



# Carcinomas of the Nasal Cavity and Paranasal Sinuses Histopathology Reporting Guide



Family/Last name

Date of birth

Given name(s)

Patient identifiers

Date of request

Accession/Laboratory number

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

[SCOPE OF THIS DATASET](#)

## NEOADJUVANT THERAPY (Note 1)

- Information not provided
- Not administered
- Administered, *specify type*

- Chemotherapy
  - Radiotherapy
  - Targeted therapy, *specify if available*
- 

- Immunotherapy, *specify if available*
- 

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

- Not specified
- Biopsy, *specify*
- Resection, *specify*
- Endoscopic nasal procedure, *specify*
- Partial maxillectomy
- Radical maxillectomy
- Orbito-maxillary resection
- Craniofacial resection
  - Open
  - Endoscopic
- Other, *specify*
- Neck (lymph node) dissection\*, *specify*
- Other, *specify*

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

## SPECIMENS SUBMITTED (select all that apply) (Note 3)

- Not specified
  - Nasal cavity
    - Septum
    - Lateral wall
    - Floor
    - Vestibule
  - Paranasal sinus(es), maxillary
  - Paranasal sinus(es), ethmoid
  - Paranasal sinus(es), frontal
  - Paranasal sinus(es), sphenoid
  - Other, *specify*
- 

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

- Cannot be assessed
  - Nasal cavity
    - Septum
      - Left
      - Right
      - Midline
      - Laterality not specified
    - Floor
      - Left
      - Right
      - Laterality not specified
    - Lateral wall
      - Left
      - Right
      - Laterality not specified
    - Vestibule
      - Left
      - Right
      - Laterality not specified
  - Paranasal sinus(es), maxillary
    - Left
    - Right
    - Laterality not specified
  - Paranasal sinus(es), ethmoid
    - Left
    - Right
    - Laterality not specified
  - Paranasal sinus(es), frontal
    - Left
    - Right
    - Laterality not specified
  - Paranasal sinus(es), sphenoid
    - Left
    - Right
    - Laterality not specified
  - Cribriform plate
    - Left
    - Right
    - Laterality not specified
  - Other, *specify including laterality*
-

**TUMOUR FOCALITY (Note 5)**

- Cannot be assessed
- Unifocal
- Multifocal, *specify number of tumours in specimen*

**TUMOUR DIMENSIONS (Note 6)**

Maximum tumour dimension (largest tumour)

 mm

Additional dimensions (largest tumour)

 mm x  mm

- Cannot be assessed, *specify*

**HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 7)**  
*(Value list from the World Health Organization Classification of Head and Neck Tumours (2017))*

- Keratinising squamous cell carcinoma
- Non-keratinising squamous cell carcinoma
- Spindle cell squamous carcinoma
- NUT carcinoma
- Other squamous cell carcinoma variant, *specify*

- Sinonasal undifferentiated carcinoma
- Lymphoepithelial carcinoma
- Neuroendocrine carcinoma
  - Small cell neuroendocrine carcinoma
  - Large cell neuroendocrine carcinoma

- Adenocarcinoma
  - Intestinal-type adenocarcinoma
  - Non-intestinal-type adenocarcinoma

- Salivary type carcinomas, *specify*

- Other carcinoma type, *specify*

- Cannot be assessed, *specify*

**HISTOLOGICAL TUMOUR GRADE (Note 8)**

- Not applicable
- GX: Cannot be assessed
- G1: Well differentiated
- G2: Moderately differentiated
- G3: Poorly differentiated
- G4: Undifferentiated
- Other, *specify*

- Cannot be assessed, *specify*

**BONE/CARTILAGE INVASION (Note 9)**

- Not identified
- Present
  - Erosive (cortical)
  - Infiltrative (medullary involvement)

- Cannot be assessed, *specify*

**PERINEURAL INVASION (Note 10)**

- Not identified
- Present
- Cannot be assessed, *specify*

**LYMPHOVASCULAR INVASION (Note 11)**

- Not identified
- Present
- Cannot be assessed, *specify*

**MARGIN STATUS (Note 12)**

**Invasive carcinoma**

- Involved

Specify margin(s), if possible

- Not involved

Distance from invasive tumour to:

Deep margin  mm

Mucosal margin  mm

- Distance not assessable

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

- Involved

Specify margin(s), if possible

- Not involved

Distance from closest margin  mm

- Distance not assessable

Specify closest margin, if possible

- Cannot be assessed, *specify*

\*\* High-grade dysplasia is synonymous with moderate/severe dysplasia.

**COEXISTENT PATHOLOGY** (select all that apply) (Note 13)

- None identified
- Carcinoma in situ
- Sinonasal papilloma
- Intestinal metaplasia
- Squamous metaplasia
- Epithelial hyperplasia
- Epithelial dysplasia, *specify*

Other, *specify*

  

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**ANCILLARY STUDIES** (Note 14)

- Not performed
- Performed, *specify*

  

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**PATHOLOGICAL STAGING (UICC TNM 8th edition)\*\*** (Note 15)

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

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

**Primary tumour (pT)\*\*\***

- TX Primary tumour cannot be assessed
- Tis Carcinoma in situ

**Maxillary sinus**

- T1 Tumour limited to the mucosa with no erosion or destruction of bone
- T2 Tumour causing bone erosion or destruction, including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
- T3 Tumour invades any of the following: bone of posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, or ethmoid sinuses
- T4a Tumour invades any of the following: anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid or frontal sinuses
- T4b Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V2), nasopharynx, or clivus

\*\*\* Note that the results of [lymph node/neck dissection](#) are derived from a separate dataset.

**Nasal cavity and ethmoid sinus**

- T1 Tumour restricted to one subsite of nasal cavity or ethmoid sinus, with or without bony invasion
- T2 Tumour involves two subsites in a single site or extends to involve an adjacent site within the nasoethmoidal complex, with or without bony invasion
- T3 Tumour extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
- T4a Tumour invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
- T4b Tumour invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than V2, nasopharynx, or clivus

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## Scope

The dataset has been developed for the reporting of resection and biopsy specimens of mucosal malignancies originating in the nasal cavities and paranasal sinuses. Neuroectodermal neoplasms (including melanoma) and sarcomas are not included. Bone, soft tissue and lymphoma protocols are separately listed.

Neck dissections and nodal excisions are dealt with in a separate dataset, and this dataset should be used in conjunction, where applicable.

For additional independent tumours, complete a separate dataset for each.

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

### Reason/Evidentiary Support

Patients affected by locally advanced sinonasal carcinomas may be treated with pre-operative chemo-radiation protocols that could result in a significant improvement in survival in selected cases.<sup>1-4</sup>

In this case, specimens should be extensively sampled and changes presumably induced by treatment should be reported as free text. Quantification of the extent of response is currently considered not relevant for clinical purposes. Type of (chemo) therapy, number of cycles, interval between last cycle of chemotherapy and local regional treatment initiation can be annotated if available.

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## Note 2 – Operative procedure (Core)

### Reason/Evidentiary Support

Different options are currently available for the surgical treatment of sinonasal malignancies, which can be chosen according to histopathology, extent of the lesion, and experience of the surgeon. Surgical approaches include craniofacial resections, endoscopic endonasal resections, and combined approaches.<sup>5-7</sup> This results in a wide range of surgical specimens submitted for histopathological analysis.

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## Note 3 – Specimens submitted (Core)

### Reason/Evidentiary Support

According to the surgical approach, different types of specimen can be submitted for histological analysis. Specimens from surgery often consist of fragmented material that should be properly labelled at the time of surgery including a description of the anatomic site and type of tissue submitted (tumour or other). Due to the difficulty in the orientation of the samples (impossible in some cases) it is recommended that margins be submitted separately, properly identified and labelled (especially in suspicious areas). Surgical resection specimens consist most often of the maxillary bone and adjacent anatomic structures removed according to the extent of the tumour.<sup>8</sup>

For additional independent tumours use separate datasets. A single bilateral tumour can be reported as “midline”.

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## Note 4 – Tumour site (Core)

### Reason/Evidentiary Support

The sinonasal tract consists of the nasal cavity and the paranasal sinuses (maxillary, ethmoid, frontal, and sphenoid). The nasal cavity can be further subdivided into the nasal septum, floor, lateral wall, and vestibule. Among sinonasal tract carcinomas, the most common site of tumour origin is the maxillary sinus, followed by the nasal cavity and ethmoid sinus. It is rare for carcinomas to arise from the frontal or sphenoid sinuses.<sup>9-13</sup>

The precise tumour site within the sinonasal tract is important to record. First, different staging schemes are utilized for maxillary sinus carcinomas and those arising in the ethmoid sinus or nasal cavity.<sup>14</sup> Second, there is prognostic importance to the tumour location. For example, carcinomas primary to the nasal cavity have been shown to have an improved prognosis over carcinomas primary to the paranasal sinuses, likely because nasal carcinomas give rise to symptoms (e.g. nasal obstruction or epistaxis) and this come to clinical attention sooner.<sup>9,13,15,16</sup> In addition, among maxillary sinus carcinomas, those arising from the anterior-inferior portion have a better prognosis than those arising from the superior-posterior portion, likely because the latter group has easier access to structures such as the orbit or skull base.<sup>14</sup> Finally, certain carcinomas are closely associated with specific sinonasal sub-sites. For example, intestinal-type adenocarcinomas and neuroendocrine carcinomas occur most often in the ethmoid sinuses, while squamous cell carcinoma occurs most often in the maxillary sinus.<sup>17-20</sup>

It is recognized that some carcinomas, particularly highly aggressive types like sinonasal undifferentiated carcinoma or NUT carcinoma, usually affect more than one sinonasal anatomic sub-site. In this case, every affected site should be selected.

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## **Note 5 – Tumour focality (Non-core)**

### **Reason/Evidentiary Support**

Multiple, different histologic primaries should be reported in separate datasets. “Multifocal” can be used for microscopic foci of in situ or invasive carcinoma adjacent to the primary.

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## **Note 6 – Tumour dimensions (Core and Non-core)**

### **Reason/Evidentiary Support**

The maximum diameter of the tumour should be possibly assessed on the unfixed specimen to avoid size underestimation resulting from formalin fixation-induced shrinkage. Care should be taken not to overestimate tumour size by including areas of adjacent non-neoplastic tissue. The gross assessment of tumour size should be confirmed microscopically and in cases where non-neoplastic tissue has been mistakenly incorporated into the tumour measurement, tumour size should be adjusted accordingly. If tumour dimensions are estimated only microscopically, then “at least” should be added to indicate that the measurement is an underestimation resulting from fixation and tissue processing.

The option “Cannot be assessed” can be used when the tumour is submitted in fragments, as in endoscopic resections. In these cases, radiographic imaging may also be considered to determine tumour dimensions.

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## **Note 7 – Histological tumour type (Core)**

### **Reason/Evidentiary Support**

All sinonasal tumours should be given a type based on the most recent edition of the World Health Organization (WHO) Classification of Head and Neck Tumours.<sup>21</sup> The list of histologic types discussed in the chapter on sinonasal tumours in the 4<sup>th</sup> Edition of the WHO does not include some squamous cell carcinoma variants and salivary gland type tumours because they are described in sections devoted to other sites where they are more commonly encountered.

The sinonasal tract gives rise to a very large and diverse group of carcinomas, which may arise from the surface epithelium or the underlying seromucinous glands. Squamous cell carcinoma is, by far, the most common tumour to occur in the sinonasal tract, and it is subdivided primarily into keratinizing and non-keratinizing subtypes. Additional subtypes (e.g. spindle cell, basaloid, adenosquamous) are rare but should be noted if present. Sinonasal undifferentiated carcinoma, lymphoepithelial carcinoma, NUT carcinoma, and neuroendocrine carcinomas are also recognized tumour types of presumed surface origin. Adenocarcinomas of the sinonasal tract can be of surface

or seromucinous gland origin. The surface-type adenocarcinomas should be subdivided into intestinal and non-intestinal types, while the seromucinous (minor salivary) gland carcinomas should be typed by the WHO classification of salivary gland tumours; adenoid cystic carcinoma is most common.

Additional tumour types were included as provisional entities in the WHO classification may be mentioned at the pathologist’s discretion. These include human papillomavirus (HPV)-related multiphenotypic sinonasal carcinoma, *SMARCB1* (INI1) deficient sinonasal carcinoma, and sinonasal renal cell-like adenocarcinoma.

Accurate tumour typing is important because specific tumour types are associated with different prognoses and, in some cases, different treatments. For example, sinonasal undifferentiated carcinoma and NUT carcinoma have very poor outcomes while low-grade forms of non-intestinal type adenocarcinoma behave in a very indolent manner. As another example, lymphoepithelial carcinoma is known to respond well to external beam radiation, while salivary-type adenocarcinomas are, as a group, not highly radiosensitive.

Diagnostic accuracy is also expected to take on additional importance in the future as targeted, molecular-based therapies become more prominent. A notable example is NUT carcinoma, for which trials using bromodomain inhibitors are ongoing.<sup>22</sup> The use of targeted therapies may also be an option for certain intestinal-type adenocarcinomas in the future.<sup>23,24</sup>

## WHO classification of tumours of the nasal cavity, paranasal sinuses and skull base<sup>a21</sup>

Descriptor	ICD-O codes
<b>Carcinomas</b>	
Keratinising squamous cell carcinoma	8071/3
Non-keratinising squamous cell carcinoma	8072/3
Spindle cell squamous carcinoma	8074/3
Lymphoepithelial carcinoma	8082/3
Sinonasal undifferentiated carcinoma	8020/3
NUT carcinoma	8023/3
Neuroendocrine carcinoma	
Small cell neuroendocrine carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Adenocarcinoma	
Intestinal-type adenocarcinoma	8144/3
Non-intestinal-type adenocarcinoma	8140/3

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

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## **Note 8 – Histological tumour grade (Core)**

### **Reason/Evidentiary Support**

A tiered grading system is used for squamous cell carcinoma (based on degree of differentiation) and should also be used sinonasal adenocarcinoma (which, according to the WHO Classification can be distinguished in low and high grade), as well as some salivary gland tumours (e.g. adenoid cystic carcinoma, mucoepidermoid carcinoma, etc.). Squamous cell carcinomas are graded with a 3-tiered system based on the degree the tumour cells differentiate. Undifferentiated tumours that show virtually no evidence of histologic differentiation should be considered grade 4. Salivary gland neoplasms have grading systems unique to some tumours that generally require quantification and assessment of a number of histologic features.<sup>25</sup> The grading of non-salivary-gland-type adenocarcinomas is based on the presence of necrosis and mitotic activity.<sup>26</sup> Tubulo-papillary intestinal type adenocarcinoma can be graded as well, moderately, or poorly differentiated, while mucinous adenocarcinomas are either moderately differentiated (alveolar) or poorly differentiated (signet ring cell).<sup>27</sup> Finally, grading can also be performed with neuroendocrine carcinomas; however, within the sinonasal tract, almost all cases are high grade. The reproducibility and prognostic value of the various grading systems remain debatable.

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## **Note 9 – Bone/cartilage invasion (Core)**

### **Reason/Evidentiary Support**

Bone and/or cartilage invasion is a frequent finding in sinonasal carcinomas. Both bone erosion and destruction have to be reported as part of the definition of the primary tumour in the TNM staging system.

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## **Note 10 – Perineural invasion (Core)**

### **Reason/Evidentiary Support**

The frequency of perineural invasion in sinonasal carcinomas is lower than other head and neck sites, and varies according to the histologic subtype, being most frequent in adenoid cystic carcinoma, sinonasal undifferentiated carcinoma and squamous cell carcinoma.<sup>28,29</sup> In sinonasal carcinomas, perineural invasion is associated with a high rate of positive margins, with maxillary origin, and with previous surgical treatment, but it is not an independent prognostic factor of outcome.<sup>28</sup>

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## Note 11 – Lymphovascular invasion (Core)

### Reason/Evidentiary Support

It consists in the presence of neoplastic cells within an endothelial-lined space, either lymphatic or venous, and should be distinguished from retraction artefact. Immunohistochemical staining for an endothelial marker may help in this distinction.

Lymphovascular invasion is reported in up to 60% of sinonasal squamous cell carcinomas, but its clinical significance at this anatomic site remains to be determined.<sup>28</sup>

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## Note 12 – Margin status (Core)

### Reason/Evidentiary Support

Ideally, the resection specimen would be handed over from surgeon to pathologist directly for orientation and clarification of surgical margins. Failing this, the margins should be labelled by the surgeon and/or illustrated with a diagram. Specimens from endoscopic tumour resections should also be labelled. If the margins are sent separately, for frozen section or otherwise, identification of their site in relation to the resection specimen should be clarified by the surgeon. The surgical margins, both mucosal and deep, should be thoroughly sampled. A positive or close margin will usually result in postoperative radiotherapy and treatment associated morbidity at this site may be severe. Skin and bone margins may also require documentation depending upon the type of resection.

Evidence relating to margins at this specific site is lacking and therefore extrapolated from other head and neck sites, the oral cavity being the most studied. The literature would generally support 5 mm as a prognostically relevant pathologic **clear** margin.<sup>30,31</sup> This is best considered the minimum acceptable margin and is not a guarantee of lack of local recurrence which can be up to 25% with a clear margin.<sup>31,32</sup> Values ranging from 3 mm to 7 mm have been put forward.<sup>30,33</sup> In lower stage tumours, without other adverse variables, a margin less than 5 mm may be adequate<sup>34,35</sup> so that in considering adjuvant therapy, other features of the tumour must be taken into account. The evaluation of margins and the treatment choices should also be made considering the complex anatomy of this area. For example, a sinonasal adenocarcinoma can have pushing margins at the periorbital tissues without infiltration, and in this case no orbital exenteration is needed to achieve clear margins >5 mm.

There is no agreed-upon definition of what constitutes a **close** margin, as the effective cut off varies between studies depending upon anatomic subsite, tumour stage and other adverse pathologic variables.<sup>36</sup> Tumours with close margins carry an increased risk for local recurrence<sup>30,36,37</sup> but there is significantly better overall survival than for involved margins.<sup>38</sup>

Several studies support the definition of a **positive** margin to be invasive carcinoma at the margin<sup>30,35,38</sup> although <1 mm is also used.<sup>39</sup> Most studies also consider carcinoma in situ/high-grade

dysplasia as a positive margin.<sup>30</sup> The presence of dysplasia at the margin is associated with a significant risk of local recurrence<sup>40</sup> and development of a second primary.<sup>41</sup> Information regarding the distance of invasive carcinoma, carcinoma in situ, or high-grade dysplasia from the nearest margin should be recorded where possible.

While there is no standard recommendation for the other histologic types of carcinoma, adherence to the recommendations for squamous cell carcinoma is acceptable.

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## Note 13 – Coexistent pathology (Non-core)

### Reason/Evidentiary Support

The presence of coexistent pathology can be used as evidence for histologic classification of the tumour. This is especially true with spindle cell carcinoma or other less differentiated variants of squamous cell carcinoma that arise from and are often associated with overlying squamous dysplasia/carcinoma in situ.<sup>42</sup>

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## Note 14 – Ancillary studies (Non-core)

### Reason/Evidentiary Support

Ancillary studies are variably needed for the diagnosis of specific entities at this site. For example, NUT carcinoma is recognized by the presence of nuclear protein in testis (NUT) gene rearrangement or positivity with the C52 monoclonal antibody against NUT protein.<sup>43</sup> The diagnosis of HPV-related multiphenotypic sinonasal carcinoma requires HPV specific testing as part of the tumour definition,<sup>44</sup> while for the diagnosis of *SMARCB1* (INI1)-deficient carcinoma, loss of nuclear immunohistochemical staining for INI1 is needed.<sup>45</sup>

In poorly differentiated malignancies, immunohistochemical markers can be used to assign a tumour to a specific category. p40, p63 and cytokeratin 5/6 are useful markers of squamous differentiation, while markers of intestinal differentiation, such as cytokeratin 20 and CDX2, help in the diagnosis of intestinal type adenocarcinoma. Neuroendocrine carcinomas can be diagnosed with the support of positive staining with at least one neuroendocrine marker.

A subset of sinonasal carcinomas appears to be related to high risk HPV, including non-keratinizing squamous cell carcinoma, basaloid squamous cell carcinoma, papillary squamous cell carcinoma, adenosquamous carcinoma, and conventional keratinizing squamous cell carcinoma.<sup>46-51</sup> However, the clinical significance of these findings is still debated, and HPV testing is considered investigational in this context.

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## Note 15 – Pathological staging (Core)

### Reason/Evidentiary Support

The TNM classification attempts to describe the anatomic extent of cancer. 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. The objective of this classification is to aid the clinician in planning treatment, give some indication of prognosis, assist in the evaluation of the results of therapy and facilitate exchange of information.

By American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) 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 TNM, as opposed to the clinical classification, and is based on gross and microscopic examination of the resected tumour. pT entails a resection of the primary tumour or biopsy 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 metastatic lesions.

For identification of special cases of 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 (ie, 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. The R classifier for residual tumour is not recommended for use in the setting of head and neck cancers.

### TNM Descriptors

#### T – Primary Tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ

For the pN classification of regional lymph nodes, see International Collaboration on Cancer Reporting (ICCR) *Nodal excisions and neck dissection specimens* dataset.<sup>52</sup>

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