19,35 Thus, p16 is considered ‘core’ in oropharyngeal SCCs. Additional HPV-specific testing is recommended at the discretion of the pathologist and may be important for accurate determination of viral status in certain scenarios (i.e., non- core). HPV specific testing should be considered when p16 is equivocal or there is discordance between the p16 result and tumour morphology, in low HPV prevalence geographic regions, and as required for clinical trials.7

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

Programmed cell death-ligand 1 (PD-L1) expression has been used as predictive biomarker for checkpoint inhibitor therapy since the anti-programmed cell death-1 receptor (PD-1) antibodies, nivolumab and pembrolizumab, have been approved for the treatment of patients with recurrent and/or unresectable metastatic head and neck SSC,91-94 with various cutoffs of expression associated with betters responses, although not in all patients.95 There are two scoring systems for PD-L1 expression, tumour proportion score (TPS) and combined positive score (CPS). CPS is the preferred scoring system in head and neck cancers.

For neuroendocrine neoplasms core elements are neuroendocrine markers, epithelial markers, and Ki-67 proliferation index. The diagnosis of neuroendocrine neoplasms (specifically NETs and NECs) must be confirmed immunohistochemically, with positive reaction for neuroendocrine markers (synaptophysin, chromogranin, INSM1) and for epithelial markers (pancytokeratin, cytokeratin). Furthermore, a proliferation index as determined by Ki-67 immunohistochemical analysis is recommended for grading all NETs, helping to confirm NECs, and p53 and Rb1 may be helpful in the distinction between NET and NEC, especially G3 NET from NEC.40,44,96

**Note 6 – Extent of invasion**

Extent of tumour invasion is a key parameter used to assign appropriate T category for both oropharyngeal and nasopharyngeal carcinomas.18,19 T category provides important prognostic information and, therefore, must be documented for resection specimens.45-50 Because nasopharyngectomies are uncommon and performed as a salvage treatment option, there is limited prognostic data but pathologic T category appears to correlate with outcomes even in this setting.24,51 It should be noted that the Tis (carcinoma in situ) category does not apply to either HPV-associated oropharyngeal or EBV-associated nasopharyngeal SCCs.

Tumour depth of invasion (DOI) is also not a component of the T category for either nasopharyngeal or oropharyngeal carcinomas regardless of virus status. DOI should not be reported, especially for HPV and

EBV-associated SCCs, which often arise from crypt mucosa deep to the surface and the point of origin cannot be determined nor can an accurate depth measured.

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

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

**Note 7 – Lymphovascular invasion**

The presence or absence of lymphovascular invasion should be documented if carcinoma is clearly identified within endothelial-lined spaces. This must be carefully distinguished from retraction artefacts. It is not necessary to distinguish between small lymphatics and venous channels. While the presence of nodal metastases indicates that lymphatic invasion must be present, this element should only be reported as positive when lymphovascular invasion is identified microscopically in the primary tumour specimen.

Otherwise, it should be listed as ‘not identified’. Several retrospective studies on surgically-treated oropharyngeal SCC show a statistically significant decrease in prognosis for patients with lymphovascular

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

Cases that are still equivocal after taking additional steps may be reported as ‘indeterminate’ for lymphovascular invasion, but this designation should be sparingly used and it is useful to provide the reason in a comment in the report.

**Note 8 – Perineural invasion**

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

**Note 9 – Margin status**

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

Because of the uncertainty and difficulty (if not impossibility) of telling in situ from invasive (‘metastasis- capable’) SCC in crypt-derived (usually viral-associated) tumours of the oropharynx and nasopharynx, the reporting is simplified here just as ‘distance of closest carcinoma’ to the margin, without reference to invasive or in situ.

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

**Note 10 – Pathological staging**

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

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

By UICC/AJCC convention,18,19 the designation ‘T’ refers to a primary tumour that has not been previously treated. The symbol ‘p’ refers to the pathologic classification of the stage, as opposed to the clinical classification, and is based on gross and microscopic examination. pT entails a resection of the primary tumour adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate lymph node metastasis, and pM implies microscopic examination of distant lesions. There is no pathologic M0 category as this designation requires clinical evaluation and imaging. Clinical classification (cTNM) is usually carried out by the referring physician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathological staging is usually performed after surgical resection of the primary tumour and depends on documentation of the anatomic extent of disease, whether or not the primary tumour has been completely removed. If a biopsied tumour is not resected for any reason (e.g., when technically unfeasible) and if the highest T and N categories or the M1 category of the tumour can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer, and thus this information provided.

**Primary tumour (pT)**

p16 POSITIVE OROPHARYNX (HPV-ASSOCIATED)

Tx Primary tumour cannot be assessed

T0 No evidence of primary tumour, but p16 positive cervical node(s) involved

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

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 (HPV-INDEPENDENT)

Tx Primary tumour cannot be assessed

T0 No evidence of primary tumour

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

Tx Primary tumour cannot be assessed

T0 No evidence of primary tumour, but EBV-positive (EBV-associated) cervical node(s) involved

Tis Carcinoma in situ

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

**TNM Descriptors**

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

The ‘m’ suffix indicates the presence of multiple primary tumours in a single site and is recorded in parentheses: pT(m)NM.

The ‘y’ prefix indicates those cases in which classification is performed during or following initial multimodality therapy (i.e., neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy). The cTNM or pTNM category is identified by a ‘y’ prefix. The ycTNM or ypTNM categorises the extent of tumour actually present at the time of that examination. The ‘y’ categorisation is not an estimate of tumour prior to multimodality therapy (i.e., before initiation of neoadjuvant therapy).

The ‘r’ prefix indicates a recurrent tumour when staged after a documented disease-free interval, and is identified by the ‘r’ prefix: rTNM.

For the pN classification of regional lymph nodes, see ICCR Nodal excisions and neck dissection specimens dataset.102

Reporting of pathological staging categories (pT,pN,pM) is based on the evidence available to the pathologist at the time of reporting. As indicated in UICC TNM8 and AJCC TNM8,18,19 the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.

Pathological staging should not be reported if the submitted specimen is insufficient for definitive staging, especially with biopsy samples (core needle, incisional or excisional). Staging is based on the submitted resection, and even if there is grossly residual disease or there is tumour at the margin, pT staging should only be reported on findings in the resection specimen and/or at operation.18,19

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

Referenties

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.
2. International Collaboration on Cancer Reporting (2024). *Head & Neck datasets*. Available from: https://[www.iccr-cancer.org/datasets/published-datasets/head-neck/](http://www.iccr-cancer.org/datasets/published-datasets/head-neck/) (Accessed 31st July 2024).
3. 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.
4. 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.
5. 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.
6. 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.
7. WHO Classification of Tumours Editorial Board (2024). *Head and Neck Tumours, WHO Classification of Tumours, 5th Edition, Volume 10.* IARC Press, Lyon.
8. De Felice F, Humbert-Vidan L, Lei M, King A and Guerrero Urbano T (2020). Analyzing oropharyngeal cancer survival outcomes: a decision tree approach. *Br J Radiol* 93(1111):20190464.
9. Lee VH, Kwong DL, Leung TW, Choi CW, O'Sullivan B, Lam KO, Lai V, Khong PL, Chan SK, Ng CY, Tong CC, Ho PP, Chan WL, Wong LS, Leung DK, Chan SY, So TH, Luk MY and Lee AW (2019). The addition of pretreatment plasma Epstein-Barr virus DNA into the eighth edition of nasopharyngeal cancer TNM stage classification. *Int J Cancer* 144(7):1713-1722.
10. Chen YP, Ismaila N, Chua MLK, Colevas AD, Haddad R, Huang SH, Wee JTS, Whitley AC, Yi JL, Yom SS, Chan ATC, Hu CS, Lang JY, Le QT, Lee AWM, Lee N, Lin JC, Ma B, Morgan TJ, Shah J, Sun Y and Ma J (2021). Chemotherapy in Combination With Radiotherapy for Definitive-Intent Treatment of Stage II- IVA Nasopharyngeal Carcinoma: CSCO and ASCO Guideline. *J Clin Oncol* 39(7):840-859.
11. Ng WT, Soong YL, Ahn YC, AlHussain H, Choi HCW, Corry J, Grégoire V, Harrington KJ, Hu CS, Jensen K, Kwong DL, Langendijk JA, Le QT, Lee NY, Lin JC, Lu TX, Mendenhall WM, O'Sullivan B, Ozyar E, Pan JJ, Peters LJ, Poh SS, Rosenthal DI, Sanguineti G, Tao Y, Wee JT, Yom SS, Chua MLK and Lee AWM (2021). International Recommendations on Reirradiation by Intensity Modulated Radiation Therapy for Locally Recurrent Nasopharyngeal Carcinoma. *Int J Radiat Oncol Biol Phys* 110(3):682-695.
12. 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.
13. Golusiński W and Golusińska-Kardach E (2019). Current Role of Surgery in the Management of Oropharyngeal Cancer. *Front Oncol* 9:388.
14. 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):1263-70
15. 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.
16. Wei WI and Sham JS (2005). Nasopharyngeal carcinoma. *Lancet* 365(9476):2041-2054.
17. Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y and Ma J (2019). Nasopharyngeal carcinoma. *Lancet* 394(10192):64-80.
18. Brierley JD, Gospodarowicz MK and Wittekind C (eds) (2016). *Union for International Cancer Control. TNM Classification of Malignant Tumours, 8th Edition*, Wiley, USA.
19. 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.
20. 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.
21. 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.
22. 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.
23. Wong EHC, Liew YT, Loong SP and Prepageran N (2020). Five-year Survival Data on the Role of Endoscopic Endonasal Nasopharyngectomy in Advanced Recurrent rT3 and rT4 Nasopharyngeal Carcinoma. *Ann Otol Rhinol Laryngol* 129(3):287-293.
24. Thamboo A, Patel VS and Hwang PH (2021). 5-year outcomes of salvage endoscopic nasopharyngectomy for recurrent nasopharyngeal carcinoma. *J Otolaryngol Head Neck Surg* 50(1):12.
25. International Collaboration on Cancer Reporting (2024). *Carcinomas of the major salivary glands Histopathology Reporting Guide. 2nd edition*. Available from: [https://www.iccr-](https://www.iccr-cancer.org/datasets/published-datasets/head-neck/salivary-glands/) [cancer.org/datasets/published-datasets/head-neck/salivary-glands/](https://www.iccr-cancer.org/datasets/published-datasets/head-neck/salivary-glands/) (Accessed 31st July 2024).
26. Skálová A, Hyrcza MD and Leivo I (2022). Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Salivary Glands. *Head Neck Pathol* 16(1):40-53.
27. 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.
28. 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.
29. Hay AJ, Migliacci J, Karassawa Zanoni D, McGill M, Patel S and Ganly I (2019). Minor salivary gland tumors of the head and neck-Memorial Sloan Kettering experience: Incidence and outcomes by site and histological type. *Cancer* 125(19):3354-3366.
30. Mete O and Wenig BM (2022). Update from the 5th Edition of the World Health Organization Classification of Head and Neck Tumors: Overview of the 2022 WHO Classification of Head and Neck Neuroendocrine Neoplasms. *Head Neck Pathol* 16(1):123-142.
31. 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.
32. de Sousa LG, Lazar Neto F, Dal Lago EA, Sikora A, Hanna E, Moreno A, Phan J, Glisson BS, Bell D and Ferrarotto R (2023). Human papillomavirus status and prognosis of oropharyngeal high-grade neuroendocrine carcinoma. *Oral Oncol* 138:106311.
33. 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&Ite> mid=577 (Accessed 16th March 2024).
34. International Collaboration on Cancer Reporting (2024). *Carcinomas of the hypopharynx, larynx and trachea Histopathology Reporting Guide. 2nd edition*. Available from: [https://www.iccr-](https://www.iccr-cancer.org/datasets/published-datasets/head-neck/larynx/) [cancer.org/datasets/published-datasets/head-neck/larynx/](https://www.iccr-cancer.org/datasets/published-datasets/head-neck/larynx/) (Accessed 31st July 2024).
35. Lewis JS, Jr., Beadle B, Bishop JA, Chernock RD, Colasacco C, Lacchetti C, Moncur JT, Rocco JW, Schwartz MR, Seethala RR, Thomas NE, Westra WH and Faquin WC (2018). Human Papillomavirus Testing in Head and Neck Carcinomas: Guideline From the College of American Pathologists. *Arch Pathol Lab Med* 142(5):559-597.
36. 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.
37. 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.
38. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman CC, Redmond KP and Gillison ML (2010). Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 363(1):24-35.
39. Yip KW, Shi W, Pintilie M, Martin JD, Mocanu JD, Wong D, MacMillan C, Gullane P, O'Sullivan B, Bastianutto C and Liu FF (2006). Prognostic significance of the Epstein-Barr virus, p53, Bcl-2, and survivin in nasopharyngeal cancer. *Clin Cancer Res* 12(19):5726-5732.
40. 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.
41. 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.
42. 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.
43. 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.
44. 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.
45. Kumar B, Cipolla MJ, Old MO, Brown NV, Kang SY, Dziegielewski PT, Durmus K, Ozer E, Agrawal A, Carrau RL, Schuller DE, Leon ME, Pan Q, Kumar P, Wood V, Burgers J, Wakely PE, Jr. and Teknos TN (2016). Surgical management of oropharyngeal squamous cell carcinoma: Survival and functional outcomes. *Head Neck* 38 Suppl 1:E1794-1802.
46. Faraji F, Kumar A, Voora R, Soliman SI, Cherry D, Courtney PT, Finegersh A, Guo T, Cohen E, Califano JA, 3rd, Mell L, Rose B and Orosco RK (2024). Transoral Surgery in HPV-Positive Oropharyngeal Carcinoma: Oncologic Outcomes in the Veterans Affairs System. *Laryngoscope* 134(1):207-214.
47. Keane FK, Chen YH, Neville BA, Tishler RB, Schoenfeld JD, Catalano PJ and Margalit DN (2015). Changing prognostic significance of tumor stage and nodal stage in patients with squamous cell carcinoma of the oropharynx in the human papillomavirus era. *Cancer* 121(15):2594-2602.
48. Price JM, West CM, Mistry HB, Betts G, Bishop P, Kennedy J, Dixon L, Homer JJ, Garcez KP, Lee LW, McPartlin A, Sykes AJ and Thomson DJ (2021). Improved survival prediction for oropharyngeal cancer beyond TNMv8. *Oral Oncol* 115:105140.
49. Zhan KY, Eskander A, Kang SY, Old MO, Ozer E, Agrawal AA, Carrau RL, Rocco JW and Teknos TN (2017). Appraisal of the AJCC 8th edition pathologic staging modifications for HPV-positive oropharyngeal cancer, a study of the National Cancer Data Base. *Oral Oncol* 73:152-159.
50. He T, Yan RN, Chen HY, Zeng YY, Xiang ZZ, Liu F, Shao BF, Ma JC, Wang XR and Liu L (2021). Comparing the 7th and 8th editions of UICC/AJCC staging system for nasopharyngeal carcinoma in the IMRT era. *BMC Cancer* 21(1):327.
51. Ho AS, Kaplan MJ, Fee WE, Jr., Yao M, Sunwoo JB and Hwang PH (2012). Targeted endoscopic salvage nasopharyngectomy for recurrent nasopharyngeal carcinoma. *Int Forum Allergy Rhinol* 2(2):166-173.
52. 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.
53. Haughey BH and Sinha P (2012). Prognostic factors and survival unique to surgically treated p16+ oropharyngeal cancer. *Laryngoscope* 122 Suppl 2:S13-33.
54. 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.
55. 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.
56. 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.
57. Sher DJ, Adelstein DJ, Bajaj GK, Brizel DM, Cohen EEW, Halthore A, Harrison LB, Lu C, Moeller BJ, Quon H, Rocco JW, Sturgis EM, Tishler RB, Trotti A, Waldron J and Eisbruch A (2017). Radiation therapy for oropharyngeal squamous cell carcinoma: Executive summary of an ASTRO Evidence- Based Clinical Practice Guideline. *Pract Radiat Oncol* 7(4):246-253.
58. Smith BD (2009). Prognostic factors in patients with head and neck cancer. In: *Head and Neck Cancer: A Multidisciplinary Approach*, Harrison LB, Sessions RB and Hong WK (eds), Lippincott Williams and Wilkins, Philadelphia, USA.
59. 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.
60. Kompelli AR, Morgan P, Li H, Harris W, Day TA and Neskey DM (2019). Prognostic Impact of High-Risk Pathologic Features in HPV-Related Oropharyngeal Squamous Cell Carcinoma and Tobacco Use. *Otolaryngol Head Neck Surg* 160(5):855-861.
61. Tassone P, Crawley M, Bovenzi C, Zhan T, Keane W, Cognetti D, Luginbuhl A and Curry J (2017). Pathologic Markers in Surgically Treated HPV-Associated Oropharyngeal Cancer: Retrospective Study, Systematic Review, and Meta-analysis. *Ann Otol Rhinol Laryngol* 126(5):365-374.
62. Poupore NS, Chen T, Nguyen SA, Nathan CO and Newman JG (2022). Transoral Robotic Surgery for Oropharyngeal Squamous Cell Carcinoma of the Tonsil versus Base of Tongue: A Systematic Review and Meta-Analysis. *Cancers (Basel)* 14(15):3837.
63. Magliocca KR, Kaka AS, Barrow EM, Studer MB, Griffith CC, Ernst J, Meade T, Balicki A, Boyce BJ, Schmitt NC, Bur AM, Schmitt AC, Jackson R, Steuer CE, Beitler JJ and Patel MR (2023). Specimen- Based Resection Margins and Local Control during Transoral Robotic Surgery for Oropharyngeal HPV- Mediated Squamous Cell Carcinoma. *ORL J Otorhinolaryngol Relat Spec* 85(2):80-87.
64. Kaur V, Rooney A and Horton BJ (2023). Prognostic significance of extra-nodal extension and positive surgical margins in HPV positive oropharyngeal squamous cell carcinoma. *Am J Otolaryngol* 44(4):103877.
65. Molony P, Kharytaniuk N, Boyle S, Woods RSR, O'Leary G, Werner R, Heffron C, Feeley L and Sheahan P (2017). Impact of positive margins on outcomes of oropharyngeal squamous cell carcinoma according to p16 status. *Head Neck* 39(8):1680-1688.
66. 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.
67. Brandwein-Gensler M, Teixeira MS, Lewis CM, Lee B, Rolnitzky L, Hille JJ, Genden E, Urken ML and Wang BY (2005). Oral squamous cell carcinoma: histologic risk assessment, but not margin status, is strongly predictive of local disease-free and overall survival. *Am J Surg Pathol* 29(2):167-178.
68. 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.
69. 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.
70. Holcomb AJ, Herberg M, Strohl M, Ochoa E, Feng AL, Abt NB, Mokhtari TE, Suresh K, McHugh CI, Parikh AS, Sadow P, Faquin W, Faden D, Deschler DG, Varvares MA, Lin DT, Fakhry C, Ryan WR and Richmon JD (2021). Impact of surgical margins on local control in patients undergoing single- modality transoral robotic surgery for HPV-related oropharyngeal squamous cell carcinoma. *Head Neck* 43(8):2434-2444.
71. 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.
72. 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.
73. D'Souza G, Zhang HH, D'Souza WD, Meyer RR and Gillison ML (2010). Moderate predictive value of demographic and behavioral characteristics for a diagnosis of HPV16-positive and HPV16-negative head and neck cancer. *Oral Oncol* 46(2):100-104.
74. Chung CH and Gillison ML (2009). Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. *Clin Cancer Res* 15(22):6758-6762.
75. [IARC Working Group on the Evaluation of Carcinogenic Risks to Humans](https://pubmed.ncbi.nlm.nih.gov/?term=IARC%2BWorking%2BGroup%2Bon%2Bthe%2BEvaluation%2Bof%2BCarcinogenic%2BRisks%2Bto%2BHumans%5BCorporate%2BAuthor%5D) (2007). Human papillomaviruses. *IARC Monogr Eval Carcinog Risks Hum* 90:1-636.
76. Broglie MA, Haerle SK, Huber GF, Haile SR and Stoeckli SJ (2013). Occult metastases detected by sentinel node biopsy in patients with early oral and oropharyngeal squamous cell carcinomas: impact on survival. *Head Neck* 35(5):660-666.
77. Sedghizadeh PP, Billington WD, Paxton D, Ebeed R, Mahabady S, Clark GT and Enciso R (2016). Is p16-positive oropharyngeal squamous cell carcinoma associated with favorable prognosis? A systematic review and meta-analysis. *Oral Oncol* 54:15-27.
78. Lewis JS, Jr., Beadle B, Bishop JA, Chernock RD, Colasacco C, Lacchetti C, Moncur JT, Rocco JW, Schwartz MR, Seethala RR, Thomas NE, Westra WH and Faquin WC (2017). Human Papillomavirus Testing in Head and Neck Carcinomas: Guideline From the College of American Pathologists. *Arch Pathol Lab Med*. 142(5):559-597.
79. Hong A, Jones D, Chatfield M, Lee CS, Zhang M, Clark J, Elliott M, Harnett G, Milross C and Rose B (2013). HPV status of oropharyngeal cancer by combination HPV DNA/p16 testing: biological relevance of discordant results. *Ann Surg Oncol* 20 Suppl 3:S450-458.
80. Lewis JS, Jr., Chernock RD, Ma XJ, Flanagan JJ, Luo Y, Gao G, Wang X and El-Mofty SK (2012). Partial p16 staining in oropharyngeal squamous cell carcinoma: extent and pattern correlate with human papillomavirus RNA status. *Mod Pathol* 25(9):1212-1220.
81. Shinn JR, Davis SJ, Lang-Kuhs KA, Rohde S, Wang X, Liu P, Dupont WD, Plummer D, Jr., Thorstad WL, Chernock RD, Mehrad M and Lewis JS, Jr. (2021). Oropharyngeal Squamous Cell Carcinoma With Discordant p16 and HPV mRNA Results: Incidence and Characterization in a Large, Contemporary United States Cohort. *Am J Surg Pathol* 45(7):951-961.
82. Mehanna H, Taberna M, von Buchwald C, Tous S, Brooks J, Mena M, Morey F, Grønhøj C, Rasmussen JH, Garset-Zamani M, Bruni L, Batis N, Brakenhoff RH, Leemans CR, Baatenburg de Jong RJ, Klussmann JP, Wuerdemann N, Wagner S, Dalianis T, Marklund L, Mirghani H, Schache A, James JA, Huang SH, O'Sullivan B, Nankivell P, Broglie MA, Hoffmann M, Quabius ES and Alemany L (2023). Prognostic implications of p16 and HPV discordance in oropharyngeal cancer (HNCIG-EPIC-OPC): a multicentre, multinational, individual patient data analysis. *Lancet Oncol* 24(3):239-251.
83. Craig SG, Anderson LA, Moran M, Graham L, Currie K, Rooney K, Robinson M, Bingham V, Cuschieri KS, McQuaid S, Schache AG, Jones TM, McCance D, Salto-Tellez M, McDade SS and James JA (2020). Comparison of Molecular Assays for HPV Testing in Oropharyngeal Squamous Cell Carcinomas: A Population-Based Study in Northern Ireland. *Cancer Epidemiol Biomarkers Prev* 29(1):31-38.
84. Nauta IH, Rietbergen MM, van Bokhoven A, Bloemena E, Lissenberg-Witte BI, Heideman DAM, Baatenburg de Jong RJ, Brakenhoff RH and Leemans CR (2018). Evaluation of the eighth TNM classification on p16-positive oropharyngeal squamous cell carcinomas in the Netherlands and the importance of additional HPV DNA testing. *Ann Oncol* 29(5):1273-1279.
85. Prigge ES, Arbyn M, von Knebel Doeberitz M and Reuschenbach M (2017). Diagnostic accuracy of p16(INK4a) immunohistochemistry in oropharyngeal squamous cell carcinomas: A systematic review and meta-analysis. *Int J Cancer* 140(5):1186-1198.
86. Thamboo A, Tran KH, Ye AX, Shoucair I, Jabarin B, Prisman E and Garnis C (2022). Surveillance tools for detection of recurrent nasopharyngeal carcinoma: An evidence-based review and recommendations. *World J Otorhinolaryngol Head Neck Surg* 8(3):187-204.
87. Stenmark MH, McHugh JB, Schipper M, Walline HM, Komarck C, Feng FY, Worden FP, Wolf GT, Chepeha DB, Prince ME, Bradford CR, Mukherji SK, Eisbruch A and Carey TE (2014). Nonendemic HPV-positive nasopharyngeal carcinoma: association with poor prognosis. *Int J Radiat Oncol Biol Phys* 88(3):580-588.
88. Dogan S, Hedberg ML, Ferris RL, Rath TJ, Assaad AM and Chiosea SI (2014). Human papillomavirus and Epstein-Barr virus in nasopharyngeal carcinoma in a low-incidence population. *Head Neck* 36(4):511-516.
89. Robinson M, Suh YE, Paleri V, Devlin D, Ayaz B, Pertl L and Thavaraj S (2013). Oncogenic human papillomavirus-associated nasopharyngeal carcinoma: an observational study of correlation with ethnicity, histological subtype and outcome in a UK population. *Infect Agent Cancer* 8(1):30.
90. Petrelli F, Cin ED, Ghidini A, Carioli D, Falasca V, De Stefani A, Moleri G, Ardito R, Luciani A, Nardone M and Capriotti V (2023). Human papillomavirus infection and non-oropharyngeal head and neck cancers: an umbrella review of meta-analysis. *Eur Arch Otorhinolaryngol* 280(9):3921-3930.
91. Ferris RL, Blumenschein G, Jr., Fayette J, Guigay J, Colevas AD, Licitra L, Harrington K, Kasper S, Vokes EE, Even C, Worden F, Saba NF, Iglesias Docampo LC, Haddad R, Rordorf T, Kiyota N, Tahara M, Monga M, Lynch M, Geese WJ, Kopit J, Shaw JW and Gillison ML (2016). Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* 375(19):1856-1867.
92. Cohen EEW, Soulières D, Le Tourneau C, Dinis J, Licitra L, Ahn MJ, Soria A, Machiels JP, Mach N, Mehra R, Burtness B, Zhang P, Cheng J, Swaby RF and Harrington KJ (2019). 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.
93. 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.
94. 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.
95. 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.
96. 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.
97. 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.
98. van Gysen K, Stevens M, Guo L, Jayamanne D, Veivers D, Wignall A, Pang L, Guminski A, Lee A, Hruby G, Macleod P, Taylor A and Eade T (2019). Validation of the 8(th) edition UICC/AJCC TNM staging system for HPV associated oropharyngeal cancer patients managed with contemporary chemo- radiotherapy. *BMC Cancer* 19(1):674.
99. Mizumachi T, Homma A, Sakashita T, Kano S, Hatakeyama H and Fukuda S (2017). Confirmation of the eighth edition of the AJCC/UICC TNM staging system for HPV-mediated oropharyngeal cancer in Japan. *Int J Clin Oncol* 22(4):682-689.
100. Machczyński P, Majchrzak E, Niewinski P, Marchlewska J and Golusiński W (2020). A review of the 8th edition of the AJCC staging system for oropharyngeal cancer according to HPV status. *Eur Arch Otorhinolaryngol* 277(9):2407-2412.
101. Würdemann N, Wagner S, Sharma SJ, Prigge ES, Reuschenbach M, Gattenlöhner S, Klussmann JP and Wittekindt C (2017). Prognostic Impact of AJCC/UICC 8th Edition New Staging Rules in Oropharyngeal Squamous Cell Carcinoma. *Front Oncol* 7:129.
102. 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/](http://www.iccr-cancer.org/datasets/published-datasets/head-neck/nodal-excisions/) (Accessed 31st July 2024).
103. Wittekind C, Brierley JD, van Eycken AL and van Eycken E (eds) (2019). *TNM Supplement: A Commentary on Uniform Use, 5th Edition*, Wiley, USA.
1. Bij neoplasmata van kleine speekselklieren moet de optie “speekselkliercarcinoom (specificeer)” gekozen worden. Het histologische subtype kan vervolgens gespecificeerd worden volgens de lijst opgenomen in het standaardrapport “Grote speekselklieren”. [↑](#footnote-ref-1)
2. De aan- of afwezigheid van peritumorale perineurale invasie kan invloed hebben op de behandeling en prognose. Het gaat hierbij om peritumorale perineurale invasie langs of voorbij de tumorgrens, en dus niet om intratumorale uitbreiding. Voor nasofaryngeale carcinomen is deze informatie niet noodzakelijk. Voor meer informatie, zie ‘Note 8 – Perineural invasion’ onderaan dit document. [↑](#footnote-ref-2)
3. De definitie van ' Definitieve minimale tumorvrije marge’ is niet gestandaardiseerd, maar in de orofarynx wordt een marge als positief beschouwd als er invasief carcinoom of ernstige dysplasie/ in situ carcinoom aanwezig is in het snedevlak. Er is geen duidelijk morfologisch onderscheid tussen invasief en in situ carcinoom voor HPV-geassocieerde orofaryngeale carcinomen, dus alle carcinomen in het snedevlak moeten worden beschouwd als ingenomen. Voor meer informatie, zie ‘Note 9 – Margin status’ onderaan dit document. [↑](#footnote-ref-3)
4. De definitie van ' Definitieve minimale vrije marge’ is niet gestandaardiseerd, maar in de orofarynx wordt een marge als positief beschouwd als er invasief carcinoom of ernstige dysplasia/ in situ carcinoom aanwezig is in het snedevlak. Deze variabele is enkel van toepassing voor HPV-onafhankelijke orofaryngeale tumoren en aandoeningen van het tonsillaire oppervlak. Voor meer informatie, zie ‘Note 9 – Margin status’ onderaan dit document. [↑](#footnote-ref-4)
5. De pathologische stadiëring is gebaseerd op de ‘TNM Classification of Malignant Tumours’ (8e editie, UICC). Een beschrijving van elke pT-categorie is beschikbaar in ‘Note 10 – Pathological staging’ onderaan dit document. [↑](#footnote-ref-5)
6. Bijkomende informatie (‘notes’) overgenomen en aangepast vanuit

Chernock RD, Badoual C, Faquin WC, Hernandez-Prera J, Iyer NG, Katabi N, O’Sullivan B, Robinson M, Willems S, Helliwell T, Thompson LDR, (2024). Carcinomas of the Oropharynx and Nasopharynx Histopathology Reporting Guide. 2nd edition. International Collaboration on Cancer Reporting; Sydney, Australia. ISBN: 978-1-922324-47-4. [↑](#footnote-ref-6)