The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for the histopathological reporting of carcinomas of the nasal cavity and paranasal sinuses

February 2025

Authors: Dr Amrita Jay, University College London Hospitals NHS Trust
Dr Matt Lofthouse, Liverpool University Hospitals NHS Trust
Professor Keith Hunter, Liverpool University Hospitals NHS Trust

Unique document number	G114
Document name	Dataset for the histopathological reporting of carcinomas of the nasal cavity and paranasal sinuses
Version number	2
Produced by	Dr Amrita Jay (lead author) is a Consultant Histopathologist in Head and Neck Pathology at University College London Hospitals NHS Trust. Dr Matt Lofthouse is a Consultant Histopathologist at Liverpool University Hospitals NHS Trust. Professor Keith Hunter is a Professor of Head and Neck Pathology at the University of Liverpool and a Consultant Histopathologist at Liverpool University Hospitals NHS Trust. The authors would like to acknowledge the work done by the previous dataset authors, the expertise of the ICCR Dataset Authoring Committee and Professor Tim Helliwell for his expertise, support and encouragement.
Date active	February 2025 (to be implemented within 3 months)
Date for full review	December 2028
Comments	This document will replace the 1st edition of the *Dataset for histopathology reporting of mucosal malignancies of the nasal cavity and paranasal sinuses*, published in 2013.

	In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 10 December 2024 to 7 January 2025. Responses and authors' comments are available to view on request. **Dr Brian Rous** **Clinical Lead for Guideline Review**

The Royal College of Pathologists
6 Alie Street, London E1 8QT
Tel: 020 7451 6700
Fax: 020 7451 6701
Web: www.rcpath.org

Contents

Foreword

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

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

The following stakeholders were contacted to consult on this document:

- The British Society for Oral and Maxillofacial Pathology (BSOMP)
- The British Association of Head and Neck Oncologists (BAHNO)
- ENT-UK
- The British Association of Oral and Maxillofacial Surgeons
- The UK and Ireland Association of Cancer Registries.

The information used by the authors to develop this dataset was obtained by undertaking a search of the PubMed database from January 2010 to June 2024 (inclusive) for relevant

primary research evidence and systematic reviews on head and neck mucosal malignancies, either specifically in the sinonasal region or generally in the head and neck where these subsites can be separately identified. Key terms searched included nasal cavity and paranasal sinuses (and subsites), clinical trial, prognosis, survival, surgery, chemotherapy and radiotherapy. In addition, abstracts from selected conference proceedings from American Society of Clinical Oncology (ASCO) were screened. The recommendations are in line with those of other national pathology organisations (the College of American Pathologists, the Royal College of Pathologists of Australasia) and the United Kingdom National Multidisciplinary Guidelines for Head and Neck Cancer.[1] They incorporate the core data items and commentary from the International Collaboration on Cancer Reporting (ICCR).[2] The level of evidence for the recommendations has been summarised according to modified SIGN guidance (see Appendix E) and the grade of evidence is indicated in the text. No major conflicts in the evidence have been identified and minor discrepancies between studies have been resolved by expert consensus. Gaps in the evidence were identified by College members via feedback received during consultation.

No major organisational changes or cost implications have been identified that would hinder the implementation of the dataset.

A formal revision cycle for all cancer datasets takes place on a 3-yearly basis. However, each year, the College will ask the authors of the dataset, in conjunction with the relevant subspecialty advisor to the College, to consider whether or not the dataset needs to be revised. A full consultation process will be undertaken if major revisions are required, i.e. revisions to core data items (the only exception being changes to international tumour grading and staging schemes that have been approved by the Specialty Advisory Committee on Cellular Pathology and affiliated professional bodies; these changes will be implemented without further consultation). If minor revisions or changes to non-core data items are required, an abridged consultation process will be undertaken, whereby a short note of the proposed changes will be placed on the College website for 2 weeks for Fellows' attention. If fellows do not object to the changes, the short notice of change will be incorporated into the dataset and the full revised version (incorporating the changes) will replace the existing version on the College website.

The dataset has been reviewed by the Professional Guidelines team, Working Group on Cancer Services and Lay Advisory Group and was placed on the College website for consultation with the membership from 10 December 2024 to 7 January 2025. All

comments received from the Working Group and membership were addressed by the author to the satisfaction of the Chair of the Working Group and the Clinical Lead for Guideline Review.

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

1 Introduction

The dataset has been developed for the reporting of biopsy and resection specimens of the nasal cavity and paranasal sinuses. The protocol applies to primary mucosal carcinomas of the nasal cavity, including the nasal septum, and the maxillary, ethmoid, sphenoid and frontal sinuses and can be adapted for use in selected other malignancies e.g. olfactory neuroblastoma. Lymphomas and sarcomas are not included in this dataset and should be reported according to tumour type specific guidelines. Neck dissections and nodal excisions are dealt with in a separate dataset and the nasal cavity/paranasal sinus dataset should be used in conjunction with this, where applicable.

The primary purposes of this document are:

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

Optimal reporting of specimens from the head and neck area requires a partnership between the pathologist and surgeon, radiologist and oncologist. The surgeon can help the pathologist to provide the information necessary for patient management by the appropriate handling and labelling of the specimen in the operating theatre. The regular discussion of cases at multi-disciplinary team (and other clinicopathological) meetings and correlation with pre-operative imaging studies are important in maintaining and developing this partnership and providing optimal care to patients.[3]

The core pathological data are summarised as proformas that may be used as the main reporting format or may be combined with free text as required. The lymph node dataset is

common to all head and neck sites. Individual centres may wish to expand the detail in some sections, e.g. for sites and subsites, to facilitate the recording of data for specific tumour types.

The guidelines within this dataset should be implemented because certain features of invasive mucosal carcinomas (subtype, location, extent and grade of the primary carcinoma, the pattern of invasion and proximity of carcinoma to resection margins) have been shown to be related to clinical outcome.[4–7]

These features may therefore be important in:

- deciding on the most appropriate treatment for individual patients, including the extent of surgery and the use and choice of adjuvant radiotherapy, chemotherapy or targeted therapies[3, 8]
- monitoring changing patterns of disease, particularly by cancer registries
- allowing correlation of tumour location and extent in resection specimens with preoperative imaging
- allowing the accurate and equitable comparison of different surgical units, to identify good surgical and pathological practice
- aiding the selection and comparison of patients in clinical trials.

1.1 Target users and health benefits of this guideline

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

1.2 Design of this protocol

RCPath recognises the authority of internationally accepted guidance documents (World Health Organisation (WHO) classification of tumours,[8] American Joint committee on cancer (AJCC),[4] / Union for International Cancer Control (UICC),[5] TNM Classification of

Malignant Tumours, and International Collaboration on Cancer Reporting (ICCR),[2] and to promote consistent reporting practice, adopts the recommendations of these organisations. This structured reporting protocol has been developed using the framework and data items specified in the ICCR dataset on cancers of the nasal cavity and paranasal sinuses.[2] The current protocol includes all the ICCR cancer dataset elements as well as additional information, elements and commentary. Core ICCR references have been updated to include relevant new information from 2018 to June 2024.

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

Although tumour-infiltrating lymphocytes (TILs) are assessed as a non-core data item for oral cavity cancers, the authors consider that there is currently insufficient evidence for the inclusion of TILs in data recorded for sinonasal carcinomas.

2 Clinical information required for the diagnosis of carcinomas of the nasal cavity and paranasal sinuses

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

- patient name
- date of birth
- sex
- hospital and NHS number (where appropriate) or other patient identification number

Clinical information should include:

- duration of symptoms
- details of the surgery and whether the intent is curative or palliative.
- details of previous pathology reports and history of cancer at sinonasal or at other anatomical sites.

- core clinical data items (see section 5)
- clinical TNM stage (for correlation with pathological findings)
- history of previous biopsy, resection, radiotherapy, chemotherapy or immunotherapy, as this may influence the interpretation of the histological changes and should prompt a comment on the extent of any response to treatment.

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

The following should also be recorded:

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

Details of the legal basis of data sharing with the Cancer Registries can be accessed through the National Disease Registration Service.

3 Receipt and preparation of specimens before dissection

Resection specimens should be orientated by the surgeon and may be pinned or sutured to an appropriate mount (e.g. cork board, polystyrene block, foam sponge, KliniTray™), if desired. The surgeon should indicate surgically critical margins using metal tags or sutures. Fixation is in neutral buffered formalin for 24–48 hours in a container of adequate size (the volume of fixative should be 10 times that of the tissue). Resection specimens identified as a biohazard risk should be fixed for at least 48 hours (e.g. HIV, tuberculosis). If tissue is sent fresh from theatres, this should reach the pathology laboratory promptly.

Photography and radiography (if containing bone) of the specimen is advised to record the extent of the disease and the sites from which tissue blocks are selected. The location of the tissue blocks should be recorded on the images and should be available for reporting

the resection margin status. Surgical margins should be painted with an appropriate marker dye to facilitate assessment of tumour proximity to the margins.

4 Specimen handling and block selection

4.1 Introduction

The specimen handling and preparation protocol described below is based on contemporary practice and should be regarded as a guide only; it may need to be modified in individual cases. A detailed dissection protocol is beyond the scope of these guidelines, but a summary of dissection methods and block selection is included to facilitate recording of the core data items. More detail can be found, for example, in the relevant sections of the RCPath document *Tissue Pathways for Head and Neck Pathology* and other guidelines.[9, 10] It is particularly important to record the macroscopic dimensions of the tumour, location, the extent, closest margins and any gross invasion of bone.

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

4.2 Selection and recording of blocks for histology

A wide range of surgical procedures ranging from endoscopic resection to craniofacial resection may be encountered (see notes for core data 2 and 3). The general principles of dissection to ensure that accurate diagnostic and prognostic information e.g. on tissues invaded and margin status are relevant to all specimen types, but some data may be provided based on ‘best estimate’, particularly when specimens are fragmented.

Note that if the patient has been enrolled in a clinical trial, the trial protocol may dictate specific requirements in the macroscopic examination of the tumour and the selection of blocks. Also, if the specimen has been sampled for biobanking, this should be noted in the macroscopic description.

Sampling should be as follows:

- at least 1 block per 10 mm diameter of tumour, including 1 selected to demonstrate the maximum depth of invasion. Embed the whole tumour if less than 20 mm
- blocks of defined mucosal, deep and bone margins

- blocks to identify tumour extent across bony walls of nasal cavity and sinuses in all planes. This should include all landmarks required for staging purposes (example orbital, pterygoid region, infratemporal fossa, all walls of maxillary sinus, ethmoid, sphenoid, dura etc)
- at least 1 block of non-neoplastic mucosa.
- one specified block for molecular testing, in which the tumour content should be formally assessed. It is preferable that a megablock is not used and that this tissue has not been decalcified.

A methodical, text-based block key and/or photographic record of blocks taken should be available and preferably included in the surgical report. This is important particularly if cases are subject to internal or external review. If this information is not included in the final pathology report, it should be available on the laboratory computer system and provided to the reviewing pathologist. Recording the origin/designation of tissue blocks also facilitates retrieval of blocks for further immunohistochemical or molecular analysis, research studies, or clinical trials.

5 Core data items

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

1 ICCR	**Descriptor**	**Core/Non-core**	**Responses**
	Previous therapy	Core	• Information not provided • Not administered • Administered, specify type – Chemotherapy – Radiotherapy – Targeted therapy, specify if available – Immunotherapy, specify if available
Previous therapy comments: 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.[11–14] 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 therapy, number of cycles, interval between last cycle of chemotherapy and local regional treatment initiation can be annotated if available.

[Level of evidence – GPP.]

2 ICCR	Descriptor	Core/Non-core	Responses
	Operative procedure	Core	• Not specified OR • Biopsy, specify • Resection, specify – Open – Endoscopic – Combined – En bloc – Piecemeal • Neck (lymph node) dissection* (see separate dataset) • Other, specify

Operative procedure comments:

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.[15–17] This results in a wide range of surgical specimens submitted for histopathological analysis.

RCPath additional comments:

If a neck dissection specimen is submitted, please use the separate neck dissection dataset.

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

3 ICCR	Descriptor	Core/Non-core	Responses
	Specimens submitted	Core	• Not specified OR • Nasal cavity • Septum • Floor • Lateral wall

			• Vestibule – Paranasal sinus(es), maxillary – Paranasal sinus(es), ethmoid – Paranasal sinus(es), frontal – Paranasal sinus(es), sphenoid – Other, specify

Specimens submitted comments:

According to the surgical approach, different types of specimens 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.[10]

Specimens from increasingly common endoscopic operations consist of fragmented material. Due to the difficulty in the orientation of such samples (impossible in some cases), it is recommended that margins be submitted separately, properly identified, and labelled (especially in suspicious areas).

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

RCPath additional comments:

Irregular mucosal / mucoperiosteal wide local excisions should be orientated on a template with the various excision margins clearly labelled. Extended maxillectomy / craniofacial resections with irregular soft tissue margins may also require orientation, when distorted by tumour.

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

4 ICCR	Descriptor	Core/Non-core	Responses
	Tumour site	Core	• Cannot be assessed OR • Nasal cavity • Septum • Floor • Lateral wall • Vestibule – Paranasal sinus(es), maxillary – Paranasal sinus(es), ethmoid – Paranasal sinus(es), frontal – Paranasal sinus(es), sphenoid

			– Cribriform plate – Orbit • Cranial cavity • Other, specify

Tumour site comments:

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 except for neuroendocrine tumours in the sphenoid of pituitary origin.[18–22]

The precise tumour site within the sinonasal tract is important to record. First, different staging schemes are utilised for maxillary sinus carcinomas and those arising in the ethmoid sinus or nasal cavity.[5] 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.[18, 22–24] 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.[4, 5] 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.[25–27]

It is recognised that some carcinomas affect more than 1 sinonasal anatomic sub-site. In this case, every affected site should be selected.

RCPath additional comments:

For carcinomas that involve more than 1 site, the principal site of involvement (tumour epicentre) should be recorded and coded; this may not be the site of origin. If required, the involvement of associated sites can be noted to facilitate staging. Sites and subsites should be recorded according to the UICC nomenclature.[5]

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

5 ICCR	**Descriptor**	**Core/Non-core**	**Responses**
	Tumour laterality	Core	Single selection value list: • Not specified • Right • Left • Midline

RCPath additional comments:

The rationale for including laterality is the same as for tumour site.[5]

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

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

Table 1: Histological tumour type

WHO classification of tumours of the nasal cavity, paranasal sinuses and skull base 5th edition

Keratinising squamous cell carcinoma
Non-keratinising squamous cell carcinoma
Other squamous cell carcinoma variant, specify (Papillary, verrucous, spindle cell, acantholytic, adenosquamous, carcinoma cuniculatum)
NUT carcinoma
Sinonasal undifferentiated carcinoma
Sinonasal lymphoepithelial carcinoma
SW1/SNF complex deficient sinonasal carcinoma
Teratocarcinosarcoma
HPV-related multiphenotypic sinonasal carcinoma
Neuroendocrine carcinoma – Small cell neuroendocrine carcinoma – Large cell neuroendocrine carcinoma – Carcinoma admixed with neuroendocrine carcinoma
Adenocarcinoma – Intestinal-type adenocarcinoma – Non-intestinal-type adenocarcinoma – Salivary type carcinoma, specify
Other tumour type, specify – Olfactory neuroblastoma
Cannot be assessed, specify

Histological tumour type comments:

All sinonasal tumours should be classified based on the most recent edition of the WHO Classification of Head and Neck Tumours, 5th edition, 2023 (Appendix A).[8] The list of histologic types discussed in the chapter on sinonasal tumours in the WHO 5th edition does not include salivary gland type tumours or neuroendocrine tumours because they are described in sections devoted to those topics, but are still to be included here (see ICCR

Carcinomas of the major salivary glands dataset for types).[28] Neuroendocrine neoplasms, specifically carcinomas (small cell and large cell) develop in this site and are recorded here. Neuroendocrine tumours grade 1 and 2 are vanishingly rare, and thus are not specifically included, but can be entered in 'other'.

The sinonasal tract gives rise to a very large and diverse group of malignant tumours. Accurate tumour typing is important because specific tumour types are associated with different prognoses and, in some cases, different treatments.

Diagnostic accuracy is expected to take on additional importance in the future as targeted, molecular-based therapies become more prominent. While routine histologic examination has historically been the mainstay for diagnosis, an increasingly large number of sinonasal malignancies require ancillary testing to diagnose (see section on ancillary studies).[8]

RCPath additional comments:

Accurate tumour typing is essential as prognosis and therapeutic protocol are dependent on the tumour subtype.[8] Due to the wide range of tumours that occur in this anatomic region, immunohistochemistry and molecular diagnostics may be required for accurate diagnosis. Whilst routine immunohistochemical techniques to assess the expression of pan cytokeratin / specific cytokeratin's and those used for screening for undifferentiated round and spindle cell tumours are routinely available in most cellular pathology units, for other markers (such as NUT, INI1, BRG1, IDH2, NKX2.2 and INSM1), referral to specialist centres for immunohistochemical and / or molecular testing may be necessary.

A temporary diagnosis of 'Carcinoma, not otherwise specified' with an explanatory comment (further tests pending) may be given if a diagnosis cannot be further refined with the testing methods available to the pathologist.

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

7 ICCR	Descriptor	Core/Non-core	Responses
	Histological tumour grade	Core	• Not applicable • GX: Cannot be assessed • G1: Well differentiated • G2: Moderately differentiated • G3: Poorly differentiated • Undifferentiated – High grade transformation • Other, specify • Cannot be assessed, specify

Histological tumour grade comments:

The applicability of tumour grading in the sinonasal tract is dependent on the histologic type (see Table 2). Most newly described entities have no established grading scheme, but rather are known to have inherent biologic behaviour e.g., NUT carcinoma is very aggressive, while HPV-related multiphenotypic sinonasal carcinoma is relatively indolent.[29–31]

Several grading systems for each tumour type are available, with differing merits and, as such, recording which system has been applied is more clinically meaningfully (use 'specify') to state the system used according to the guidance in the current WHO Classification.[8]

Table 2: Applicable grading schemes for sinonasal tumour types

Histologic tumour type	Grading scheme
Keratinising squamous cell carcinoma	Well-, moderately-, or poorly-differentiated
Non-keratinising squamous cell carcinoma	Not applicable
NUT carcinoma	Not applicable
SWI/SNF complex-deficient sinonasal carcinoma	Not applicable
Sinonasal lymphoepithelial carcinoma	Not applicable
Sinonasal undifferentiated carcinoma	Not applicable
Neuroendocrine carcinoma	High grade
HPV-related multiphenotypic sinonasal carcinoma	Not applicable
Intestinal-type sinonasal adenocarcinoma	Emerging data to support well-, moderately-, or poorly-differentiated scheme[31]
Non-intestinal type sinonasal adenocarcinoma	Low grade or high grade
Salivary-type adenocarcinoma	See major salivary glands dataset[28]
Teratocarcinosarcoma	Not applicable

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

8 ICCR	Descriptor	Core/Non-core	Responses
	Extent of invasion	Core	• Not identified • Bone/cartilage invasion – Erosive (cortical) – Infiltrative (medullary involvement) – Soft tissue infiltration – Skull base involvement – Invasion of skin – Invasion of orbital tissues – Other, specify • Cannot be assessed, specify

Bone and/or cartilage invasion is a frequent finding in sinonasal carcinomas. Both bone erosion and destruction must be reported as part of the definition of the primary tumour in the TNM staging system.[5]

Soft tissue infiltration and skull base involvement are incorporated into the staging.

RCPath additional comments:

Depending on the tumour location, it is necessary to identify which bony wall is infiltrated as this affects staging. For example, if tumour is in maxillary sinus, mention if bony wall infiltrated is anterior, posterior, orbital floor, medial, lateral or palatal / alveolar).

[Level of evidence B – The presence of bone involvement is important for accurate staging of nasal and paranasal sinus malignancies.]

9 ICCR	**Descriptor**	**Core/Non-core**	**Responses**
	Lymphovascular invasion	Core	• Not identified • Present • Indeterminate • Cannot be assessed, specify

Lymphovascular invasion comments:

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

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

RCPath additional comments:

One small study (48 cases) indicates high grade and lymphovascular invasion had a significant association with survival outcomes in sinonasal squamous cell carcinoma.[32] Lymphovascular invasion and tumour inoperability were predictive of cancer specific survival.[33]

There is insufficient evidence to justify separating intratumoural and extratumoural vessels in reports.

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

10	**Descriptor**	**Core/Non-core**	**Responses**

ICCR	Perineural invasion	Core	• Not identified • Present • Indeterminate • Cannot be assessed, specify

Perineural invasion comments:

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.[34, 35]

In sinonasal carcinomas, perineural invasion is associated with a high rate of positive margins, with maxillary origin, and with previous surgical treatment, with variable results with respect to outcome.[36]

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

11 ICCR	**Descriptor**	**Core/Non-core**	**Responses**

	Margin status	Core	• Involved
			  – Specify margin(s), if possible
			• Not involved
			  – Distance from invasive tumour to:
			  ○ Deep margin ___ mm
			  ○ Mucosal margin ___ mm
			  – Distance not assessable.
			• Cannot be assessed, specify

Margin status comments:

As endoscopic procedures are now the predominant sinonasal tumour resections, margins are most often sent as numerous separate, fragmented specimens. Therefore, margins can usually only be reported as positive or negative, with distance to margin being impossible to determine. The significance of positive margins has been historically extrapolated from studies on oral cavity tumours[6, 37] but there is increasing evidence to support a worse outcome for sinonasal tumours as well.[34, 38–41]

Surface dysplasia and carcinoma in situ are exceedingly rare in sinonasal carcinomas, but secondary surface spread from an invasive carcinoma can be seen.[30] For the purposes of this dataset, a margin with intraepithelial carcinoma should be regarded as positive for invasive carcinoma.

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

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

12 ICCR	Descriptor	Core/Non-core	Responses
	Precursor lesions	Core	• Not applicable • Not present • Present (e.g. squamous papilloma, surface dysplasia)

Precursor lesions comments:

It is well established that sinonasal papillomas (especially the inverted and oncocytic subtypes) may give rise to sinonasal carcinomas, most often SCC but rarely other types.[42, 43] Surface dysplasia is rare in the sinonasal tract, but it is a characteristic precursor lesion in human papillomavirus (HPV)-related multiphenotypic sinonasal carcinoma.[30] It has been suggested that some sinonasal non-salivary adenocarcinomas may arise from respiratory epithelial adenomatoid hamartoma or seromucinous hamartoma, but the precursor role of these lesions is unresolved.

RCPath additional comments:

Background sinonasal mucosal pathology (hamartomatous and metaplastic changes) should be recorded as free text. Metaplastic changes may be seen near intestinal type adenocarcinomas.[44, 45]

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

13 ICCR	Descriptor	Core/Non-core	Responses
	Ancillary studies	Core and non-core (depending on diagnostic considerations)	• Not performed • Performed, specify

Ancillary tests comments:

While keratinising SSC – the most common sinonasal malignancy – can be diagnosed by routine microscopy, ancillary techniques are becoming increasingly necessary to diagnose many sinonasal tumours (see Table 3). If the specific technique is not performed, then a note to that effect should be entered, along with the most likely candidate category (i.e., if NUT immunohistochemistry is not available, state non-keratinising SSC, and suggest it may be in this category).

While parts of this element are deemed core, consideration should be given to temporarily downgrading these to non-core until resources allow.

Table 3: A summary of ancillary techniques for each sinonasal tumour type

Histologic tumour type	Ancillary techniques
Keratinising squamous cell carcinoma	Not needed in most cases (non-core).
Non-keratinising squamous cell carcinoma	Diffuse expression of squamous markers (e.g., p40, CK5/6) required (core). Negative CD99 is useful to exclude adamantinoma-like Ewing sarcoma, and negative NUT to

	exclude NUT carcinoma (non-core). Many are HPV-related, but HPV testing not currently required (non-core).
NUT carcinoma	Demonstration of *NUT* gene rearrangement or positivity with monoclonal antibody against NUT protein is required (core).[46]
SWI/SNF complex-deficient sinonasal carcinoma	Loss of expression of either SMARCB1 or SMARCA4 by immunohistochemistry is required (core).[47, 48]
Sinonasal lymphoepithelial carcinoma	Usually positive for EBV by in situ hybridisation.[49] Useful but not required (non-core).
Sinonasal undifferentiated carcinoma	Diagnosis of exclusion, so other similar-appearing entities (e.g., non-keratinising squamous cell carcinoma, NUT carcinoma, SWI/SNF complex-deficient sinonasal carcinomas) must be excluded (core).[50]
Neuroendocrine carcinoma	Positive staining with at least 1 specific neuroendocrine marker (synaptophysin, chromogranin, INSM1) and an epithelial marker required (core). Other tumours which express these markers must be excluded, e.g., olfactory neuroblastoma, teratocarcinosarcoma.
HPV-related multiphenotypic sinonasal carcinoma	HPV-specific testing (in situ hybridisation or PCR) is required (core). Testing should include type 33 which is most common.[30]
Intestinal-type sinonasal adenocarcinoma	Immunostaining with CDX2 and CK20 is useful but not required (non-core).[51]
Non-intestinal type sinonasal adenocarcinoma	Often positive for SOX10, S100, and DOG1, with a subset showing nuclear beta-catenin expression, but not required for diagnosis (non-core).[52, 53]
Salivary-type adenocarcinoma	See ICCR dataset: carcinomas of the major salivary glands. Histopathology reporting guide [28]
Teratocarcinosarcoma	SMARCA4 is often completely or partially lost, and beta-catenin staining is frequently nuclear. Useful in a limited sample, but not required to diagnose (non-core).[54]
RCPath additional comments: In poorly differentiated malignancies, immunohistochemical markers can be used to assign a tumour to a specific category. Please also refer to notes on specific tumour types (section 11). *[Level of evidence C – The basis in evidence for inclusion is well-conducted case-control or cohort studies.]*	

6 Non-core data items

NC1	Descriptor	Core/Non-core	Responses

ICCR	Tumour dimensions	Non-core	• Maximum tumour dimension (largest tumour) ___ mm • Additional dimensions (largest tumour) ___ mm x ___ mm • Cannot be assessed, specify
Tumour dimensions comments: For en-bloc resections, tumour size should be recorded based on gross examination of an unfixed specimen. In this anatomic site, however, tumour size does not affect staging. Moreover, due to the prevalence of endoscopic procedures resulting in fragmented specimens, it is often not possible to determine tumour size with accuracy. The option 'cannot be assessed' should be used in this scenario.			

7 Diagnostic coding and staging

7.1 General comments

Pathological staging should be undertaken using UICC TNM8 (Appendix B). Where there are multifocal tumours, UICC TNM8 rule 5 states that the tumour with the highest T category should be categorised, and the multifocal nature noted by the suffix (m) or the number of invasive foci noted in parenthesis.[5]

Tumours should be allocated an appropriate SNOMED/SNOMED-CT code according to the functionality of the laboratory information system. Codes for the more common tumours are provided in Appendix A.

7.2 Staging

14 ICCR	Descriptor	Core/Non-core	Responses
	Pathological staging (UICC TNM 8th edition)	Core	TNM descriptors (see Appendix B) plus, if applicable: • m – multiple primary tumours • r – recurrent • y – during or following multimodality therapy
Staging comments:			

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 evaluating clinician before treatment during initial evaluation of the patient or when pathologic classification is not possible.

Pathological staging is usually performed after surgical resection of the primary tumour and depends on documentation of the anatomic extent of disease and whether the primary tumour has been completely removed. If a biopsied tumour is not resected for any reason (e.g., when technically unfeasible) and if the highest T and N categories or the M1 category of the tumour can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied even though total removal of the primary cancer was not performed.

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.

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, the final stage grouping of a patient's tumour is based on a combination of pathological staging and other clinical and imaging information.[4, 5]

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.[4]

The reference document *TNM Supplement: A Commentary on Uniform Use (5th Edition)* may be of assistance when staging.[55]

RCPath additional comments:

Some ongoing clinical trials may be using an earlier version of the TNM classification (e.g. TNM7). If this applies, then an earlier staging scheme can be added, in addition to TNM8.

8 Reporting of small biopsy specimens

When a biopsy specimen is received, elements specific to the biopsy should be reported and the remaining items that are applicable to surgically resected tumours omitted. The data that can be obtained from small biopsy specimens will be determined, in part, by their size. The type of carcinoma and its grade are the minimum data, as these may determine treatment. It is recognised that, in large tumours, the grade in superficial biopsy material may not be representative of the most aggressive part of the invasive front. It is not realistic to assess the tumour thickness or presence of vascular invasion in small biopsies.

9 Frozen section diagnosis

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

The assessment of the presence or absence of carcinoma at surgical resection margins is the most common indication for intra-operative frozen section diagnosis. The surgeon should select the tissue for frozen section diagnosis with care, bearing in mind that it is not usually possible to section material more than 10 mm in diameter.

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

10 Support of research and clinical trials

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

11 Specific aspects of individual tumours not covered elsewhere

11.1 Keratinising squamous cell carcinoma (kSCC)

Definition: Keratinising squamous cell carcinoma (kSCC) is an epithelial malignancy originating from surface epithelium with squamous differentiation and keratin production.

Histopathology: The tumour is formed by infiltrative and proliferative atypical epithelial cells showing glassy cytoplasm, intercellular bridges and frequent keratin production.

Immunohistochemistry: This is usually not required, but kSCC expresses pan-cytokeratins, p40, p63 and CK5/6.

Comment: There is an association with occupational exposure to chemical and cigarette smoking.[56, 57] The WHO classification recognises the following subtypes: papillary squamous cell carcinoma, verrucous carcinoma, spindle cell carcinoma, acantholytic squamous cell carcinoma, adenosquamous carcinoma and carcinoma cuniculatum.

11.2 Non-keratinising squamous cell carcinoma (nkSCC)

Definition: Non-keratinising squamous cell carcinoma (nkSCC) is an epithelial malignancy of sinonasal surface origin that shows histological and immunohistochemical evidence of squamous differentiation but has no or minimal keratinisation.

Histopathology: nkSCC is arranged as nests, lobules or ribbons with a pushing invasive front and minimal desmoplastic stromal reaction. A subset display exo-endophytic papillary architecture. The cells have high nuclear to cytoplasmic ratios and lack significant keratinisation. 2 subtypes are recognised; HPV associated non-keratinising squamous cell carcinoma and DEK:AFF2 carcinoma. HPV is recognised as an aetiological factor but, while routine testing is not advocated as prognostic benefit is not proven, it may help in selected cases to distinguish from benign lesions.[58]

Immunohistochemistry: nkSCC expresses pan-cytokeratin, p63 and p40. It is negative for neuroendocrine markers, S-100, CD99 and NUT.

Molecular diagnostics: DEK:AFF2 carcinomas are defined by recurrent DEK:AFF2 fusions[59–61] and display bland cytology often with an associated acute inflammatory cell infiltrate. The clinical course is aggressive.[62]

11.3 NUT carcinoma (NC)

Definition: NUT carcinoma (NC) is an epithelial malignancy with a monotonous appearance, genetically defined by a rearrangement of the Nuclear Protein in Testis (NUTM1) gene.[8]

Histopathology: Conventional NUT carcinoma features sheets of uniform small to medium-sized round cells with minimal cytoplasm and vesicular nucleus with prominent nucleolus. Glandular or squamous differentiation are not evident, although abrupt keratinisation may be seen. Brisk mitotic activity and necrosis are often present. Variable morphology including spindle-shaped and rhabdoid forms can occur.[63, 64]

Immunohistochemistry: A monoclonal C52 NUT antibody, displaying more than 50% tumour cell nuclear staining in a speckled pattern is acceptable for diagnosis. Tumour is usually positive for pan cytokeratin and p63.[8, 63] Synaptophysin and CD34 may be positive in some.[64] False negative staining for NUT antibody and absence of cytokeratin and p40 can occur.[46]

Molecular diagnostics: Fusion of NUTM1 gene to BRD4 t (15;19) (q14; p13.1) is detected in 78% and to BRD3 in 15%. Non bromodomain translocation partners include NSD3, ZNF532 and ZNF592.[8]

Comment: Head and neck location accounts for 40% of NUT carcinoma, sinonasal sites being most frequently involved.[8]

11.4 Sinonasal undifferentiated carcinoma (SNUC)

Definition: Sinonasal undifferentiated carcinoma (SNUC) is an aggressive, high-grade tumour presenting with high T stage, without an identifiable line of differentiation (squamous, glandular or neuroendocrine).[8]

Histopathology: It features nests, lobules, trabeculae and sheets of cells with distinct cytoplasmic boundaries, moderate amount of cytoplasm and round hyperchromatic or vesicular nucleus with prominent nucleolus. Dysplasia is rarely detected in the overlying mucosal epithelium.

Immunohistochemistry: Tumour cells express AE1/AE3, Cam 5.2 and occasionally CK7. Weak, patchy neuroendocrine marker expression (synaptophysin and chromogranin), patchy p63 expression and diffuse p16 expression, without HPV DNA detection can occur. CK5, CK40, CD45, Desmin, S100 and SOX10 are negative.[65] Antibody IDH2 11C8B1 (monoclonal) is positive in many cases of SNUC with IDH2 R172S/T mutations.[66]

Molecular diagnostics: SNUC belongs to a heterogeneous group of tumours with diverse molecular anomalies and therefore a varying clinical course.[67] IDH2 hot spot mutations (IDH2p. R172S) and to a lesser extent IDH1 mutations are present in a subset of SNUC's, which therefore may be responsive to targeted therapy.[68]

Comment: SNUC is a diagnosis of exclusion. Differential diagnoses include round cell sarcoma, poorly differentiated to undifferentiated primary carcinoma (lymphoepithelial carcinoma, NUT carcinoma, SWI/SNF rearranged carcinoma), metastatic carcinoma, melanoma and lymphoproliferative, neuroendocrine, neuroectodermal and plasma cell neoplasms.

11.5 Sinonasal lymphoepithelial carcinoma (SLC)

Definition: Sinonasal lymphoepithelial carcinoma (SLC) is an undifferentiated appearing carcinoma arising within the sinonasal tract showing an associated, prominent, non-neoplastic lymphoplasmacytic cell infiltrate, strongly associated with Epstein-Barr Virus (EBV).

Histopathology: SLC comprises a syncytium of large cells arranged in lobules, nests, trabeculae and cords associated with a dense lymphoplasmacytic infiltrate. The cells are large with round nuclei, vesicular chromatin, prominent nucleoli and ill-defined cell borders and occasionally have spindle cell morphology.[69]

Immunohistochemistry/Molecular: SLC expresses pan-cytokeratins, p40, p63 and CK5/6. It is negative for neuroendocrine markers, S-100, lymphoid and melanocytic markers. EBER ISH is usually strongly positive.

11.6 SWI/SNF complex-deficient sinonasal carcinoma (SMARCB1 and SMARCA4)

Definition: Poorly differentiated to undifferentiated carcinomas defined by loss of 1 of the SWI/SNF complex subunit, either SMARCB1 or SMARCA4 and without histologic features of other specific types of carcinoma.[8]

Subtypes: SMARCB1-deficient sinonasal carcinoma, SMARCB1-deficient sinonasal adenocarcinoma, SMARCA4-deficient sinonasal carcinoma.

11.6.1 SMARCB1-deficient carcinoma

Histopathology: Tumour has varied morphology consisting of monomorphic predominantly basaloid (60%), or plasmacytoid / rhabdoid (33%) cells.[70, 71] Squamous and glandular

differentiation are not usually seen and although colonisation of surface epithelium may occur, epithelial dysplasia is not identified.[47]

Immunohistochemistry: Tumour cells are SMARCB1 (INI1) negative and positive for pan cytokeratin (AE1/AE3, Cam 5.2) (97%), variably for CK5 (64%), p63, p40 (55%) and CK7 (48%). Occasional weak, focal expression of neuroendocrine markers is seen (8–18%) and p16 is positive in some. NUT is negative. High risk HPV and EBV are not detected.[47]

11.6.2 SMARC B1 deficient adenocarcinoma

Histopathology: Tumour features oncocytoid/plasmacytoid cells with glandular differentiation, consisting of tubules and cribriform structures with intracellular or intraluminal mucin. Some present yolk sac tumour-like features. Nuclear pleomorphism, high mitotic rate and necrosis are usually present.

Immunohistochemistry: Tumour cells are SMARCB1 (INI1) negative and positive for CK7. CDX2, CK20 and p40 are occasionally positive. Some tumours, especially those displaying yolk sac tumour morphology express corresponding markers (glypican-3, SALL4, HepPar-1, PLAP and AFP).[72]

Comment: Differential diagnosis includes intestinal and non-intestinal adenocarcinoma, myoepithelial carcinoma and metastasis from non-head and neck sites, the latter in view of overlapping immunophenotype in some cases.

11.6.3 SMARCA4-deficient carcinoma

Histopathology: Tumour features undifferentiated large epithelioid cells with vesicular nuclei and prominent nucleoli, as well as rare rhabdoid and basaloid cells arranged in nests, trabeculae and sheets, with frequent necrotic areas. Squamous and glandular differentiation are not seen.

Immunohistochemistry: Tumour cells are negative for SMARCA4 (BRG1) and rarely for SMARCA2, but SMARCB1 is retained. Expression of pan cytokeratin and rarely CK7 is seen. Occasionally, there is focal, often weak expression of synaptophysin, chromogranin-A and CD56. CK5, p63, p40, p16 and NUT are negative.[71] High risk HPV and EBV are not detected.

Comment: Differential diagnosis includes small and large cell neuroendocrine carcinoma and teratocarcinosarcoma. Distinction from the former is based on neuroendocrine cytoarchitectural features and immunohistochemistry. The latter, which also displays SMARCA4 loss, can be distinguished by the presence of teratomatous components.[71]

11.7 Teratocarcinosarcoma

Definition: Teratocarcinosarcoma is a malignant sinonasal tract neoplasm with mixed epithelial, mesenchymal, and primitive neuroepithelial elements.

Histopathology: The epithelial elements can include squamous (both keratinising and non-keratinising) and glandular. The mesenchymal component is frequently hypercellular, non-descript spindle cells, although defined smooth muscle, cartilage and osteoblastic elements are described. The neuroepithelial tissues are primitive epithelioid cells with a patchy neurofibrillary background.

Immunohistochemistry: Expression commonly reflects the constituent elements; cytokeratin expression in epithelial tissues and neuroendocrine marker expression in neuroepithelial tissues. Germ cell tumour markers are negative. A subset demonstrates SMARCA4 loss and others nuclear B-catenin expression.[54, 73]

11.8 HPV-related multiphenotypic sinonasal carcinoma (HMSC)

Definition: Human papillomavirus (HPV)-related multiphenotypic sinonasal carcinoma (HMSC) is an epithelial neoplasm displaying features of both surface derived and minor salivary gland derived elements associated with transcriptionally active HPV.

Histopathology: HMSC has features of a salivary-type carcinoma, classically biphasic ductal and myoepithelial differentiation, often with cribriform architecture resembling adenoid cystic carcinoma, and a squamous cell component, often as high-grade surface dysplasia.[30]

Immunohistochemistry: The myoepithelial salivary components express p40, p63, SMA and calponin and the ductal components express CD117. Both salivary elements are positive for SOX10 and S-100. Expression of p16 is an unreliable indicator of HPV in these tumours and a HPV specific test, including HPV 33, is required for diagnosis.[74]

11.9 Sinonasal neuroendocrine carcinoma (NEC)

Head and neck neuroendocrine tumour classification in WHO 5th edition has been aligned with the WHO-IARC unified framework,[75] where the term neuroendocrine carcinoma (NEC) is only used for poorly differentiated neuroendocrine neoplasms. The NEC category is subdivided into large cell neuroendocrine carcinoma (LCNEC) and small cell neuroendocrine carcinoma (SCNEC).

11.9.1 Large cell neuroendocrine carcinoma (LCNEC)

Definition: LCNEC is a poorly differentiated neuroendocrine carcinoma composed of cells with plentiful eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli.

Histopathology: LCNEC displays nested or trabecular growth sometimes with palisading, rosette formation and central necrosis. The tumour cells are usually larger than the diameter of 3 lymphocytes and have abundant eosinophilic cytoplasm. The nuclei have coarse to speckled chromatin and prominent nucleoli. Mitoses are > 10 per mm^2.

Immunohistochemistry: LCNEC express cytokeratins, especially those of low molecular weight like CAM5.2, and neuroendocrine markers (synaptophysin, chromogranin and INSM1. The Ki-67 proliferation index is greater than 20%.

11.9.2 Small cell neuroendocrine carcinoma (SCNEC)

Definition: SCNEC is a poorly differentiated neuroendocrine carcinoma composed of epithelioid cells with scant cytoplasm, hyperchromatic nuclei, fine granular chromatin, inconspicuous nucleoli, a high mitotic count and frequent necrosis.

Histopathology: As above. The tumour cells are usually smaller than the diameter of 3 lymphocytes. Apoptotic debris and necrosis are common.

Immunohistochemistry: SCNEC express pan-cytokeratins often in a perinuclear “dot-like” pattern, and neuroendocrine markers (synaptophysin, chromogranin and INSM1).[76] TTF1 is positive in some.[77] The Ki-67 proliferation index is greater than 20%.

Comment: High grade neuroendocrine carcinoma may occasionally express p16 due to Rb loss. However, they are HPV negative and should not be misinterpreted as HPV related non-keratinising carcinoma which generally has a better prognosis.[78]

11.10 Sinonasal adenocarcinoma

Subtypes: Intestinal type, non-intestinal type, salivary type

11.10.1 Intestinal-type adenocarcinoma (ITAC)

Definition: A gland-forming malignant epithelial neoplasm of the sinonasal tract, morphologically akin to primary intestinal adenocarcinoma.

Histopathology: Tumour features variable cell types, mainly columnar cells and fewer goblet, Paneth and endocrine cells, arranged as tubules, exophytic papillary fronds, cribriform, glandular or solid islands, in an inflamed stroma. Mucous cell-rich tumours may display alveolar or cribriform pattern or scattered signet ring cells in a background of

mucinous deposits. Intestinal metaplasia is occasionally seen in the surrounding respiratory mucosa.[8] Cytological atypia, mitotic activity and necrosis are prominent in poorly differentiated tumours.

Immunohistochemistry: Tumour cells express pancytokeratin and CK20, as well as CDX2, Villin, MUC2 and SATB2.[8, 79] A proportion express CK7, CEA and neuroendocrine markers.

Molecular diagnostics: p53 is the most frequently mutated gene, whilst few display APC, KRAS and BRAF mutations. NGS has identified molecular alterations affecting pathways including PI3K, MAPK/ERK, WNT and DNA repair.[80]

Comment: Tumour has predilection for ethmoid sinus and nasal cavity and affects males in their 50s and 60s more often than females. It is high grade, presenting frequent recurrences and invasion of adjacent sites, but lymph node and distant metastasis is rare. Tumour development has a well-known association with prolonged occupational exposure to hard wood dust, as well as with leather, cork, various metals and chemicals.

11.10.2 Non intestinal type adenocarcinoma

Definition: A gland-forming malignancy lacking intestinal-type features or characteristics of salivary gland type tumours.[8]

Histopathology: Grading is binary (low and high grade), based on growth and invasion pattern, cytological atypia and mitotic activity. Low grade tumours have tubular or papillary morphology composed of crowded glands displaying complex, often cribriform architecture with minimal intervening stroma. Lining epithelium is a single layer of cuboidal to columnar cells with pale eosinophilic cytoplasm. Mitotic activity is negligible, and necrosis absent.[8] Renal cell-like adenocarcinoma is a subtype featuring cuboidal to columnar cells with clear to pale eosinophilic cytoplasm and a monomorphic low-grade appearance.[81] High grade tumours usually have a solid architecture, brisk mitotic activity, and necrosis.[82] ETV6-rearranged low-grade adenocarcinoma is composed of cuboidal to columnar cells displaying eosinophilic cytoplasm and basal nuclei, in tubulo-trabecular arrangement.

Immunohistochemistry: Tumour cells express CK7, S100, SOX10 and p53 and occasionally DOG1. Intestinal markers CDX2, villin, MUC2 and SATB2 are rare to absent and p40 is usually negative.[82] Nuclear expression of Beta catenin is seen in a subset of low-grade tumours with squamous morules.[83] Focal neuroendocrine markers may be seen in high grade tumours. ETV6 rearranged adenocarcinoma expresses CK7, SOX10, DOG1

and GCDFP15.[84] S100 is positive focally, whilst GATA3 and mammaglobin are largely negative. Renal cell like adenocarcinoma is positive for CD10 and CAIX, but negative for Pax 8 and RCC marker.[81]

Molecular diagnostics: A subset feature ETV6-NTRK/RET mutations and a few have CTNNB1 mutation.[83, 84]

Comment: Tumour affects a wide age range and predilection for nasal cavity and ethmoid is seen. Outcome is dependent on grade. Association with high-risk HPV and sinonasal papilloma seen in some high-grade tumours.

11.11 Olfactory neuroblastoma (ONB)

Definition: Malignant neuroectodermal neoplasm derived from the specialised sensory olfactory neuroepithelium.

Histopathology: Classically, uniform cells with salt and pepper chromatin arranged as well delineated lobules and nests. However, higher grade tumours show more nuclear pleomorphism, lack neuropil and display increased mitotic rates and necrosis making identification challenging.

Immunohistochemistry: Diffuse expression of synaptophysin and chromogranin with S-100 expression in sustentacular cells. Focal cytokeratin expression is acceptable. Somatostatin receptor 2 is consistently expressed in ONB; this may be of possible therapeutic benefit.[85]

Comment: Anatomically, primary ONB is confined to the cribriform plate, superior turbinate and the superior half of the nasal septum.[86] Grading using the Hyams grading system is advised as there are prognostic outcome differences.[87] There is ongoing controversy regarding the amount of keratin expression in ONB and some authors have proposed alternate entities, such as olfactory carcinoma, arising in this anatomical site to improve separation from neuroendocrine carcinoma.[88] This is an evolving area and not currently recognised in the WHO classification.

12 Criteria for audit

The following are recommended by the RCPath as key assurance and key performance indicators:[89, 90]

- cancer resections should be reported using a template or proforma, including items listed in the English COSD, which are, by definition, core data items in RCPath cancer

datasets. NHS trusts are required to implement the structured recording of core pathology data in the COSD.

  - standard: 95% of reports must contain structured data.

- histopathology cases must be reported, confirmed and authorised within 7 and 10 calendar days of the procedure.

  - standard: 80% of cases must be reported within 7 calendar days and 90% within 10 calendar days.

- The inclusion of SNOMED or SNOMED-CT codes:

  - standard: 95% reports should have T, M and P codes.

- The availability of pathology reports and data at MDT meetings:

  - standard: 90% of cases discussed at MDT meetings where biopsies or resections have been taken should have pathology reports/core data available for discussion

  - standard: 90% of cases where pathology has been reviewed for the MDT meeting should have the process of review recorded.

13 References

1. Homer JJ, Winter SC, Abbey EC, Aga H, Agrawal R, Ap Dafydd D *et al.* Head and Neck Cancer: United Kingdom National Multidisciplinary Guidelines, Sixth Edition. *J Laryngol Otol* 2024;138:S1–S224.
2. Bishop JA, Agaimy A, Bal M, Franchi A, Gallia GL, Kahn S *et al. Carcinomas of the Nasal Cavity and Paranasal Sinuses Histopathology Reporting Guide.* Accessed October 2024. Available at: www.iccr-cancer.org/datasets/published-datasets/head-neck/nasal-cavity/
3. NICE. *Cancer of the upper aerodigestive tract: assessment and management in people aged 16 and over.* Accessed October 2024. Available at: www.nice.org.uk/guidance/ng36
4. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK *et al.* (eds). *AJCC Cancer Staging Manual (8th edition)*. Springer, Switzerland: Springer Cham, 2017.
5. Brierley JD, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours (8th Edition)*. Oxford: Wiley-Blackwell, 2017.
6. Hinni ML, Ferlito A, Brandwein-Gensler MS, Takes RP, Silver CE, Westra WH *et al.* Surgical margins in head and neck cancer: a contemporary review. *Head Neck* 2013;35:1362–1370.
7. Meier JD, Oliver DA, Varvares MA. Surgical margin determination in head and neck oncology: current clinical practice. The results of an International American Head and Neck Society Member Survey. *Head Neck* 2005;27:952–958.
8. WHO Classification of Tumours Editorial Board. *Head and Neck Tumours (5th Edition)*. Lyon, France: International Agency for Research on Cancer, 2024.
9. The Royal College of Pathologists. *Tissue pathways for oral and head and neck pathology.* Accessed October 2024. Available at: www.rcpath.org/profession/guidelines/cancer-datasets-and-tissue-pathways.html
10. Slootweg PJ. Complex head and neck specimens and neck dissections. How to handle them. *J Clin Pathol* 2005;58:243–248.
11. Nibu K, Sugasawa M, Asai M, Ichimura K, Mochiki M, Terahara A *et al.* Results of multimodality therapy for squamous cell carcinoma of maxillary sinus. *Cancer* 2002;94:1476–1482.
12. Samant S, Robbins KT, Vang M, Wan J, Robertson J. Intra-arterial cisplatin and concomitant radiation therapy followed by surgery for advanced paranasal sinus cancer. *Arch Otolaryngol Head Neck Surg* 2004;130:948–955.
13. Madison Michael L, 2nd, Sorenson JM, Samant S, Robertson JH. The treatment of advanced sinonasal malignancies with pre-operative intra-arterial cisplatin and concurrent radiation. *J Neurooncol* 2005;72:67–75.
14. Licitra L, Suardi S, Bossi P, Locati LD, Mariani L, Quattrone P *et al.* Prediction of TP53 status for primary cisplatin, fluorouracil, and leucovorin chemotherapy in ethmoid sinus intestinal-type adenocarcinoma. *J Clin Oncol* 2004;22:4901–4906.
15. Meccariello G, Deganello A, Choussy O, Gallo O, Vitali D, De Raucourt D, Georgalas C. Endoscopic nasal versus open approach for the management of

sinonasal adenocarcinoma: A pooled-analysis of 1826 patients. *Head Neck* 2016;38 Suppl 1:E2267–E2274.

16. Roxbury CR, Ishii M, Richmon JD, Blitz AM, Reh DD, Gallia GL. Endonasal Endoscopic Surgery in the Management of Sinonasal and Anterior Skull Base Malignancies. *Head Neck Pathol* 2016;10:13–22.
17. Llorente JL, Lopez F, Suarez C, Hermsen MA. Sinonasal carcinoma: clinical, pathological, genetic and therapeutic advances. *Nat Rev Clin Oncol* 2014;11:460–472.
18. Ansa B, Goodman M, Ward K, Kono SA, Owonikoko TK, Higgins K *et al.* Paranasal sinus squamous cell carcinoma incidence and survival based on Surveillance, Epidemiology, and End Results data, 1973 to 2009. *Cancer* 2013;119:2602–2610.
19. Robin PE, Powell DJ, Stansbie JM. Carcinoma of the nasal cavity and paranasal sinuses: incidence and presentation of different histological types. *Clin Otolaryngol Allied Sci* 1979;4:431–456.
20. Sanghvi S, Khan MN, Patel NR, Yeldandi S, Baredes S, Eloy JA. Epidemiology of sinonasal squamous cell carcinoma: a comprehensive analysis of 4994 patients. *Laryngoscope* 2014;124:76–83.
21. Takahashi Y, Bell D, Agarwal G, Roberts D, Xie TX, El-Naggar A *et al.* Comprehensive assessment of prognostic markers for sinonasal squamous cell carcinoma. *Head Neck* 2014;36:1094–1102.
22. Turner JH, Reh DD. Incidence and survival in patients with sinonasal cancer: a historical analysis of population-based data. *Head Neck* 2012;34:877–885.
23. Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T. Nasal and paranasal sinus carcinoma: are we making progress? A series of 220 patients and a systematic review. *Cancer* 2001;92:3012–3029.
24. Thorup C, Sebbesen L, Dano H, Leetmaa M, Andersen M, Buchwald C *et al.* Carcinoma of the nasal cavity and paranasal sinuses in Denmark 1995-2004. *Acta Oncol* 2010;49:389–394.
25. Klintenberg C, Olofsson J, Hellquist H, Sokjer H. Adenocarcinoma of the ethmoid sinuses. A review of 28 cases with special reference to wood dust exposure. *Cancer* 1984;54:482–488.
26. Mitchell EH, Diaz A, Yilmaz T, Roberts D, Levine N, DeMonte F *et al.* Multimodality treatment for sinonasal neuroendocrine carcinoma. *Head Neck* 2012;34:1372–1376.
27. Smith SR, Som P, Fahmy A, Lawson W, Sacks S, Brandwein M. A clinicopathological study of sinonasal neuroendocrine carcinoma and sinonasal undifferentiated carcinoma. *Laryngoscope* 2000;110:1617–1622.
28. Thompson LDR, Bishop JA, Hyrcza MD, Ihrler S, Leivo I, Nagao T *et al.* *Carcinomas of the Major Salivary Glands Histopathology Reporting Guide.* Accessed October 2024. Available at: www.iccr-cancer.org/datasets/published-datasets/head-neck/salivary-glands/
29. Chau NG, Ma C, Danga K, Al-Sayegh H, Nardi V, Barrette R *et al.* An Anatomical Site and Genetic-Based Prognostic Model for Patients With Nuclear Protein in Testis (NUT) Midline Carcinoma: Analysis of 124 Patients. *JNCI Cancer Spectr* 2020;4:pkz094.

30. Bishop JA, Andreasen S, Hang JF, Bullock MJ, Chen TY, Franchi A *et al.* HPV-related Multiphenotypic Sinonasal Carcinoma: An Expanded Series of 49 Cases of the Tumor Formerly Known as HPV-related Carcinoma With Adenoid Cystic Carcinoma-like Features. *Am J Surg Pathol* 2017;41:1690–1701.

31. de Gabory L, Waubant A, Verillaud B, Michel J, Malard O, Rumeau C *et al.* Multicenter study to assess surgical treatments of 452 sinonasal intestinal-type adenocarcinomas: A REFCOR study. *Eur J Surg Oncol* 2023;49:39–46.

32. Parikh AS, Fuller JC, Lehmann AE, Goyal N, Gray ST, Lin DT. Prognostic Impact of Adverse Pathologic Features in Sinonasal Squamous Cell Carcinoma. *J Neurol Surg B Skull Base* 2021;82:e114–e119.

33. Wong DJ, Smee RI. Sinonasal carcinomas - A single-centre experience at Prince of Wales Hospital, Sydney, Australia, from 1994 to 2016. *J Med Imaging Radiat Oncol* 2020;64:450–459.

34. Sacks PL, Alvarado R, Sacks R, Kalish L, Campbell R, Harvey R. Prognostic factors and outcomes in minimal access resections of skull base and sinonasal epithelial malignancy. *ANZ J Surg* 2022;92:3253–3258.

35. Gil Z, Carlson DL, Gupta A, Lee N, Hoppe B, Shah JP, Kraus DH. Patterns and incidence of neural invasion in patients with cancers of the paranasal sinuses. *Arch Otolaryngol Head Neck Surg* 2009;135:173–179.

36. Schmitd LB, Scanlon CS, D'Silva NJ. Perineural Invasion in Head and Neck Cancer. *J Dent Res* 2018;97:742–750.

37. Baddour HM, Jr., Magliocca KR, Chen AY. The importance of margins in head and neck cancer. *J Surg Oncol* 2016;113:248–255.

38. Ferrari M, Mattavelli D, Tomasoni M, Raffetti E, Bossi P, Schreiber A *et al.* The MUSES *: a prognostic study on 1360 patients with sinonasal cancer undergoing endoscopic surgery-based treatment: *MUlti-institutional collaborative Study on Endoscopically treated Sinonasal cancers. *Eur J Cancer* 2022;171:161–182.

39. Arosio AD, Bernasconi DP, Valsecchi MG, Pacifico C, Battaglia P, Bignami M *et al.* Patterns of recurrences in sinonasal cancers undergoing an endoscopic surgery-based treatment: Results of the MUSES* on 940 patients: *MUlti-institutional collaborative Study on Endoscopically treated Sinonasal cancers. *Oral Oncol* 2022;134:106123.

40. Torabi SJ, Spock T, Cardoso B, Chao J, Morse E, Manes RP, Judson BL. Margins in Sinonasal Squamous Cell Carcinoma: Predictors, Outcomes, and the Endoscopic Approach. *Laryngoscope* 2020;130:E388–E396.

41. Jafari A, Shen SA, Qualliotine JR, Orosco RK, Califano JA, DeConde AS. Impact of margin status on survival after surgery for sinonasal squamous cell carcinoma. *Int Forum Allergy Rhinol* 2019;9:1205–1211.

42. Maisch S, Mueller SK, Traxdorf M, Weyerer V, Stoehr R, Iro H *et al.* Sinonasal papillomas: A single centre experience on 137 cases with emphasis on malignant transformation and EGFR/KRAS status in "carcinoma ex papilloma". *Ann Diagn Pathol* 2020;46:151504.

43. Nudell J, Chiosea S, Thompson LD. Carcinoma ex-Schneiderian papilloma (malignant transformation): a clinicopathologic and immunophenotypic study of 20 cases combined with a comprehensive review of the literature. *Head Neck Pathol* 2014;8:269–286.

44. Vivanco B, Llorente JL, Perez-Escuredo J, Alvarez Marcos C, Fresno MF, Hermsen MA. Benign lesions in mucosa adjacent to intestinal-type sinonasal adenocarcinoma. *Patholog Res Int* 2011;2011:230147.

45. Franchi A, Palomba A, Miligi L, Ranucci V, Innocenti DR, Simoni A *et al.* Intestinal metaplasia of the sinonasal mucosa adjacent to intestinal-type adenocarcinoma. A morphologic, immunohistochemical, and molecular study. *Virchows Arch* 2015;466:161–168.

46. Haack H, Johnson LA, Fry CJ, Crosby K, Polakiewicz RD, Stelow EB *et al.* Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. *Am J Surg Pathol* 2009;33:984–991.

47. Agaimy A, Hartmann A, Antonescu CR, Chiosea SI, El-Mofty SK, Geddert H *et al.* SMARCB1 (INI-1)-deficient Sinonasal Carcinoma: A Series of 39 Cases Expanding the Morphologic and Clinicopathologic Spectrum of a Recently Described Entity. *Am J Surg Pathol* 2017;41:458–471.

48. Agaimy A, Jain D, Uddin N, Rooper LM, Bishop JA. SMARCA4-deficient Sinonasal Carcinoma: A Series of 10 Cases Expanding the Genetic Spectrum of SWI/SNF-driven Sinonasal Malignancies. *Am J Surg Pathol* 2020;44:703–710.

49. Alhazzani H, Alabood S, Alhussien A, Alsadah S, Alghulikah A, Asiri S, Alarifi I. Lymphoepithelial Carcinoma Originated from the Sinonasal Cavity: Case Report and Literature Review. *Case Rep Otolaryngol* 2023;2023:4217102.

50. Agaimy A, Franchi A, Lund VJ, Skalova A, Bishop JA, Triantafyllou A *et al.* Sinonasal Undifferentiated Carcinoma (SNUC): From an Entity to Morphologic Pattern and Back Again-A Historical Perspective. *Adv Anat Pathol* 2020;27:51–60.

51. Franchi A, Massi D, Palomba A, Biancalani M, Santucci M. CDX-2, cytokeratin 7 and cytokeratin 20 immunohistochemical expression in the differential diagnosis of primary adenocarcinomas of the sinonasal tract. *Virchows Arch* 2004;445:63–67.

52. Rooper LM, Thompson LDR, Gagan J, Hwang JSG, London NR, Mikula MW *et al.* Low-grade non-intestinal-type sinonasal adenocarcinoma: a histologically distinctive but molecularly heterogeneous entity. *Mod Pathol* 2022;35:1160–1167.

53. Purgina B, Bastaki JM, Duvvuri U, Seethala RR. A Subset of Sinonasal Non-Intestinal Type Adenocarcinomas are Truly Seromucinous Adenocarcinomas: A Morphologic and Immunophenotypic Assessment and Description of a Novel Pitfall. *Head Neck Pathol* 2015;9:436–446.

54. Rooper LM, Agaimy A, Gagan J, Simpson RHW, Thompson LDR, Trzcinska AM *et al.* Comprehensive Molecular Profiling of Sinonasal Teratocarcinosarcoma Highlights Recurrent SMARCA4 Inactivation and CTNNB1 Mutations. *Am J Surg Pathol* 2023;47:224–233.

55. Wittekind C, Brierley J, Lee A, Van Eycken E. *TNM Supplement: A Commentary on Uniform Use (5th Edition)*. Oxford, UK: Wiley-Blackwell, 2019.

56. Elgart K, Faden DL. Sinonasal Squamous Cell Carcinoma: Etiology, Pathogenesis, and the Role of Human Papilloma Virus. *Curr Otorhinolaryngol Rep* 2020;8:111–119.

57. Lewis JS, Jr. Sinonasal Squamous Cell Carcinoma: A Review with Emphasis on Emerging Histologic Subtypes and the Role of Human Papillomavirus. *Head Neck Pathol* 2016;10:60–67.

58. El-Mofty SK, Lu DW. Prevalence of high-risk human papillomavirus DNA in nonkeratinizing (cylindrical cell) carcinoma of the sinonasal tract: a distinct clinicopathologic and molecular disease entity. *Am J Surg Pathol* 2005;29:1367–1372.

59. Yang W, Lee KW, Srivastava RM, Kuo F, Krishna C, Chowell D *et al.* Immunogenic neoantigens derived from gene fusions stimulate T cell responses. *Nat Med* 2019;25:767–775.

60. Bishop JA, Gagan J, Paterson C, McLellan D, Sandison A. Nonkeratinizing Squamous Cell Carcinoma of the Sinonasal Tract With DEK-AFF2: Further Solidifying an Emerging Entity. *Am J Surg Pathol* 2021;45:718–720.

61. Kuo YJ, Lewis JS, Jr., Zhai C, Chen YA, Chernock RD, Hsieh MS *et al.* DEK-AFF2 fusion-associated papillary squamous cell carcinoma of the sinonasal tract: clinicopathologic characterization of seven cases with deceptively bland morphology. *Mod Pathol* 2021;34:1820–1830.

62. Rooper LM, Agaimy A, Dickson BC, Dueber JC, Eberhart CG, Gagan J *et al.* DEK-AFF2 Carcinoma of the Sinonasal Region and Skull Base: Detailed Clinicopathologic Characterization of a Distinctive Entity. *Am J Surg Pathol* 2021;45:1682–1693.

63. Luo W, Stevens TM, Stafford P, Miettinen M, Gatalica Z, Vranic S. NUTM1-Rearranged Neoplasms-A Heterogeneous Group of Primitive Tumors with Expanding Spectrum of Histology and Molecular Alterations-An Updated Review. *Curr Oncol* 2021;28:4485–4503.

64. Bishop JA, Westra WH. NUT midline carcinomas of the sinonasal tract. *Am J Surg Pathol* 2012;36:1216–1221.

65. Wadsworth B, Bumpous JM, Martin AW, Nowacki MR, Jenson AB, Farghaly H. Expression of p16 in sinonasal undifferentiated carcinoma (SNUC) without associated human papillomavirus (HPV). *Head Neck Pathol* 2011;5:349–354.

66. Dogan S, Frosina D, Fayad M, de Oliveira TB, Alemar B, Rosenblum M *et al.* The role of a monoclonal antibody 11C8B1 as a diagnostic marker of IDH2-mutated sinonasal undifferentiated carcinoma. *Mod Pathol* 2019;32:205–215.

67. Dogan S, Vasudevaraja V, Xu B, Serrano J, Ptashkin RN, Jung HJ *et al.* DNA methylation-based classification of sinonasal undifferentiated carcinoma. *Mod Pathol* 2019;32:1447–1459.

68. Dogan S, Chute DJ, Xu B, Ptashkin RN, Chandramohan R, Casanova-Murphy J *et al.* Frequent IDH2 R172 mutations in undifferentiated and poorly-differentiated sinonasal carcinomas. *J Pathol* 2017;242:400–408.

69. Wenig BM. Lymphoepithelial-like carcinomas of the head and neck. *Semin Diagn Pathol* 2015;32:74–86.

70. Bishop JA, Antonescu CR, Westra WH. SMARCB1 (INI-1)-deficient carcinomas of the sinonasal tract. *Am J Surg Pathol* 2014;38:1282–1289.

71. Agaimy A. Proceedings of the North American Society of Head and Neck Pathology, Los Angeles, CA, March 20, 2022: SWI/SNF-deficient Sinonasal Neoplasms: An Overview. *Head Neck Pathol* 2022;16:168–178.

72. Shah AA, Jain D, Ababneh E, Agaimy A, Hoschar AP, Griffith CC *et al.* SMARCB1 (INI-1)-Deficient Adenocarcinoma of the Sinonasal Tract: A Potentially Under-

Recognized form of Sinonasal Adenocarcinoma with Occasional Yolk Sac Tumor-Like Features. *Head Neck Pathol* 2020;14:465–472.

73. Rooper LM, Uddin N, Gagan J, Brosens LAA, Magliocca KR, Edgar MA *et al.* Recurrent Loss of SMARCA4 in Sinonasal Teratocarcinosarcoma. *Am J Surg Pathol* 2020;44:1331–1339.

74. Antony VM, Kakkar A, Sikka K, Thakar A, Deo SVS, Bishop JA, Jain D. p16 Immunoexpression in sinonasal and nasopharyngeal adenoid cystic carcinomas: a potential pitfall in ruling out HPV-related multiphenotypic sinonasal carcinoma. *Histopathology* 2020;77:989–993.

75. Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E *et al.* 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* 2018;31:1770–1786.

76. Rooper LM, Bishop JA, Westra WH. INSM1 is a Sensitive and Specific Marker of Neuroendocrine Differentiation in Head and Neck Tumors. *Am J Surg Pathol* 2018;42:665–671.

77. Ordonez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. *Am J Surg Pathol* 2000;24:1217–1223.

78. Alos L, Hakim S, Larque AB, de la Oliva J, Rodriguez-Carunchio L, Caballero M *et al.* p16 overexpression in high-grade neuroendocrine carcinomas of the head and neck: potential diagnostic pitfall with HPV-related carcinomas. *Virchows Arch* 2016;469:277–284.

79. Skalova A, Sar A, Laco J, Metelkova A, Miesbauerova M, Steiner P *et al.* The Role of SATB2 as a Diagnostic Marker of Sinonasal Intestinal-type Adenocarcinoma. *Appl Immunohistochem Mol Morphol* 2018;26:140–146.

80. Sánchez-Fernández P, Riobello C, Costales M, Vivanco B, Cabal VN, García-Marín R *et al.* Next-generation sequencing for identification of actionable gene mutations in intestinal-type sinonasal adenocarcinoma. *Sci Rep* 2021;11:2247.

81. Storck K, Hadi UM, Simpson R, Ramer M, Brandwein-Gensler M. Sinonasal renal cell-like adenocarcinoma: a report on four patients. *Head Neck Pathol* 2008;2:75–80.

82. Stelow EB, Jo VY, Mills SE, Carlson DL. A histologic and immunohistochemical study describing the diversity of tumors classified as sinonasal high-grade nonintestinal adenocarcinomas. *Am J Surg Pathol* 2011;35:971–980.

83. Villatoro TM, Mardekian SK. Two Cases of Sinonasal Non-Intestinal-Type Adenocarcinoma with Squamoid Morules Expressing Nuclear beta-Catenin and CDX2: A Curious Morphologic Finding Supported by Molecular Analysis. *Case Rep Pathol* 2018;2018:8741017.

84. Andreasen S, Skalova A, Agaimy A, Bishop JA, Laco J, Leivo I *et al.* ETV6 Gene Rearrangements Characterize a Morphologically Distinct Subset of Sinonasal Low-grade Non-intestinal-type Adenocarcinoma: A Novel Translocation-associated Carcinoma Restricted to the Sinonasal Tract. *Am J Surg Pathol* 2017;41:1552–1560.

85. Cracolici V, Wang EW, Gardner PA, Snyderman C, Gargano SM, Chiosea S *et al.* SSTR2 Expression in Olfactory Neuroblastoma: Clinical and Therapeutic Implications. *Head Neck Pathol* 2021;15:1185–1191.

86. Thompson LD. Olfactory neuroblastoma. *Head Neck Pathol* 2009;3:252–259.

87. Kaur G, Kane AJ, Sughrue ME, Madden M, Oh MC, Sun MZ *et al.* The prognostic implications of Hyam's subtype for patients with Kadish stage C esthesioneuroblastoma. *J Clin Neurosci* 2013;20:281–286.

88. Rooper LM, Bishop JA, Faquin WC, Foss RD, Gallia GL, Jo VY *et al.* Sinonasal Tumors With Neuroepithelial Differentiation (Olfactory Carcinoma): Delineation of Their Pathologic and Clinical Features With Insights into Their Relationship to Olfactory Neuroblastoma and Sinonasal Carcinoma. *Am J Surg Pathol* 2022;46:1025–1035.

89. The Royal College of Pathologists. *Key assurance indicators for pathology services.* Accessed October 2024. Available at: www.rcpath.org/profession/guidelines/kpis-for-laboratory-services.html

90. The Royal College of Pathologists. *Key performance indicators.* Accessed October 2024. Available at: www.rcpath.org/profession/guidelines/kpis-for-laboratory-services.html

Appendix A SNOMED coding

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

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

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

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

WHO classification of tumours of the nasal cavity, paranasal sinuses and skull base

Morphological descriptor	SNOMED code	SNOMED CT terminology	SNOMED-CT
Keratinising squamous cell carcinoma	M-80713	Squamous cell carcinoma, keratinizing (morphologic abnormality)	18048008
Non-keratinising squamous cell carcinoma	M-80723	Squamous cell carcinoma, large cell, nonkeratinizing (morphologic abnormality)	45490001
Spindle cell squamous carcinoma	M-80743	Squamous cell carcinoma, spindle cell (morphologic abnormality)	10288008
Sinonasal lymphoepithelial carcinoma	M-80823	Lymphoepithelial carcinoma (morphologic abnormality)	7300000
Sinonasal undifferentiated carcinoma	M-8020/3	Undifferentiated carcinoma of nasal sinus (disorder)	697993003
NUT carcinoma	M-8023/3	Nuclear protein in the testis associated	733922002

		carcinoma (morphologic abnormality)	
SW1/SNF complex deficient sinonasal carcinoma	M-8044/3	SMARCA4-deficient undifferentiated tumour (morphologic abnormality)	1186933006
Teratocarcinosarcoma	M-9081/3	Teratocarcinoma (morphologic abnormality)	67830002
HPV-related multiphenotypic sinonasal carcinoma	M-8483/3	Primary undifferentiated carcinoma of nasal sinus (disorder)	1259444003
Neuroendocrine carcinoma	M-80443	Neuroendocrine carcinoma (morphologic abnormality)	1286767006
Small cell neuroendocrine carcinoma	M-8041/3	Small cell carcinoma (morphologic abnormality)	74364000
Large cell neuroendocrine carcinoma	M-8013/3	Large cell neuroendocrine carcinoma (morphologic abnormality)	128628002
Carcinoma admixed with small cell neuroendocrine carcinoma	M-8045/3	Neuroendocrine type combined small cell carcinoma (morphologic abnormality)	733844008
Carcinoma admixed with large cell neuroendocrine carcinoma	M-8013/3	Combined large cell neuroendocrine carcinoma (morphologic abnormality)	448546006
Adenocarcinoma	M-81403	Adenocarcinoma (morphologic abnormality)	1187332001
Intestinal-type adenocarcinoma	M-8144/3	Adenocarcinoma, intestinal type	25190001

		(morphologic abnormality)	
Non-intestinal-type adenocarcinoma	M-8140/3	Non-intestinal type adenocarcinoma (morphologic abnormality)	732977002
Olfactory neuroblastoma	M-95233	Olfactory neuroblastoma (morphologic abnormality)	76060004

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

SNOMED and SNOMED-CT morphology codes

Topography item	**SNOMED T code**	**SNOMED CT terminology**	**SNOMED CT code**
Nasal cavity	T-2X120	Nasal cavity structure (body structure)	279549004
Septum	T-21340	Nasal septum structure (body structure)	68426009
Floor	T-2X120	Structure of superior aspect of palate (body structure)	783037001
Lateral wall	T-2X120	Structure of lateral nasal wall (body structure)	277154009
Vestibule	T-21320	Structure of nasal vestibule (body structure)	48446007
Paranasal sinus(es), maxillary	T-22100	Maxillary sinus structure (body structure)	15924003
Paranasal sinus(es), ethmoid	T-22300	Ethmoid sinus structure (body structure)	54215007
Paranasal sinus(es), frontal	T-22200	Frontal sinus structure (body structure)	55060009

Paranasal sinus(es), sphenoid	T-22400	Sphenoid sinus structure (body structure)	24999009
Cribriform plate	T-21030	Structure of cribriform plate (body structure)	36743005
Orbit	T-Y0480	Structure of orbit proper (body structure)	363654007
Cranial cavity	T-10101	Cranial cavity structure (body structure)	1101003

Procedure codes (P)

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

Appendix B TNM classification

This provides updated information on staging using UICC TNM 8, which should be used for all tumours diagnosed after 1 January 2020.[5]

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.

Nasal cavity and ethmoid sinus

T1 Tumour restricted to 1 subsite of nasal cavity or ethmoid sinus, with or without bony invasion.

T2 Tumour involves 2 subsites in a single site or extends to involve an adjacent site within the naso-ethmoidal 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.

Residual tumour (R)

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

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

Appendix C Reporting proforma for carcinomas of the sinonasal tract

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

Neoadjuvant therapy

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

Operative procedure (Core) (select all that apply):
Not specified □
Resection: Open □ Endoscopic □ Combined □ En bloc □ Piecemeal □
specify.....
Biopsy (excisional, incisional, core biopsy) □ specify ……
Neck dissection □ specify ……

Specimens submitted (Core) (select all that apply):
Not specified □
Nasal cavity □ Left □ Right □Laterality not specified □
Paranasal sinus □ specify..... Left □ Right □ Laterality not specified □
Orbit □ specify..... Left □ Right □ Laterality not specified □
Neck (lymph node levels) □ specify..... Left □ Right □ Laterality not specified □
Other □, specify ……

Tumour site (Core) (select all that apply)

Not specified □

Nasal cavity □
Septum □
Floor □ Lateral wall □ Vestibule □
Left □ Right □ Laterality not specified □

Paranasal sinus □
Maxillary □ Left □ Right □ Laterality not specified □
Ethmoid □ Cribriform plate □
Orbit □ Left □ Right □ Laterality not specified □

Cranial cavity □ specify ……Left □ Right □ Laterality not specified □
Other: □ specify ……

Tumour dimensions (Non Core)
Maximum tumour dimension (largest tumour) …….mm
Additional dimensions …….mm
Cannot be assessed, specify ……

Histological tumour type (Core)

Multi selection value list (select all that apply):

Keratinising squamous cell carcinoma □
Other squamous cell carcinoma subtype, specify type ……
Non-keratinising squamous cell carcinoma □

NUT carcinoma □
SWI/SNF complex-deficient sinonasal carcinoma □
Sinonasal lymphoepithelial carcinoma □
Sinonasal undifferentiated carcinoma □
Teratocarcinosarcoma □
HPV-related multiphenotypic sinonasal carcinoma □

Neuroendocrine neoplasm □
Small cell neuroendocrine carcinoma □
Large cell neuroendocrine carcinoma □
Carcinoma mixed with neuroendocrine carcinoma □
Other (specify type) ……

Adenocarcinoma □
Intestinal-type adenocarcinoma □
Non-intestinal-type adenocarcinoma □
Salivary gland-type carcinoma □ specify type ……

Histological tumour grade (Core)

Not applicable □

Grade 1, well differentiated, low grade □

Grade 2, moderately differentiated, intermediate grade □

Grade 3, poorly differentiated, high grade □

Undifferentiated □

High grade transformation □

Grading system used, specify ……
Cannot be assessed, specify ……

(Use Grade 1, 2 and 3 only for neuroendocrine tumours; neuroendocrine carcinomas are considered high grade by definition and are therefore not graded).

Extent of invasion
Not identified □
Bone invasion □ / Cartilage invasion □ Erosive □ Infiltrative □
Cannot be assessed □ specify
Soft tissue infiltration □
Skull base involvement □
Invasion of skin □
Invasion of orbital tissues □
Other □ specify ……**…**
Cannot be assessed □ specify reason ……

Lymphovascular invasion
Not identified □
Present □
Indeterminate □ specify reason ……

Perineural invasion
Not identified □
Present □
Indeterminate, specify reason ……

Margin status (Core)
Invasive carcinoma
Involved □ specify location of margin(s) (if possible) ……..
Not Involved □ Specify closest margins (if possible) ……mm.
Cannot be assessed □ specify reason …….

Precursor lesions
Not applicable □
Not present □
Present (e.g., sinonasal papilloma (type), surface dysplasia), specify …….

Ancillary studies
Not performed □ Performed □
Non-keratinising squamous cell carcinoma □
Positive □ Pancytokeratin □ p40 □ p63 □ CK5/6 □ Others, specify …….
Negative □ CD99 □ NKX2.2 □ NUT □ Others, specify …….

If performed, specify (select) all that apply
INI1 □ Retained □ Deficient □ Not performed □
BRG1 □ Retained □ Deficient □ Not performed □

NUT carcinoma
Positive □
NUT immunohistochemistry □
NUTM1 gene rearrangement □, specify technique …….

SWI/SNF complex-deficient sinonasal carcinoma
INI1 Retained □ Deficient □
BRG1 Retained □ Deficient □

Sinonasal undifferentiated carcinoma
Positive □ Pancytokeratin □ CK7 □ IDH1/2 □
Negative □ p40/p63 □ CK5/6 □ CD99 □ NKX2.2 □ NUT □
INI1 Retained □ Deficient □
BRG1 Retained □ Deficient □

HPV-related multiphenotypic sinonasal carcinoma
Positive □ p16 immunohistochemistry (screening) □
Positive □ HPV-specific testing □ specify technique …….....

Neuroendocrine carcinoma
Positive □ CAM5.2/CK-pan □ Synaptophysin □ Chromogranin □ INSM1 □
Ki-67 proliferation index □ specify ……%
Rb Retained □ Deficient □

Keratinising squamous cell carcinoma
Positive □ Pancytokeratin □ p40 □ p63 □ CK5/6 □

Sinonasal lymphoepithelial carcinoma
Positive □ Pancytokeratin □ p16 □ EBER in situ hybridisation □

Teratocarcinosarcoma
Positive □ Nuclear ß-catenin □
BRG1 (SMARCA4) Retained □ Deficient □

Intestinal type adenocarcinoma
Positive □ CK20 □ CDX2 □ SATB2 □ Villin □ CK7 □

Non-intestinal-type sinonasal adenocarcinoma
Positive □ CK7 □ SOX10 □ DOG1 □ Nuclear ß-catenin □
Negative □ CK20 □ CDX2 □

Other ancillary studies: …….....

Representative blocks for ancillary studies (Best blocks with viable tumour and normal tissue):
…….....

Pathological staging (Core) (UICC TNM 8th edition, only if applicable)
pTNM stage pT.....

Appendix D Reporting proforma for carcinomas of the sinonasal tract (list format)

Core or non-core	Element name	Values
Core	Previous therapy	• Information not provided • Not administered • Administered, specify type – Chemotherapy – Radiotherapy – Targeted therapy, specify if known – Immunotherapy, specify if known
Core	Operative procedure	• Not specified OR • Biopsy, specify • Resection, specify – Open – Endoscopic – Combined – En bloc – Piecemeal • Neck (lymph node) dissection* (see separate dataset) • Other, specify
Core	Specimens submitted	• Not specified OR • Nasal cavity – Septum – Floor

		– Lateral wall – Vestibule • Paranasal sinus(es), maxillary • Paranasal sinus(es), ethmoid • Paranasal sinus(es), frontal • Paranasal sinus(es), sphenoid • Other, specify
Core	Tumour site	• Cannot be assessed OR • Nasal cavity • Septum • Floor • Lateral wall • Vestibule • Paranasal sinus(es), maxillary • Paranasal sinus(es), ethmoid • Paranasal sinus(es), frontal • Paranasal sinus(es), sphenoid • Cribriform plate • Orbit • Cranial cavity Other, specify
Core	Tumour laterality	• Not specified • Right • Left • Midline

Core	Histological tumour type	• 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
		• SW1/SNF complex deficient sinonasal carcinoma
		• Teratocarcinosarcoma
		• HPV-related multiphenotypic sinonasal carcinoma
		• Neuroendocrine carcinoma
		  – Small cell neuroendocrine carcinoma
		  – Large cell neuroendocrine carcinoma
		  – Carcinoma admixed with neuroendocrine carcinoma
		• Adenocarcinoma
		  – Intestinal-type adenocarcinoma
		  – Non-intestinal-type adenocarcinoma
		  – Salivary type carcinoma, specify
		• Other carcinoma type, specify
		• Olfactory neuroblastoma
		• Cannot be assessed, specify

Core	Histological tumour grade	• Not applicable • GX: Cannot be assessed • G1: Well differentiated • G2: Moderately differentiated • G3: Poorly differentiated

		• Undifferentiated – High grade transformation • Other, specify • Cannot be assessed, specify
Core	Extent of invasion	• Not identified • Bone/cartilage invasion – Erosive (cortical) – Infiltrative (medullary involvement) – Soft tissue infiltration – Skull base involvement – Invasion of skin – Invasion of orbital tissues – Other, specify • Cannot be assessed, specify
Core	Perineural invasion	• Not identified • Present • Indeterminate • Cannot be assessed, specify
Core	Lymphovascular invasion	• Not identified • Present • Indeterminate • Cannot be assessed, specify
Core	Margin status	• Involved – Specify margin(s), if possible • Not involved – Distance from invasive tumour to: Deep margin ___ mm Mucosal margin ___ mm Distance not assessable

		• Cannot be assessed, specify
Core	Precursor lesions	• Not applicable • Not present • Present (e.g.squamous papilloma, surface dysplasia)
Core and non-core	Ancillary studies	• Not performed • Performed, specify
Non-core	Tumour dimensions	• Maximum tumour dimension (largest tumour) ___ mm – Additional dimensions (largest tumour) – ___ mm x ___ mm • Cannot be assessed, specify

Appendix E Summary table – explanation of grades of evidence

(Modified from Palmer K *et al. BMJ* 2008;337:1832)

Grade (level) of evidence	Nature of evidence
Grade A	At least 1 high-quality meta-analysis, systematic review of randomised controlled trials or a randomised controlled trial with a very low risk of bias and directly attributable to the target cancer type or A body of evidence demonstrating consistency of results and comprising mainly well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias, directly applicable to the target cancer type.
Grade B	A body of evidence demonstrating consistency of results and comprising mainly high-quality systematic reviews of case-control or cohort studies and high-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relation is causal, and which are directly applicable to the target cancer type. or Extrapolation evidence from studies described in A.
Grade C	A body of evidence demonstrating consistency of results and including well-conducted case-control or cohort studies and high- quality case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relation is causal, and which are directly applicable to the target cancer type or Extrapolation evidence from studies described in B.
Grade D	Non-analytic studies such as case reports, case series or expert opinion or Extrapolation evidence from studies described in C.

Good practice point (GPP)	Recommended best practice based on the clinical experience of the authors of the writing group.

Appendix F AGREE II guideline monitoring sheet

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

AGREE standard	Section of guideline
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Introduction
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The views and preferences of the target population (patients, public, etc.) have been sought	Foreword
6 The target users of the guideline are clearly defined	Introduction
Rigour of development	
7 Systematic methods were used to search for evidence	Foreword
8 The criteria for selecting the evidence are clearly described	Foreword
9 The strengths and limitations of the body of evidence are clearly described	Foreword
10 The methods for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	Foreword and Introduction
12 There is an explicit link between the recommendations and the supporting evidence	All sections
13 The guideline has been externally reviewed by experts prior to its publication	Foreword
14 A procedure for updating the guideline is provided	Foreword
Clarity of presentation	
15 The recommendations are specific and unambiguous	All sections
16 The different options for management of the condition or health issue are clearly presented	All sections
17 Key recommendations are easily identifiable	All sections
Applicability	
18 The guideline describes facilitators and barriers to its application	Foreword
19 The guideline provides advice and/or tools on how the recommendations can be put into practice	Appendices A–D

20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	Section 12
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interests of guideline development group members have been recorded and addressed	Foreword