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Standards and datasets for reporting cancers
Dataset for ocular retinoblastoma histopathology reports

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	This document replaces the 2nd edition of *Dataset for ocular retinoblastoma histopathology reports*, published in 2010.
	Dr David Bailey
	Vice-President for Advocacy and Communications

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 and allowing clinicians to provide a high standard of care for patients and appropriate management for specific clinical circumstances. It may rarely be necessary or even desirable to depart from the guidelines in the interests of specific patients and special circumstances. The clinical risk of departing from the guidelines should be assessed by the relevant multidisciplinary team (MDT); just as adherence to the guidelines may not constitute defence against a claim of negligence, so a decision to deviate from them should not necessarily be deemed negligent.

Each dataset contains **core data items** 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 items 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 90% of reports on cancer resections should record a full set of core data items. Other, **non-core, data items** are described. These may be included 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.

Approval from the following stakeholders has been obtained:

- members of the British Association of Ophthalmic Pathology involved in retinoblastoma reporting

- the National Specialist Ophthalmic Pathology Service

- UK paediatric pathologists involved in retinoblastoma reporting (Birmingham and London).

The original literature search was conducted from PUBMED. Some of the evidence is classed as Grade A, many of the papers as Grade B and some as Grade C according to the criteria published by Palmer and Nairn.[6] The dataset is therefore evidence based and robust.

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 three-yearly basis. However, each year, the College will ask the author of the dataset, in conjunction with the relevant sub-specialty adviser to the College, to consider whether or not the dataset needs to be updated or 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 two weeks for members' attention. If members 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 WGCS and was on the College website for consultation with the membership from 20 October to 18 November 2014. All comments received from the WGCS and memberships were addressed by the author to the satisfaction of the WGCS Chair and the Vice-President for Advocacy and Communications.

1   Introduction

The proper handling of an eye enucleated for retinoblastoma is critical because certain macroscopic and microscopic features contribute to the staging of the tumour that determine prognosis and post-enucleation therapy. It is therefore highly recommended that retinoblastoma enucleation specimens are handled by ophthalmic pathologists working in specialist ophthalmic pathology centres or by pathologists outside specialist ophthalmic pathology centres, only if they highly experienced in handling and reporting these specimens Enucleation for retinoblastoma is done in patients with advanced intraocular disease and if there has been failure of conservative treatment.

This proposal for the reporting of ocular retinoblastoma should be implemented for the following reasons:

- staging of the disease

- the determination of whether adjuvant treatment (chemotherapy or radiotherapy) is required,[1] based on the histological identification of 'high-risk factors' (HRFs) for metastasis. These HRFs include involvement of the anterior segment structures, choroid, the sclera, extraocular spread, retrolaminar optic nerve involvement and involvement of the optic nerve surgical resection margin

- to provide prognostic information

- to provide accurate data for cancer registration

- potentially to assist in selecting patients for future trials of adjuvant therapy

- to provide data for clinical audit and effectiveness

- to provide a database for research.

The synoptic proforma (Appendix C) is based on the International Union Against Cancer/American Joint Committee on Cancer TNM staging system 7th edition.[2] The proforma may be used as the main reporting format or may be combined with free text. Further guidelines on how to dissect ophthalmic specimens for the diagnosis of ocular retinoblastoma can be found in the references at the end of this document.[3,4]

The published proceedings of the consensus meetings from the International Retinoblastoma Staging Working Group (IRSWG) on the pathology guidelines for the examination of enucleated eyes and evaluation of prognostic risk factors in retinoblastoma[4] have been a major step forward in standardising the number of blocks to be taken, the technique of fresh tissue sampling for molecular testing and the assessment of massive or significant choroidal invasion. This is now defined as a maximum diameter (thickness or width) of an invasive focus of tumour measures 3 mm or more in diameter and, additionally, as a helpful landmark, when most of these tumours reach at least the inner fibres of the scleral tissue. The proposed criterion for focal choroidal invasion has been defined as a tumour focus of less than 3 mm in any diameter (thickness or width) and not reaching the sclera. Post-IRSWG guideline validation studies have noted a difference in reporting of histological high-risk factors when comparing the pre-IRSWG and post-IRSWG histopathological handling of enucleations for retinoblastoma. More cases with massive choroidal invasion, optic nerve and anterior segment invasion have been noted with the post-IRSWG approach, resulting in more cases receiving chemotherapy.[5]

Target users and health benefits of this guideline

The target primary users of the dataset are trainee and consultant cellular pathologists and, on their behalf, the suppliers of IT products to laboratories. The secondary users are surgeons and oncologists, cancer registries and the National Cancer Intelligence Network. Standardised cancer reporting and multidisciplinary team (MDT) working reduce the risk of histological misdiagnosis and help to ensure that clinicians have all of the relevant pathological information required for tumour staging, management and prognosis. Collection of standardised cancer specific data also provides information for healthcare providers, epidemiologists, and facilitates international benchmarking and research.

2 Clinical information required on request form

- Clinical staging.

- Laterality of eye that has been enucleated/exenterated.

- Previous therapy to enucleated/exenterated eye.

- Status of other eye (unilateral/bilateral tumour).

- Family history of retinoblastoma.

- Extraocular spread noted by surgeon during enucleation.

- Any history of extraocular malignancy.

3 Specimen receipt and fresh tumour sampling

The most common specimen type is an enucleation for retinoblastoma. Very rarely, exenterations will be received.

3.1 Fresh tumour sampling

In specialist ocular pathology centres, the eyeball is usually received fresh in order for the tumour to be sampled for molecular analysis, to determine whether the tumour is of hereditary type or sporadic type. Recent international guidelines[4] have defined a consensus approach of how best to sample fresh tumour and pathologists are encouraged to refer to this publication.[4] In brief, the optic nerve is measured and the surgical resection margin is sampled first. This prevents contamination of the optic nerve margin by friable retinoblastoma tumour tissue if the globe is opened first.

The preferred technique is the opening of a window in the sclera at the edge of the area containing most of the tumour. The window can be made using a trephine or with a sharp blade. Fresh tumour is obtained from areas without necrosis.

3.2 Fixation of specimens

After sampling, enucleations usually require 24 hours fixation in 10% buffered formalin and exenterations usually 48 hours. Exenteration specimens may be complete or limited. For orientation purposes, the lashes of the upper lid are longer than those of the lower lid and the upper lid possesses a fold; the medial canthus possesses a caruncle and puncta.

4   Specimen handling and block selection

4.1   Macroscopic description

Enucleation specimens often have the following measurements taken:

- antero-posterior globe diameter (normal 22–23 mm)

- horizontal globe diameter (normal 22–23 mm)

- vertical globe diameter (normal 22–23 mm).

External inspection may reveal leukocoria,[7] a pseudohypopyon,[7] iris rubeosis[7] tumour expansion of the optic nerve surgical margin and areas of extraocular spread.

The globe may be transilluminated with a bright light source (fibre-optic). Any trans-illumination defects are noted in terms of location and size, and may be outlined on the scleral surface by ink. The tumour sampling site is noted.

Exenteration specimens are usually performed in some cases of gross extraocular retinoblastoma spread. The specimen usually has the following measurements made: maximum antero-posterior, horizontal and vertical measurements. Any relevant external features are described. The external soft tissue margins should be painted in suitable dye for margin assessment and orientation purposes.

4.2   Block taking

a) Enucleation specimens

The following four blocks should be taken: [4]

- optic nerve margin

- main tumour block with pupil and optic nerve (PO block)

- two blocks containing the calottes (remainder of ocular tissue after obtaining the PO block).

b) Exenteration specimens

For exenteration specimens, similar blocks to the above are taken:

- optic nerve resection margin

- tumour with the nearest orbital soft tissue and or cutaneous margins.

4.3   Microtomy of the specimen

The most important aspect of the microtomy is obtaining 'multiple' longitudinal sections through the optic nerve head and optic nerve (PO block). This is to assess the degree of any optic nerve invasion. There is no evidence base to inform how many sections need to be cut and examined to detect optic nerve invasion. If macroscopic extraocular spread and/or choroidal invasion is observed, these areas should be sampled for histological confirmation. There is no evidence base to support how many sections need to be cut or examined to detect massive or focal choroidal invasion, microscopic intrascleral and microscopic extraocular spread. Some authorities serially section the entire eyeball;[7] this is expensive in terms of time and resources.[8] Until an evidence base is established, this dataset is not prescriptive, as long as pupil-optic nerve block (PO), the caps and optic nerve resection margin are cut at multiple levels. Such sectioning is in line with recent international guidelines.[4]

5 Core data items

5.1 Macroscopic data

State specimen type (enucleation, partial or complete exenteration).

Number of tumour foci[9–12]

State whether unifocal or multifocal (bilateral is usually derived from clinical history). This requires histological confirmation. Sometimes it is difficult to determine this macroscopically due to tumour size or confluence. True multifocality indicates a germ-line mutation in the retinoblastoma gene[9] (see section 5.2).

[Tumour multifocality indicates germ-line mutation in retinoblastoma gene – level of evidence B.]

Choroidal invasion[4,13–18]

Macroscopically observed choroidal invasion should be confirmed histologically (see section 5.2).

[Level of evidence B.]

Extraocular spread[14,19,20]

Extraocular spread is the worst prognostic factor for death from retinoblastoma. It is associated with a ten-times greater risk of metastasis compared to intraocular confined tumours and carries a 90% mortality within two years of the diagnosis.[19] Macroscopically observed trans-scleral/extraocular extension should be confirmed histologically (see section 5.2).

[Extraocular spread is an indicator of poor prognosis – level of evidence B.]

5.2 Microscopic data

Number of tumour foci[9–12]

A macroscopic observation of suspected multifocal tumour requires histological confirmation. Sometimes, an apparently macroscopic unifocal tumour reveals microscopic multifocal tumour. It is sometimes difficult to distinguish true multifocal tumour from extensive seeding from a unifocal endophytic tumour. Artefactual seeding is composed of small groups of tumour cells, usually with many necrotic cells present inside natural spaces of the eye (e.g. vascular, choroidal and suprachoroidal space, anterior chamber, or subarachnoid space of the optic nerve).[4] It is important to distinguish a unifocal tumour from a multifocal one, as multifocality indicates a germ-line mutation in the retinoblastoma gene.[8] This has long-term prognostic implications, because the heritable form carries a greater risk of developing second malignant neoplasm,[9,10] the most common being osteosarcoma.[12]

[Tumour multifocality indicates germ-line mutation in retinoblastoma gene – level of evidence B.]

The degree of optic nerve invasion[13–15,19,21,22]

The histopathological presence of optic nerve invasion is a highly predictive factor for death from metastatic retinoblastoma. Mortality increases with increasing extent of optic nerve invasion.

The following grading applies to degree of optic nerve invasion:[4]

- prelaminar

- laminar

- retrolaminar

- tumour at optic nerve surgical margin.

Retrolaminar invasion and tumour at the surgical margin carry a worse prognosis with respect to metastatic rate and mortality. Once the tumour crosses the lamina cribrosa, there is a higher chance of tumour cells having easy access to the pia-arachnoid, with spread to the central nervous system via the cerebrospinal fluid.[13] The use of adjuvant chemotherapy for retrolaminar optic nerve invasion alone with a clear optic nerve stump is controversial.[14,18,23–25] Evidence suggests that retrolaminar optic nerve invasion with concomitant choroidal or scleral invasion is a better predictor of extraocular relapse and may benefit from adjuvant chemotherapy than retrolaminar optic nerve invasion alone.[25] Guidelines issued in the UK by the Childhood Cancer and Leukaemia Group (CCLG) recommend chemotherapy in patients with retrolaminar optic nerve involvement with or without concomitant choroidal invasion as well as for isolated optic nerve resection margin involvement.[23]

[Level of evidence B.]

Choroidal invasion[4,13–18]

Recent consensus has been reached for definitions of choroidal invasion.[4] Massive or significant choroidal invasion is defined as a maximum diameter (thickness or width) of an invasive focus of tumour measuring 3 mm or more in diameter and, additionally, as a helpful landmark, when most of these tumours reach at least the inner fibres of the scleral tissue. The proposed criterion for focal choroidal invasion has been defined as a tumour focus of less than 3 mm in any diameter (thickness or width) and not reaching the sclera. A prospective analysis of the prognostic power of these new definitions of choroidal invasion is awaited.

Guidelines issued in the UK by CCLG recommend chemotherapy to patients with "deep choroidal invasion" with or without retro-laminar optic nerve involvement.[23]

[Level of evidence A.]

Intrascleral infiltration[4,14,16,25–26]

Any degree of intrascleral invasion (via any route) is associated with choroidal invasion and is associated with extraocular recurrence and death form metastatic tumour. Recent evidence suggests benefit from adjuvant chemotherapy in reducing extraocular recurrence.[25–26]

[Level of evidence B.]

Microscopic extraocular spread[4,14,19–20]

Extraocular spread is the worst prognostic factor for death from retinoblastoma. It is associated with a ten-times greater risk of metastasis compared to intraocular confined tumours and carries 90% mortality within two years of the diagnosis.[20] It is an indication for adjuvant chemotherapy.

[Level of evidence B.]

5.3 Unfavourable histological high-risk factors (HRFs) for metastasis[14,18,23–24,27–29]

Several studies have shown that adjuvant chemotherapy prevents the development of metastatic disease in children with unfavourable histological features, despite the absence of a large randomised controlled trial. Currently identified high-risk histopathological features that are indications for adjuvant therapy (chemotherapy and radiotherapy) are:

- invasion of the anterior chamber and the anterior chamber structures (iris, ciliary body and trabecular meshwork)

- extraocular spread

- involvement of the optic nerve surgical resection margin

- retro-laminar optic nerve invasion

- intrascleral invasion

- choroidal invasion.

[Level of evidence B.]

5.4 Retinocytoma

Rarely, a retinocytoma tumour may be encountered. This is a benign retinal tumour with characteristic clinical features. These tumours are composed of benign appearing cells and fleurettes, without necrosis or mitotic figures.[31–33] In the largest series to date, there was a 4% transformation to malignant retinoblastoma.[34] The presence of a retinocytoma has similar genetic implications to retinoblastoma.[32–33]

[The presence of retinocytoma indicates germ-line mutation in retinoblastoma gene – level of evidence B.]

5.5 Effects of pre enucleation chemotherapy on the histological appearance of retinoblastoma[35-38]

Several studies have assessed the histological regression patterns of retinoblastoma after pre-enucleation chemotherapy. The changes include regression of the tumour, calcification, cystic space formation, gliosis, necrosis, basal residual well-differentiated component with retinoma-like and/or retinocytoma-like features. In some cases, thromboembolic complications can occur after intra-arterial chemotherapy.

6 Non-core data items

Macroscopic

- Size of tumour.[30]

- Vitreous seeding.[15,19]

Microscopic

- Degree of tumour differentiation:[16] there is no consensus of how to assess the degree of differentiation in ocular retinoblastoma. Whilst there is agreement that poorly differentiated/undifferentiated tumours show no rosette formation, many criteria have been proposed for the assessment of degrees of differentiation in retinoblastoma.[14–16,19] These focus on the extent of fluerettes, Flexner-Wintersteiner and Homer-Wright rosettes present.

- Tumour growth (exophytic or endophytic).[30]

- Tumour related features, e.g. iris neovascularisation[7] peripheral anterior synechiae, cataract.

- Basophilic staining of blood vessels.[19]

- Non-tumour related lesions: congenital angle or congenital corneal anomaly.

7 TNM pathological staging (7th edition UICC)[2]

The recommendation is to use the 7th edition (see Appendix A).[2] The 7th edition incorporates the recommendations of the International Retinoblastoma Staging Working Group[5] for precisely defining the degree of choroidal invasion. In the 6th edition of TNM, choroidal invasion was classed as 'focal' and 'massive' but undefined.

8 SNOMED coding

See Appendix B.

9 Reporting of small biopsy specimens

This is not applicable because fine needle aspiration cytology or open flap biopsies seed tumour, therefore these biopsy techniques are not recommended.

10 Reporting of frozen sections

Not applicable.

11 Audit criteria

Audits recommended by The Royal College of Pathologists as key performance indicators (KPIs) (see *Key Performance Indicators – Proposals for implementation*, July 2013, on www.rcpath.org/clinical-effectiveness/kpi) are as follows:

- Cancer resections must 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. English Trusts are required to implement the structured recording of core pathology data in the COSD by January 2014.

  Standard: 95% of reports must contain structured data.

- Histopathology cases that are reported, confirmed and authorised within seven and ten calendar days of the procedure.

  Standard: 80% of cases must be reported within seven calendar days and 90% within ten calendar days.

The following standard is also suggested:

- Completeness of histopathology core items recorded.

  Standard: reports should contain 100% of the core items.

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Appendix A   TNM pathological classification of ocular retinoblastoma (ICD-O C69.2) (TNM 7th edition)[2]

In bilateral cases, the eyes should be classified separately. The classification does not apply to complete spontaneous regression of the tumour. There should be histological confirmation of the disease in an enucleated eye.

The regional lymph nodes are the preauricular, submandibular, and cervical lymph nodes.

T   Primary tumour

pTX   Primary tumour cannot be assessed

pT0   No evidence of primary tumour

pT1   Tumour confined to the eye with no optic nerve or choroidal invasion

pT2   Tumour with minimal optic nerve and /or choroidal invasion

pT2a   Tumour superficially invades optic nerve head but does not extend past lamina cribrosa or tumour exhibits focal choroidal invasion

pT2b   Tumour superficially invades optic nerve head but does not extend past lamina cribrosa and exhibits focal choroidal invasion

pT3   Tumour with significant optic nerve and /or choroidal invasion

pT3a   Tumour invades optic nerve past lamina cribrosa but not to surgical resection line or tumour exhibits massive choroidal invasion

pT3b   Tumour invades optic nerve past lamina cribrosa but not to surgical resection line and exhibits massive choroidal invasion

pT4   Tumour invades optic nerve to resection line or exhibits extraocular extension elsewhere

pT4a   Tumour invades optic nerve to resection line but no extraocular extension identified

pT4b   Tumour invades optic nerve to resection line and extraocular extension identified.

pN   Regional lymph nodes

pNX   Regional lymph nodes cannot be assessed

pN0   No regional lymph node involvement

pN1   Regional lymph node involvement (preauricular, cervical)

pN2   Distant lymph node involvement.

pM   Distant metastasis

M0   No distant metastasis

pM1   Distant metastasis

pM1a   Single metastasis to sites other than CNS

pM1b   Multiple metastases to sites other than CNS

pM1c   CNS metastasis

pM1d   Discrete mass(es) without leptomeningeal and/or cerebral spinal fluid (CSF) involvement

pM1e   Leptomeningeal and/or CSF involvement.

Appendix B   SNOMED codes

SNOMED T codes

Topographical codes	SNOMED	SNOMED CT terminology	SNOMED CT code
Eye	TAA000 (SNOMED 3/RT)	Structure of eye proper (body structure)	81745001
Both eyes	TAA180 (SNOMED 3/RT)	Structure of both eyes (body structure)	40638003
Orbit	TD1480 (SNOMED 3) T-D14AD (SNOMED RT)	Entire orbital region (body structure)	39607008

SNOMED M codes

Morphological codes	SNOMED	SNOMED CT terminology	SNOMED CT code
Retinoblastoma	M95103	Retinoblastoma (morphologic abnormality)	19906005
Retinoblastoma, differentiated	M95113	Retinoblastoma, differentiated (morphologic abnormality)	26019009
Retinoblastoma, diffuse	M95133	Retinoblastoma, diffuse (morphologic abnormality)	128793008
Retinoblastoma, spontaneously regressed	M95141	Retinoblastoma, spontaneously regressed (morphologic abnormality)	128794002
Retinocytoma	M95100	Retinocytoma (morphologic abnormality)	128913004
Radiation effect on tissue	M11600	Radiation injury (morphologic abnormality)	81018009

SNOMED P (Procedure) codes

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 C   Reporting proforma for ocular retinoblastoma

Surname: .... Forenames: .... Date of birth:........................ Sex: M / F

Hospital: .... Hospital no: .... NHS/CHI number: ....

Date specimen taken: .... Date of receipt:............................ Date of reporting: ....

Report no: .... Pathologist: .... Surgeon: ....

MACROSCOPIC DESCRIPTION

Specimen type: Enucleation □   Partial exenteration □   Complete exenteration □

Site: Left eye □   Right eye □

Number of tumour foci: Unifocal □   Multifocal □   Cannot be assessed □

Ocular structures involved:

Anterior chamber □   Iris □   Angle □   Ciliary body □

Vitreous □   Optic disc □   Choroid □   Sclera □

Extraocular spread/orbit □   Cannot be assessed □

HISTOLOGY

Retinoblastoma present: Yes □   No □

Retinocytoma present   Yes □   No □

Number of tumour foci: Unifocal □   Multifocal □   Cannot be assessed □

Optic nerve invasion: Present □   Not identified □

    If optic nerve invasion present:

    Degree of optic nerve invasion: Prelaminar □   Laminar □   Retrolaminar □

    Optic nerve resection margin**:**   Involved □   Not involved □

Anterior chamber/iris/angle/ ciliary body invasion: Present □   Not identified □

Massive choroidal invasion: Present □   Not identified □

Focal choroidal invasion: Present □   Not identified □

Intrascleral invasion: Present □   Not identified □

Extrascleral /orbit invasion   Present □   Not identified □

Comments

Pathological staging   (y)pT   (y)pN   (y)pM   (TNM 7th edition)

SNOMED codes   T………../ M…………

Signature………………………   **Date**…………………

Appendix D   Proforma in list format

Element name	Values	Implementation notes
Specimen type	Single selection value list: • enucleation • partial exenteration • complete exenteration	
Site	Single selection value list: • left eye • right eye	
Number of tumour foci (macroscopic)	Single selection value list: • unifocal • multifocal • cannot be assessed	
Ocular structures involved	Multi select value list (choose all that apply) • anterior chamber • iris • angle • ciliary body • vitreous • optic disc • choroid • sclera • extraocular spread/orbit • cannot be assessed	
Retinoblastoma present	Single selection value list: • yes • no	
Retinocytoma present	Single selection value list: • yes • no	
Number of tumour foci (microscopic)	Single selection value list: • unifocal • multifocal • cannot be assessed	
Optic nerve invasion	Single selection value list: • present • not identified	
Degree of optic nerve invasion	Single selection value list: • prelaminar • laminar • retrolaminar • not applicable	Not applicable if optic nerve invasion not identified
Optic nerve resection margin	Single selection value list: • involved • not involved • not applicable	Not applicable if optic nerve invasion not identified
Anterior chamber/iris/angle/ ciliary body invasion:	Single selection value list: • present • not identified	

Focal choroidal invasion:	Single selection value list: • present • not identified	
Intrascleral invasion:	Single selection value list: • present • not identified	
Extrascleral /orbit invasion	Single selection value list: • present • not identified	
UICC TNM version 7 pT stage	Single selection value list: • pTX • pT0 • pT1 • pT2a • pT2b • pT3a • pT3b • pT4a • pT4b • ypTX • ypT0 • ypT1 • ypT2a • ypT2b • ypT3a • ypT3b • ypT4a • ypT4b	
UICC TNM version 7 pN stage	Single selection value list: • pNX • pN0 • pN1 • pN2 • ypNX • ypN0 • ypN1 • ypN2	
UICC TNM version 7 pM stage	Single selection value list: • M0 • pM1a • pM1b • pM1c • pM1d • pM1e	
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables	
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables	

Appendix E   Summary table – Explanation of levels of evidence

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

Level of evidence	Nature of evidence
Level A	At least one 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.
Level 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.
Level 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.
Level 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 monitoring sheet

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

AGREE standard	Section of dataset
Scope and purpose	
1 The overall objective(s) of the guideline is (are) specifically described	1
2 The clinical question(s) covered by the guidelines is (are) specifically described	Foreword and 1
3 The patients to whom the guideline is meant to apply are specifically described	1
Stakeholder involvement	
4 The guideline development group includes individuals from all the relevant professional groups	Foreword
5 The patients' views and preferences have been sought	N/A*
6 The target users of the guideline are clearly defined	1
7 The guideline has been piloted among target users	Feedback from previous edition
Rigour of development	
8 Systematic methods were used to search for evidence	Foreword
9 The criteria for selecting the evidence are clearly described	Foreword
10 The methods used for formulating the recommendations are clearly described	Foreword
11 The health benefits, side effects and risks have been considered in formulating the recommendations	1
12 There is an explicit link between the recommendations and the supporting evidence	3–5, 10
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	3–5
16 The different options for management of the condition are clearly presented	3–5
17 Key recommendations are easily identifiable	3–5
18 The guideline is supported with tools for application	Appendix C
Applicability	
19 The potential organisational barriers in applying the recommendations have been discussed	Foreword
20 The potential cost implications of applying the recommendations have been considered	Foreword
21 The guideline presents key review criteria for monitoring and/audit purposes	3–9
Editorial independence	
22 The guideline is editorially independent from the funding body	Foreword
23 Conflicts of interest of guideline development members have been recorded	Foreword

*   The Lay Advisory Committee (LAC) of The Royal College of Pathologists has advised that there is no reason to consult directly with patients or the public regarding this dataset because it is technical in nature and intended to guide pathologists in their practice. The authors will refer to the LAC for further advice if necessary.