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

Standards and datasets for reporting cancers

Dataset for histopathological reporting of ocular retinoblastoma

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Comments	This document will replace the 3rd edition of *Dataset for ocular retinoblastoma histopathology reports* published in 2014. In accordance with the Collegeôs pre-publications policy, this document was on The Royal College of Pathologistsôwebsite for consultation from 1 November to 29 November 2017. Responses and authorsôcomments are available to view on request. **Dr Lorna Williamson** Director of Publishing and Engagement

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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.

Each Dataset contains core data items that are mandated for inclusion in the Cancer Outcomes and Services Dataset (COSD ï 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
- National Specialist Ophthalmic Pathology Service
- UK paediatric pathologists involved in retinoblastoma reporting (Birmingham and London)
- UK ocular oncologists who look after ocular retinoblastoma patients (Birmingham and London)
- Retinoblastoma Group of the Children's Cancer and Leukaemia Group (CCLG) UK.

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 adapted SIGN criteria published by Palmer and Nairn[1] (Appendix E). Therefore, the dataset is 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 subspecialty 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 membersô 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 Clinical Effectiveness department, Working Group on Cancer Services and Lay Governance Group and placed on the College website for consultation

with the membership from 1 November to 29 November 2017. All comments received from the Working Group and membership have been addressed by the authors to the satisfaction of the Chair of the Working Group and the Director of Publishing and Engagement.

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 Clinical Effectiveness department and are available on request. The authors have declared no conflicts of interest.

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 determines prognosis and post-enucleation therapy. 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,[2] based on the histological identification of ôhistological high-risk factorsô (HHRFs) for metastasis. These HHRFs include involvement of the anterior chamber, iris, ciliary body, trabecular meshwork, Schlemmôs canal, choroid, 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
- to potentially 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 *TNM Classification of Malignant Tumours (8th edition)* from the Union for International Cancer Control (UICC).[3] The synoptic 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.[4,5]

1.1 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, oncologists, cancer registries and the National Cancer Intelligence Network. Standardised cancer reporting and multidisciplinary team 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 and epidemiologists, and facilitates international benchmarking and research.

2 Clinical information required on request form

The clinical information needed includes:

- 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 commonest specimen type is an enucleation for retinoblastoma. Very rarely, exenterations will be received.

3.1 Fresh tumour sampling

In specialist ocular pathology or paediatric 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 have defined a consensus approach of how to best sample fresh tumour and pathologists are encouraged to refer to this publication.[5] Briefly, 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 should have the following measurements taken:

- anteroï posterior globe diameter (normal 22ï 23 mm)
- horizontal globe diameter (normal 22ï 23 mm)
- vertical globe diameter (normal 22ï 23 mm).

External inspection may reveal leukocoria,[6] a pseudohypopyon,[6] iris rubeosis,[6] 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 transillumination defects are noted in terms of location and size, and should be outlined on the scleral surface by ink. The tumour sampling site should be noted.

Exenteration specimens are performed in some cases of gross extraocular retinoblastoma spread. The specimen usually has the following measurements taken: maximum anteroï posterior, horizontal and vertical. 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

4.2.1 Enucleation specimens

The following four blocks should be taken:[5]

- 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). The calottes should be bread-sliced and put on edge in order to maximise the chances of detecting choroidal, scleral and extrascleral invasion.[5]

4.2.2 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 ómultipleô 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 are 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[6] ï this is expensive in terms of time and resources.[7] Until an evidence base is established, this dataset is not prescriptive, as long as the PO block, the callotes and optic nerve resection margin are cut at multiple levels. Such sectioning is in line with recent international guidelines.[5]

5 Core data items

5.1 Macroscopic data

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

5.1.1 Number of tumour foci[8ï 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 owing to tumour size or confluence. True multifocality indicates a germline mutation in the retinoblastoma gene[9] (see section 5.2).

[Level of evidence B and C – tumour multifocality indicates germline mutation in retinoblastoma gene.]

5.1.2 Choroidal invasion[5,13ï 18]

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

[Level of evidence – B and C.]

5.1.3 Extraocular spread[5,14,19,20]

Extraocular spread is the worst prognostic factor for death from retinoblastoma. It is associated with a 10-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).

[Level of evidence B and C – extraocular spread is an indicator of poor prognosis.]

5.2 Microscopic data

5.2.1 Number of tumour foci[8ï 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).[5] It is important to distinguish a unifocal tumour from a multifocal one, as multifocality indicates a germline mutation in the retinoblastoma gene.[8] This has long-term prognostic implications, since the heritable form carries a greater risk of developing second malignant neoplasm, the commonest being osteosarcoma.[8ï 12]

[Level of evidence B and C – tumour multifocality indicates germline mutation in retinoblastoma gene.]

5.2.2 The degree of optic nerve invasion[13ï 15,19ï 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:[5]

- pre-laminar
- laminar
- post-laminar
- tumour at optic nerve surgical margin
- involvement of meningeal space.

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] In the *TNM Classification of Malignant Tumours (8th edition)* from the UICC,[3] pre-laminar and laminar invasion are classed as pT2a, post-laminar as pT3b and involvement of the optic nerve surgical margin and meningeal space as pT4.[3]

[Level of evidence – B and C.]

5.2.3 Choroidal invasion[5,13–18]

Massive or significant choroidal invasion is a solid tumour nest measuring more than 3 mm in width or thickness or multiple foci of tumour totalling more than 3 mm, or any full thickness choroidal involvement.

Focal choroidal invasion is a solid nest of tumour <3 mm in any diameter (thickness or width).

[Level of evidence – B and C.]

5.2.4 Intrascleral infiltration[5,14,16,23,24]

Any degree of intrascleral invasion (via any route) is associated with choroidal invasion and extraocular recurrence and death from metastatic tumour.

[Level of evidence – B and C.]

5.2.5 Microscopic extraocular spread[5,14,19,20]

Extraocular spread is the worst prognostic factor for death from retinoblastoma. It is associated with a 10-times greater risk of metastasis compared to intraocular confined tumours and carries a 90% mortality within two years of the diagnosis.[19] It is an indication for adjuvant chemotherapy.

[Level of evidence – B and C.]

5.3 Unfavourable HHRFs for metastasis[14,18,23–32]

Several studies have shown that adjuvant chemotherapy, with or without radiotherapy, in children with unfavourable histological features can reduce the risk of developing metastatic disease. However, there continues to be debate within the retinoblastoma clinical community about which children to treat.

Currently identified high-risk histopathological features are:

- invasion of the anterior chamber, iris, ciliary body, trabecular meshwork and Schlemm's canal
- involvement of the optic nerve surgical resection margin
- retrolaminar optic nerve invasion
- intrascleral invasion
- massive choroidal invasion
- extraocular spread.

In the UK, the presence of anterior chamber invasion, massive choroidal invasion, post-laminar optic nerve invasion and intrascleral invasion are considered to be indications for adjuvant chemotherapy following enucleation. Involvement of the optic nerve surgical margin is an indication for more intensive chemotherapy and orbital radiotherapy.[29] Children with focal choroidal invasion have an event-free survival of 99% compared with 94% in those with massive choroidal invasion.[30]

[Level of evidence – B and C.]

5.4 Retinocytoma[33–36]

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. In the largest series to date, there was a 4% transformation to malignant retinoblastoma. The presence of a retinocytoma has similar genetic implications to retinoblastoma.[33i 36]

[Level of evidence – B and C.]

6 Non-core data items

6.1 Macroscopic data

The macroscopic data required is size of tumour.[37]

6.2 Microscopic data

Items include:

- degree of tumour differentiation:[16]
  - in the *Cancer Staging Manual (8th edition)* from the American Joint Committee on Cancer (AJCC), G1 is defined as tumour with areas of retinoma (flueurettes or neuronal differentiation); G2 as tumour with many rosettes (Flexner-Wintersteiner or Homer-Wright); G3 as tumour with occasional rosettes (Flexner-Wintersteiner or Homer-Wright); and G4 as tumour with poorly differentiated cells without rosettes and/or extensive areas (more than half of the tumour) of anaplasia[38]
- tumour anaplasia
  - grading of anaplasia may be a useful measurement to standard histopathologic criteria in identifying retinoblastoma that does not have high-risk histologic features but still has an increased risk of metastasis and may need adjuvant therapy[39]
- presence of vitreous seeds, which are predictive of tumour recurrence post chemotherapy[15,19]
- tumour growth pattern (exophytic or endophytic).[3]

7 TNM pathological staging (UICC 8th edition)[3]

The recommendation is to use the *TNM Classification of Malignant Tumours (8th edition)* from the UICC (see Appendix A).[3]

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 can seed the tumour, therefore these biopsy techniques are not recommended.

10 Reporting of frozen sections

Not applicable**.**

11 Audit criteria

As recommended by the RCPath as key performance indicators (see Key Performance Indicators ï Proposals for implementation, July 2013, www.rcpath.org/profession/clinical-effectiveness/key-performance-indicators-kpi.html):

- 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.
  - standard: 95% of reports must contain structured data
- histopathology cases should be 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.

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Appendix A TNM pathological classification of ocular retinoblastoma (UICC 8th edition)[3]

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 pre-auricular, 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 intraocular invasion

- pT2a Focal choroidal invasion and pre- or intra-laminar invasion of the optic nerve head
- pT2b Tumour invasion of stroma of iris and/or trabecular meshwork and/or Schlemm's canal

pT3 Tumour with significant local invasion

- pT3a Choroidal invasion larger than 3 mm in diameter or multiple foci of invasion totalling more than 3 mm or any full thickness involvement
- pT3b Retrolaminar invasion of optic nerve without invasion of transected end of optic nerve
- pT3c Partial thickness involvement of sclera within the inner two-thirds
- pT3d Full thickness invasion into outer third of the sclera and/or invasion into or around emissary channels

pT4 Extraocular extension: Tumour invades optic nerve at transected end, in meningeal space around the optic nerve, full thickness invasion of the sclera with invasion of episclera, adipose tissue, extraocular muscle, bone, conjunctiva or eyelid

pN Regional lymph nodes

pNX Regional lymph nodes cannot be assessed

pN0 No regional lymph node involvement

pN1 Regional lymph node involvement

pM Distant metastasis

cM0 No distant metastasis

pM1 Distant metastasis

- pM1a Single or multiple metastasis to sites other than CNS
- pM1b Metastasis to CNS parenchyma of CSF fluid

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: é é é é é é é é .

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

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

MACROSCOPIC DESCRIPTION

Specimen type: Enucleation Ĭ Partial exenteration Ĭ Complete exenteration Ĭ
Other Ĭ é é é é é .

Site: Left eye Ĭ Right eye Ĭ

After sectioning:

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

Site of tumour: Clock hours:é é

Ocular structures involved

Anterior chamber Ĭ Iris Ĭ Angle Ĭ Ciliary body Ĭ Vitreous Ĭ
Optic disc Ĭ Choroid Ĭ Sclera Ĭ Extraocular spread/orbit Ĭ Cannot be assessed Ĭ

MACROSCOPIC COMMENTS

HISTOLOGY

Retinoblastoma present: Yes Ĭ No Ĭ
Retinocytoma present: Yes Ĭ No Ĭ

Structures involved by tumour:

Anterior chamber/iris/trabecular meshwork/Schlemm's canal invasion:	Present Ĭ (pT2b)	Not identified Ĭ
Focal choroidal invasion:	Present Ĭ (pT2a)	Not identified Ĭ
Massive choroidal invasion:	Present Ĭ (pT3a)	Not identified Ĭ
Scleral invasion:	Yes, Inner two-thirds Ĭ (pT3c) Yes, Outer third/full thickness Ĭ (pT3d)	Not identified Ĭ
Invasion into or around emissary channels:	Present Ĭ (pT3d)	Not identified Ĭ
Extrascleral/orbit invasion (pT4):	Present Ĭ	Not identified Ĭ

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

Optic nerve invasion: Present Ĭ Not identified Ĭ

If optic nerve invasion present:

Degree of optic nerve invasion: Pre-laminar (pT2a) Ĭ Laminar (pT2a) Ĭ Post-laminar (pT3b) Ĭ

Optic nerve resection margin: Involved (pT4) Ĭ Not involved Ĭ
Meningeal space: Involved (pT4) Ĭ Not involved Ĭ

Resection margins (for exenterations):

Involved Ĭ Not involved Ĭ Cannot be assessed Ĭ Not applicable Ĭ

HISTOLOGY COMMENTS

Pathological staging **pT** **pN** **pM** **(TNM 8th edition)**

SNOMED codes **T……../ M……**

Signatureé é é é é é é é **Date**é é é é é é .

Appendix D Reporting proforma for ocular retinoblastoma in list format

Element name	Values	Implementation notes
Specimen type	Single selection value list: Å Enucleation Å Partial exenteration Å Complete exenteration Å Other	
Specimen type, other, specify	Free text	Only applicable if 'Specimen type, Other' is selected.
Site	Single selection value list: • Left eye • Right eye	
Number of tumour foci (macroscopic)	Single selection value list: • Unifocal • Multifocal • Cannot be assessed	
Site of tumour, clock hours	Free text	
Ocular structures involved	Multiple 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	
Anterior chamber/iris/trabecular meshwork/Schlemm's canal invasion	Single selection value list: • Present • Not identified	
Focal choroidal invasion	Single selection value list: • Present • Not identified	

Massive choroidal invasion	Single selection value list: • Present • Not identified	
Scleral invasion	Single selection value list: • Yes, Inner two-thirds • Yes, Outer third/ full thickness • Not identified	
Extrascleral/orbit invasion	Single selection value list: • Present • Not identified	
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: • Pre-laminar • Laminar • Post-laminar • 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.
Meningeal space	Single selection value list: • Involved • Not involved • Not applicable	Not applicable if optic nerve invasion not identified.
Resection margins	Single selection value list: • Involved • Not involved • Cannot be assessed • Not applicable	
UICC TNM version 8 pT stage	Single selection value list: • pTX • pT0 • pT1 • pT2a • pT2b	

	• pT3a • pT3b • pT3c • pT3d • pT4 • ypTX • ypT0 • ypT1 • ypT2a • ypT2b • ypT3a • ypT3b • ypT3c • ypT3d • ypT4	
UICC TNM version 8 pN stage	Single selection value list: • pNX • pN0 • pN1 • ypNX • ypN0 • ypN1	
UICC TNM version 8 pM stage	Single selection value list: • Not applicable • pM1a • pM1b	
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 grades of evidence

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

Grade (level) of evidence	Nature of evidence
Grade 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.
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 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	Foreword and Introduction
2 The health question(s) covered by the guideline is (are) specifically described	Foreword and 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	5
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	2ï 7
16 The different options for management of the condition or health issue are clearly presented	2ï 7
17 Key recommendations are easily identifiable	2ï 7
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 Aï D
20 The potential resource implications of applying the recommendations have been considered	Foreword
21 The guideline presents monitoring and/or auditing criteria	11
Editorial independence	
22 The views of the funding body have not influenced the content of the guideline	Foreword
23 Competing interest of guideline development group members have been recorded and addressed	Foreword