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

Standards and datasets for reporting cancers

Dataset for histopathological reporting of ocular retinoblastoma

January 2025

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Unique document number	G055
Document name	Dataset for histopathological reporting of ocular retinoblastoma
Version number	5
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Date active	January 2025 **(to be implemented within 3 months)**
Date for full review	January 2028
Comments	This document will replace the 4th edition of *Dataset for ocular retinoblastoma histopathology reports*, published in 2018. In accordance with the College's pre-publications policy, this document was on the Royal College of Pathologists' website for consultation from 15 November to 13 December. Responses and authors' comments are available to view at https://www.rcpath.org/profession/publications/documents-in-development.html **Dr Brian Rous, Clinical Lead for Guideline Review**

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Registered charity in England and Wales, no. 261035

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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 and 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 (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 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 95% 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.

The following stakeholders were contacted to consult on this document:

- 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)
- the Retinoblastoma Interest Group of the Children's Cancer and Leukaemia Group UK.

The information used to develop this dataset was obtained by undertaking a systematic search of PubMed. Key terms searched included retinoblastoma, optic nerve invasion, choroidal invasion, high risk retinoblastoma, retinocytoma and dates searched were between May 2023 and September 2024. Published evidence was evaluated using modified SIGN guidance (see Appendix E). Consensus of evidence in the guideline was achieved by expert review. 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 sub-specialty adviser to the College, to consider whether 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 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 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 15 November to 13 December. 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 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 indicated in patients with advanced intraocular disease (clinical stage E and, in some cases, with clinical stage D), which may be diagnosed at presentation or following the failure of eye conserving treatment. Treatment of retinoblastoma may involve various strategies including lasers, chemotherapy and radiotherapy, details of which are beyond the scope of this publication.

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

- staging of the disease
- to determine whether adjuvant treatment (chemotherapy or radiotherapy) is required,[1] based on the histological identification of 'histological high-risk factors' (HHRFs) for metastasis. These HHRFs include involvement of the anterior chamber, iris, ciliary body, trabecular meshwork, Schlemm's 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).[2] 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.[3,4]

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 needs to include:

- clinical staging
- laterality of eye that has been enucleated/exenterated
- location of tumour
- 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 or paediatric pathology centres, the eyeball is usually received fresh for the tumour to be sampled for molecular analysis to determine whether the tumour is of hereditary type or sporadic type. International guidelines have defined a consensus approach of how to best sample fresh tumour; pathologists are encouraged to refer to this publication, which also contains drawings and photographs of sample

preparation.[4] 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. If the optic nerve is less than 10mm, then, at the pathologist's discretion, it can be sampled as above or the cut end can be inked and left intact.

In the UK, there are 2 techniques used to open the globe:

- a window can be made in the sclera perpendicular to the site where the tumour arises. The window can be made using a corneal trephine or with a sharp blade. Fresh tumour is sampled for genetics and tissue banking
- the fresh eye may be snap frozen in liquid nitrogen by full immersion for 10–15 seconds. The superior calotte is then removed with a sterile blade and tumour accessed directly for harvesting.

3.2 Fixation of specimens

After sampling, enucleations should be fixed for at least 24 hours in 10% buffered formalin and exenterations for 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:

- antero–posterior globe diameter
- horizontal globe diameter
- vertical globe diameter
- optic nerve length.

External inspection may reveal leukocoria, a pseudohypopyon, iris rubeosis, tumour expansion of the optic nerve surgical margin and areas of extraocular spread.[5] Sometimes, extensive intraocular tumour necrosis can give rise to a boggy quality to the episcleral tissues that may be misinterpreted as extraocular spread.

Transillumination of the globe anteriorly and posteriorly with a bright light source may be useful to localise the tumour site, but ideally this information should be provided by the clinical team prior to operation or with the specimen.

Exenteration specimens are performed in some cases of gross extraocular retinoblastoma spread. The specimen usually has the following measurements taken: maximum antero–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 4 blocks should be taken:[4]

- optic nerve margin
- main tumour block with pupil and optic nerve (PO block), which will be guided by transillumination findings and/or clinical information
- 2 blocks containing the calottes (remainder of ocular tissue after obtaining the PO block). The calottes should be bread-sliced and put on edge to maximise the chances of detecting choroidal, scleral and extrascleral invasion.[4]

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
- consideration should be given as to whether to embed the whole specimen.

4.3 Microtomy of the specimen

It is important to obtain 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.

Areas where clinical imaging or macroscopic examination demonstrates extraocular spread and/or choroidal invasion 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 or microscopic extraocular spread.

Some authorities serially section the entire eyeball[5] – this is expensive in terms of time and resources.[6] Until an evidence base is established, this dataset is not prescriptive, as long as the PO block, the calottes 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).

5.1.1 Choroidal invasion[4,7–12]

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

[Level of evidence B – Macroscopically observed choroidal invasion should be confirmed histologically.]

5.1.2 Extraocular spread[4,8,13,14]

Macroscopically observed trans-scleral/extraocular extension should be confirmed histologically (see section 5.2).

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

5.2 Microscopic data

5.2.1 The degree of optic nerve invasion[7–9,13–16]

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]

- 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.[7] In the *TNM Classification of Malignant Tumours (8th edition)* from the UICC,[2] 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.[2]

[Level of evidence B – Optic nerve invasion is a prognostic indicator.]

5.2.2 Choroidal invasion[4,7–12]

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. Consideration must be given to not double-count foci of tumour deposits apparent in adjacent sections.

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

Children with focal choroidal invasion have an event-free survival of 99%, compared with 94% in those with massive choroidal invasion.[17]

Artefactual spreading of clusters of tumour cells into the choroidal space is not uncommon.

[Level of evidence B – Choroidal invasion is a prognostic indicator.]

5.2.3 Intrascleral invasion[4,8,10,18]

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 – Scleral invasion is a prognostic indicator.]

5.2.4 Microscopic extraocular spread[4,8,13,14]

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 2 years of the diagnosis.[13]

[Level of evidence B – Extraocular spread is a prognostic indicator.]

5.3 Unfavourable HHRFs for metastasis[8,12,17–26]

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:

- involvement of the optic nerve surgical resection margin
- retrolaminar optic nerve invasion
- massive choroidal invasion >3 mm in any diameter, or multiple foci totalling more than 3 mm, or any full-thickness involvement
- intrascleral invasion intrascleral invasion
- extra-ocular spread
- invasion of the anterior chamber, iris, ciliary body, trabecular meshwork and Schlemm's canal
- extensive post-laminar optic nerve invasion (≥ 1.5 mm) with concomitant peripapillary massive choroidal invasion (> 3 mm).

Although not currently considered as a specific feature in the UICC staging document,[2] there is evidence that the combination of post-laminar optic nerve invasion of 1.5 mm or greater with concomitant peripapillary choroidal involvement greater than 3 mm is a higher risk for disease recurrence than if either of these features are seen singularly.[27] The combination of these features should be noted in the histology report and discussed at the local MDT in terms of whether there is a need for a higher degree of vigilance and more aggressive adjuvant chemotherapy in this scenario.

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.[24]

[Level of evidence B – High-risk histological risk factors (as listed) are indicators for adjuvant chemotherapy following enucleation.]

5.4 Retinocytoma[28–31]

Rarely, a retinocytoma (or retinoma) may be encountered. This is a benign retinal tumour composed of benign appearing cells and fleurettes, without necrosis or mitotic figures. The reported population of retinoma among the population with retinoblastoma varies from 1.8–3.2%. The presence of a retinocytoma has similar genetic implications to retinoblastoma.[28–31]

[Level of evidence B – Retinocytoma is a benign retinal tumour.]

6 Non-core data items

6.1 Macroscopic data

Items include:

- size of tumour[32]
- number of tumour foci[33–37]
- 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.

6.2 Microscopic data

Items include:

- degree of tumour differentiation:[10]
  - in the *Cancer Staging Manual (8th edition)* from the American Joint Committee on Cancer (AJCC), G1 is defined as tumour with areas of retinoma (fleurettes 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[9,13]
- tumour growth pattern (exophytic, endophytic or mixed)[2]
- tumour necrosis and/or necrosis of intraocular structure[40]
- number of tumour foci:[4]
  - a macroscopic observation of suspected multifocal tumour requires histological confirmation. Sometimes, an apparently macroscopic unifocal tumour reveals microscopic multifocal tumour. Multifocality was historically considered to be associated with germline mutations; however, the author's experience is that this correlates poorly with the genetic testing that is currently in place. 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] Please see section 6.4 Genetic testing.

[Level of evidence GPP – Other histological features of retinoblastoma should be commented on.]

6.3 Post-treatment histological features

The involvement of anterior structures by retinoblastoma occurs more commonly in the secondary enucleation group.[41]

Retinoblastoma patients who have received intra-arterial chemotherapy may demonstrate additional histological findings, including severe vascular complications (central retinal artery occlusion, vasculitis) and retinal changes (retinal detachment, retinopathy). Post-chemotherapy enucleations should be examined thoroughly for persisting viable tumour cells fulfilling criteria for histological high-risk features.[42,43]

[Level of evidence B – Post-chemotherapy changes should be commented on.]

6.4 Genetic testing

NHS Genomics now commissions all paediatric tumours for RNA and DNA next generation sequencing; this can be done as part of the case work-up on paraffin sections. If there is a record of discussion, then testing for whole genome sequencing can also be

performed on fresh frozen tumour tissue; this also requires the clinical team to send a patient blood sample.

It is important to recognise that the heritable form has prognostic implications, since the heritable form carries a greater risk of developing second malignant neoplasm, the most common being osteosarcoma.[33–37]

[Level of evidence B – Genetic findings can have implications for second tumour development.]

7 TNM pathological staging (UICC 8th edition)[2]

The recommendation is to use the *TNM Classification of Malignant Tumours (8th edition)* from the UICC (see Appendix A).[2]

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. Aqueous sampling for DNA studies is considered a research procedure at present.

10 Criteria for audit

The following are recommended by the RCPath as key assurance and key performance indicators:[44,45]

- 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 in a timely manner to enable commencement of chemotherapy as soon as possible after surgery, in line with the clinical needs, oncology guidelines and available pathologist resources.

11 References

1. Chantada G, Doz F, Antoneli CB, Grundy R, Clare Stannard FF, Dunkel IJ *et al.* A proposal for an international retinoblastoma staging system. *Pediatr Blood Cancer* 2006;47:801–805.

2. Brierley JD, Gospodarowicz MK, Wittekind C. *TNM Classification of Malignant Tumours (8th Edition)*. Oxford, UK: Wiley-Blackwell, 2017.

3. Ford AL, Mudhar HS, Farr R, Parsons MA. The ophthalmic pathology cut-up—Part 1: The enucleation and exenteration specimen. *Curr Diagn Pathol* 2005;11:284–290.

4. Sastre X, Chantada GL, Doz F, Wilson MW, de Davila MT, Rodriguez-Galindo C *et al.* Proceedings of the consensus meetings from the International Retinoblastoma Staging Working Group on the pathology guidelines for the examination of enucleated eyes and evaluation of prognostic risk factors in retinoblastoma. *Arch Pathol Lab Med* 2009;133:1199–1202.

5. Walton DS, Grant WM. Retinoblastoma and iris neovascularization. *Am J Ophthalmol* 1968;65:598–599.

6. Redler LD, Ellsworth RM. Prognostic importance of choroidal invasion in retinoblastoma. *Arch Ophthalmol* 1973;90:294–296.

7. Magramm I, Abramson DH, Ellsworth RM. Optic nerve involvement in retinoblastoma. *Ophthalmology* 1989;96:217–222.

8. Khelfaoui F, Validire P, Auperin A, Quintana E, Michon J, Pacquement H *et al.* Histopathologic risk factors in retinoblastoma: a retrospective study of 172 patients treated in a single institution. *Cancer* 1996;77:1206–1213.

9. Messmer EP, Heinrich T, Hopping W, de Sutter E, Havers W, Sauerwein W. Risk factors for metastases in patients with retinoblastoma. *Ophthalmology* 1991;98:136–141.

10. Tosi P, Cintorino M, Toti P, Ninfo V, Montesco MC, Frezzotti R *et al.* Histopathological evaluation for the prognosis of retinoblastoma. *Ophthalmic Paediatr Genet* 1989;10:173–177.

11. Shields CL, Shields JA, Baez KA, Cater J, De Potter PV. Choroidal invasion of retinoblastoma: metastatic potential and clinical risk factors. *Br J Ophthalmol* 1993;77:544–548.

12. Uusitalo MS, Van Quill KR, Scott IU, Matthay KK, Murray TG, O'Brien JM. Evaluation of chemoprophylaxis in patients with unilateral retinoblastoma with high-risk features on histopathologic examination. *Arch Ophthalmol* 2001;119:41–48.

13. Kopelman JE, McLean IW, Rosenberg SH. Multivariate analysis of risk factors for metastasis in retinoblastoma treated by enucleation. *Ophthalmology* 1987;94:371–377.

14. Rootman J, Ellsworth RM, Hofbauer J, Kitchen D. Orbital extension of retinoblastoma: a clinicopathological study. *Can J Ophthalmol* 1978;13:72–80.

15. Rootman J, Hofbauer J, Ellsworth RM, Kitchen D. Invasion of the optic nerve by retinoblastoma: a clinicopathological study. *Can J Ophthalmol* 1976;11:106–114.

16. Shields CL, Shields JA, Baez K, Cater JR, De Potter P. Optic nerve invasion of retinoblastoma. Metastatic potential and clinical risk factors. *Cancer* 1994;73:692–698.

17. Bosaleh A, Sampor C, Solernou V, Fandino A, Dominguez J, de Davila MT, Chantada GL. Outcome of children with retinoblastoma and isolated choroidal invasion. *Arch Ophthalmol* 2012;130:724–729.

18. Chantada GL, Dunkel IJ, de Davila MT, Abramson DH. Retinoblastoma patients with high risk ocular pathological features: who needs adjuvant therapy? *Br J Ophthalmol* 2004;88:1069–1073.

19. Cuenca A, Giron F, Castro D, Fandiño A, Guitter M, de Dávila MT, Chantada G. Microscopic scleral invasion in retinoblastoma: clinicopathological features and outcome. *Arch Ophthalmol* 2009;127:1006–1010.

20. Honavar SG, Singh AD, Shields CL, Meadows AT, Demirci H, Cater J, Shields JA. Postenucleation adjuvant therapy in high-risk retinoblastoma. *Arch Ophthalmol* 2002;120:923–931.

21. Wolff JA, Boesel CP, Dyment PG. Treatment of retinoblastoma: a preliminary report. *Int Congress Series* 1981;570:364–368.

22. Keith CG. Chemotherapy in retinoblastoma management. *Ophthalmic Paediatr Genet* 1989;10:93–98.

23. Haik BG, Dunleavy SA, Cooke C, Ellsworth RM, Abramson DH, Smith ME, Karcioglu ZA. Retinoblastoma with anterior chamber extension. *Ophthalmology* 1987;94:367–370.

24. Jenkinson H. Retinoblastoma: diagnosis and management – the UK perspective. *Arch Dis Child* 2015;100:1070–1075.

25. Aerts I, Sastre-Garau X, Savignoni A, Lumbroso-Le Rouic L, Thebaud-Leculée E, Frappaz D *et al.* Results of a multicenter prospective study on the postoperative treatment of unilateral retinoblastoma after primary enucleation. *J Clin Oncol* 2013;31:1458–1463.

26. Chantada G, Luna-Fineman S, Sitorus RS, Kruger M, Israels T, Leal-Leal C *et al.* SIOP-PODC recommendations for graduated-intensity treatment of retinoblastoma in developing countries. *Pediatr Blood Cancer* 2013;60:719–727.

27. Chévez-Barrios P, Eagle RC, Jr, Krailo M, Piao J, Albert DM, Gao Y *et al.* Study of unilateral retinoblastoma with and without histopathologic high-risk features and the role of adjuvant chemotherapy: A Children's Oncology Group study. *J Clin Oncol* 2019;37:2883–2891.

28. Margo C, Hidayat A, Kopelman J, Zimmerman LE. Retinocytoma. A benign variant of retinoblastoma. *Arch Ophthalmol* 1983;101:1519–1531.

29. Kratzke RA, Otterson GA, Hogg A, Coxon AB, Geradts J, Cowell JK, Kaye FJ. Partial inactivation of the RB product in a family with incomplete penetrance of familial retinoblastoma and benign retinal tumors. *Oncogene* 1994;9:1321–1326.

30. Munier FL, Beck-Popovic M, Chantada GL, Cobrinik D, Kivelä TT, Lohmann D *et al.* Conservative management of retinoblastoma: Challenging orthodoxy without compromising the state of metastatic grace. "Alive, with good vision and no comorbidity". *Prog Retin Eye Res* 2019;73:100764.

31. Abramson DH. Retinoma, retinocytoma, and the retinoblastoma gene. *Arch Ophthalmol* 1983;101:1517–1518.

32. Palazzi M, Abramson DH, Ellsworth RM. Endophytic vs exophytic unilateral retinoblastoma: is there any real difference? *J Pediatr Ophthalmol Strabismus* 1990;27:255–258.

33. Knudson AG, Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA* 1971;68:820–823.

34. Abramson DH. Second nonocular cancers in retinoblastoma: a unified hypothesis. The Franceschetti Lecture. *Ophthalmic Genet* 1999;20:193–204.

35. MacCarthy A, Bayne AM, Brownbill PA, Bunch KJ, Diggens NL, Draper GJ *et al.* Second and subsequent tumours among 1927 retinoblastoma patients diagnosed in Britain 1951–2004. *Br J Cancer* 2013;108:2455–2463.

36. Draper GJ, Sanders BM, Kingston JE. Second primary neoplasms in patients with retinoblastoma. *Br J Cancer* 1986;53:661–671.

37. Moll AC, Imhof SM, Bouter LM, Tan KE. Second primary tumors in patients with retinoblastoma. A review of the literature. *Ophthalmic Genet* 1997;18:27–34.

38. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK *et al.* (eds). *AJCC Cancer Staging Manual (8th edition)*. Cham, Switzerland: Springer, 2017.

39. Mendoza PR, Specht CS, Hubbard GB, Wells JR, Lynn MJ, Zhang Q *et al.* Histopathologic grading of anaplasia in retinoblastoma. *Am J Ophthalmol* 2015;159:764–776.

40. Chong EM, Coffee RE, Chintagumpala M, Hurwitz RL, Hurwitz MY, Chévez-Barrios P. Extensively necrotic retinoblastoma is associated with high-risk prognostic factors. *Arch Pathol Lab Med* 2006;130:1669–1672.

41. Fabian ID, Stacey AW, Chowdhury T, Duncan C, Karaa EK, Scheimberg I *et al.* High-risk histopathology features in primary and secondary enucleated International Intraocular Retinoblastoma Classification Group D Eyes. *Ophthalmology* 2017;124:851–858.

42. Biewald EM, Bornfeld N, Metz KA, Schluter S, Kiefer T, Radbruch A *et al.* Histopathology of retinoblastoma eyes enucleated after intra-arterial chemotherapy. *Br J Ophthalmol* 2020;104:1171–1175.

43. Vasalaki M, Fabian ID, Reddy MA, Cohen VM, Sagoo MS. Ocular oncology: advances in retinoblastoma, uveal melanoma and conjunctival melanoma. *Br Med Bull* 2017;121:107–119.

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

45. The Royal College of Pathologists. *Key performance indicators in pathology.* Available at: https://www.rcpath.org/profession/guidelines/kpis-for-laboratory-services.html

Appendix A TNM pathological classification of ocular retinoblastoma (UICC 8th 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 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 no.: ……

Date specimen taken: …… Date of receipt: ……

Date of reporting: …… Report no: ……

Pathologist: …… Surgeon: ……..

Macroscopic description

Specimen type

Enucleation □ Partial exenteration □ Complete exenteration □

Other □ …….

Site

Left eye □ Right eye □

After sectioning

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

Site of tumour: Clock hours:……

Ocular structures involved

Anterior chamber □ Optic disc □ Iris □ Choroid □ Angle □ Sclera □ Ciliary body □

Extraocular spread/orbit □ Vitreous □ Cannot be assessed □

Macroscopic comments

Histology

Retinoblastoma present: Yes □ No □

Retinocytoma present: Yes □ No □

Structures involved by tumour

Anterior chamber/iris/trabecular meshwork/Schlemm's canal invasion:

Present □ (pT2b) Not identified □

Focal choroidal invasion: Present □ (pT2a) Not identified □

Massive choroidal invasion: Present □ (pT3a) Not identified □

Scleral invasion:

Yes, inner two-thirds □ (pT3c) Yes, Outer third/full thickness □ (pT3d)
Not identified □

Invasion into or around emissary channels:

Present □ (pT3d) Not identified □

Extrascleral/orbit invasion (pT4):

Present □ Not identified □

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: Pre-laminar (pT2a) □ Laminar (pT2a) □
Post-laminar (pT3b) □

Optic nerve resection margin: Involved (pT4) □ Not involved □

Meningeal space: Involved (pT4) □ Not involved □

Resection margins (for exenterations):

Involved □ Not involved □ Cannot be assessed □ Not applicable □

Histology comments

Pathological staging pT pN pM (TNM 8th edition)

SNOMED codes T……. / M……

Signature…… Date…….

Appendix D Reporting proforma for ocular retinoblastoma in list format

Element name	Values	Implementation notes
Specimen type	Single selection value list: • Enucleation • Partial exenteration • Complete exenteration • 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 2-thirds • Yes, outer third/full thickness • Not identified	
Emissary channel invasion	Single selection value list: • Present • 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 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 population 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 population 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 population 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 guidelines of The Royal College of Pathologists comply with the AGREE II standards for good quality clinical guidelines. The sections of this guideline 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	2–9
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	2–9
16 The different options for management of the condition or health issue are clearly presented	2–9
17 Key recommendations are easily identifiable	2–9

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	10
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