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

Standards and datasets for reporting cancers

Dataset for histopathological reporting of uveal melanoma

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Contents

Foreword

The cancer datasets published by The Royal College of Pathologists are guidelines that should assist pathologists in providing a high standard of care for patients. Guidelines are systematically developed statements to assist the decisions of practitioners and patients about appropriate healthcare for specific clinical circumstances and are based on the best available evidence at the time the dataset was prepared. 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 – 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.

The stakeholders consulted for this document were:

- British Association for Ophthalmic Pathology
- National Specialist Ophthalmic Pathology Service
- UK ocular oncologists working in Specialised Commissioned Ocular Oncology Centres in Liverpool, London, Sheffield and Glasgow.

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.[1] The dataset is therefore evidence-based and robust.

No major organisational changes 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 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 fully 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 19 October to 16 November 2017. All comments received from the Working Group and membership will be addressed by the author 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

Uveal melanoma (UM) affects the iris, ciliary body and choroid, and mainly occurs in white Caucasian patients. UM has a particular propensity for hepatic metastasis. Most cases undergo conservative management with radiotherapy, although some cases are enucleated. Recently, there has been much interest in the genetics of UM with regard to prognostic categorisation. Tumours with monosomy 3 and gains in 8q harbour the highest risk for metastasis.[2–4] Tumours with monosomy 3 or gains in 8q are of intermediate risk, and tumours that are chromosomally balanced carry little risk for metastasis. Other molecular methods to prognosticate UM include gene expression profiling (GEP), which stratifies tumours into low-risk class 1A, intermediate-risk class 1B and high-risk class 2.[5,6] It is advisable to have access to technology that enables a genetic prognosis to be given, with these data being considered together with the clinical and histological features of the tumour to best determine metastatic risk.

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

1) to ascertain staging of the disease
2) to provide histological prognostic information
3) to provide accurate data for cancer registration
4) to potentially assist in selecting patients for future trials of adjuvant therapy
5) to provide data for clinical audit and effectiveness
6) to provide a database for research.

The synoptic proforma (Appendix C) is based on the *TNM Classification of Malignant Tumours (8th edition)*[7] from the Union for International Cancer Control (UICC) and the *Cancer Staging Manual (8th edition)*[8] from the American Joint Committee on Cancer (AJCC). Further guidelines on how to dissect ophthalmic specimens for the diagnosis of UM can be found in the references at the end of this document.[9]

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, specialist nurses, oncologists, endocrinologists and radiologists. It may also be of use to cancer registries.

2 Clinical information required on the specimen request form

The clinical information needed includes:

- age and sex of patient
- laterality of eye operated on
- clinical findings

- previous therapy to enucleated/exenterated eye
- any history of systemic malignancy
- previous biopsies.

3 Preparation of specimens before dissection

Five types of specimens are likely to be received from patients with suspected UM, usually in 10% buffered formalin. These are: iridectomies, local resections of ciliary body/choroidal melanomas (with or without iris and trabecular meshwork), endoresections, enucleations and exenterations.

Enucleations usually require 24 hours of fixation in 10% buffered formalin and exenterations usually 48 hours.

Sectoral iridectomy and localised resection specimens are often attached to a piece of sponge before receipt. The sponge keeps the specimen relatively flat and assists sectioning and preservation of planes for interpretation. If not, the specimen can be flattened between two cassette sponges overnight.

Endoresections of intraocular tumours usually present as tiny fragments in a large volume of fluid in a vitrectomy discard container.

Occasionally, sutured tantalum metal marker rings are seen over the scleral surface, indicating previous proton beam therapy. These are safe to handle and need to be removed prior to taking blocks.

In some UK ocular oncology centres, the enucleation may be sent unfixed to the pathology laboratory enabling fresh tumour sampling, which should be undertaken only under the supervision of the eye pathologist. In others, it will have had a cap removed opposite the tumour or a sclerotomy flap immediately under the tumour; these indicate portals of entry to sample fresh tumour for molecular genetics analysis or research.

Exenteration specimens are rarely taken for UM and may be complete or limited. Complete exenteration comprises removal of the eyelids, the globe, optic nerve, extraocular muscles, orbital fat and periosteum. 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 punctae.

4 Specimen handling and block selection

4.1 Macroscopic description

4.1.1 Iridectomy

The overall dimensions of the specimen and tumour are recorded. Painting the circumferential margins may facilitate orientation during microscopy.

4.1.2 Local resection

The specimen and tumour dimensions are recorded. The circumferential margins may be painted to facilitate measurement to the nearest margin at histology.

4.1.3 Endoresections

The total volume of fluid is estimated, along with a description of the floating tissue fragments.

4.1.4 Enucleation

Enucleation specimens often have the following measurements made:

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

The vortex veins are identified as they pass obliquely through the scleral canals.

If the globe does not have a sampling sclerotomy to disclose the location of the tumour, the globe should be transilluminated with a bright light source (fibre optic). Any shadows are noted in terms of location and size, and may be outlined on the scleral surface by ink. The shadow usually corresponds to the location of the intraocular tumour. Any gross extraocular spread of tumour is noted.

After sampling the vortex veins and optic nerve margin, the eyeball is usually sliced in the antero-posterior plane. The plane of section is dependent on the findings of external examination and transillumination. This will determine whether the initial slice will be horizontal, vertical or oblique. The aim is to end up with a central antero-posterior segment that includes the pupil, optic nerve and the main central bulk of the tumour.

The following observations are recorded after slicing the globe:

- which uveal compartment is involved (iris/ciliary body/choroid)
- tumour height and base size
- evidence of extraocular invasion
- growth pattern: focal solid mass, diffuse, ring. With small tumours, it is sometimes better to determine the growth pattern histologically (5.2.1)
- which intraocular structures are involved by the tumour. With small tumours, it is often better to determine this histologically (5.1.1)
- some authorities measure the location of the tumour from the ora serrata or optic disc edge.

4.1.5 Exenteration

Exenterations are performed in some cases of gross extraocular UM extension. The following measurements are usually 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. The specimen is usually ‘bread-sliced’ from side to side and the intraocular contents, along with any extraocular lesions, described as for an enucleation.

4.2 Block taking

4.2.1 Iridectomy specimens

The following blocks are taken:

- main tumour with nearest margin
- all circumferential margins sampled separately if possible.

4.2.2 Local resection of ciliary body and choroid

The following blocks are taken:

- main tumour with nearest margin

- all circumferential margins sampled separately if possible.

4.2.3 Endoresections

For endoresections, the fluid is spun down and the specimen handled as a cell block.

4.2.4 Enucleation specimens

The following blocks are taken:

- optic nerve margin
- vortex veins
- main tumour block with pupil and optic nerve
- calotte/cap blocks if necessary.

The optic nerve margin and vortex veins are sampled before slicing into the globe, to prevent contamination of these margins by tumour. A section of the optic nerve is taken, usually 3–4 mm behind its junction with the sclera; leaving a stump facilitates microtomy. The vortex veins are usually located 5–9 mm from the optic nerve, at 2, 5, 7 and 10 o'clock. However, there can be considerable variation in the number and locations of the veins. The vortex veins are cut transversely across, at the point where they exit the scleral canals. If a length of vortex vein is not demonstrable, some advocate making two parallel cuts into the scleral canal to, in effect, de-roof it and remove the vortex vein from the canal.

Vortex veins should be embedded longitudinally to maximise the chance of detecting intravascular UM. Vortex veins can be placed into one cassette, or if one particular vortex vein is thought to contain tumour, this could be submitted in a separate cassette.

4.2.5 Exenteration specimens

For exenteration specimens, similar blocks to the above are taken (except that it will be difficult to obtain a vortex vein sample owing to the presence of orbital soft tissue) and include:

- optic nerve resection margin
- tumour with the nearest orbital soft tissue and or cutaneous margins.

5 Core data items

5.1 Macroscopic data

5.1.1 Site of tumour

Iris melanomas are associated with a much lower mortality compared to their ciliary and choroidal counterparts,[10,11] with mortality rates ten-times lower than those for melanomas of other uveal sites.[12] Ciliary body melanomas behave comparatively worse than iris and choroid melanomas.[7,13–16]

[Level of evidence – B.]

5.1.2 Size of tumour

Tumour size (scleral basal diameter and maximum thickness) is an important prognostic factor for ciliary body and choroidal melanomas.[14–17] The 5-year mortality rates are 16%, 32% and 53% for 'small', 'medium' and 'large' tumours, respectively.[18,19] The Collaborative Ocular Melanoma Study (COMS) [20–23] has defined the following size classification based on clinical measurements:

- small tumours: smaller than medium or large tumours defined below
- medium tumours: ≥2.5 mm and ≤10 mm in maximum thickness, and ≤16 mm in basal diameter
- large tumours: >10 mm in height, or >2 mm in maximum thickness and >16 mm in basal diameter, or >8 mm in maximum thickness with optic nerve involvement.

The UICC/AJCC classification of posterior UMs (tumour size category) is predictive of prognosis.[7,8] It does not use the above COMS classification of tumours, rather the 7th UICC/AJCC TNM staging of UM designed a system on the basis of >3,300 tumours. The reader is referred to the appropriate texts[7,8,15] and Appendix A.

The most accurate tumour measurements are usually made pre-operatively by ultrasound. If the melanoma has been sampled by the surgeon after the enucleation, one can only record the size of the residual mass.

[Level of evidence – B.]

5.1.3 Extraocular extension

Extraocular extension carries a worse outcome compared to those melanomas confined to the eye[13, 23–28] and is independently associated with a higher metastatic risk. This can occur directly through the scleral collagen, perineurally, perivascularly or intravascularly into the emissary, vortex vein[27] or aqueous blood vessels.

The *TNM Classification of Malignant Tumours (8th edition)*[7] from the UICC and the *Cancer Staging Manual (8th edition)*[8] from the AJCC further subclassifies the size of the extraocular component as ≤5 mm or >5 mm.

[Level of evidence – B.]

5.2 Microscopic data

5.2.1 Growth pattern of tumour

State whether the tumour is a focal solid mass, diffuse or of ring type.

Diffuse UM is defined as a tumour thickness of 20% or less than the greatest basal dimension.[29] It grows along the choroidal plane with little focal elevation. Ring melanoma affects the anterior chamber angle and grows circumferentially along the trabecular meshwork and adjacent anterior chamber angle structures. Ring and diffuse patterns are associated with a worse prognosis and higher metastatic rate compared to a focal solid mass.[30–32]

[Level of evidence – B.]

5.2.2 Cell types present

The modified Callender classification is used for determining cell type. This has prognostic significance for tumours of the choroid and ciliary body but not for the iris.[32–35] State whether the tumour is spindle, epithelioid or mixed. Spindle A cells exhibit a slender oval nucleus, with a characteristic longitudinal nuclear groove, fine chromatin, an indistinct nucleolus and indistinct cytoplasmic borders. Spindle B cells show a plumper open nucleus, coarse chromatin and a distinct eosinophilic nucleolus, with indistinct cytoplasmic borders. Epithelioid cells are polygonal, exhibit marked nuclear pleomorphism, irregular nuclear contours, with coarse clumped chromatin, eosinophilic prominent nucleoli but with a distinct cytoplasmic border. There is no difference in prognosis between a spindle A or B cell[35] and therefore calling a melanoma ‘spindle’ type (not otherwise specified) is acceptable. Spindle

cell melanoma has a comparatively better outcome, compared with mixed and epithelioid melanomas. The prognosis worsens with an increase in epithelioid cell content.[32–35]

The AJCC has defined the histopathological tumour types with respect to cell types as follows:[8]

- spindle cell melanoma (>90% spindle cells)
- mixed cell melanoma (>10% epithelioid cells and <90% spindle cells)
- epithelioid cell melanoma (>90% epithelioid).

It is recommended that the proportion of epithelioid cells is estimated in mixed cell melanomas, owing to the large size of this group, and that the dominant cell type is noted in the report.

[Level of evidence – B.]

5.2.3 Extraocular invasion

Quite often, microscopic extraocular invasion is detected when it was not seen at gross examination.

Extraocular extension carries a worse outcome compared to those melanomas confined to the eye.[13,23–28] This can occur directly through the scleral collagen, perineurally, perivascularly or intravascularly into the emissary, vortex vein[28] or aqueous blood vessels.

The *TNM Classification of Malignant Tumours (8th edition)*[7] from the UICC and the *Cancer Staging Manual (8th edition)*[8] from the AJCC further subclassifies the size of the extraocular component as ≤5 mm or >5 mm.

Extraocular vortex vein invasion is associated with a choroidal location, large tumour size and adverse genetic tumour signatures.[26]

[Level of evidence – B.]

5.2.4 Mitotic count[36–38]

This is independently associated with metastatic risk, with higher counts associated with shorter survival. A total of 40 high power fields are counted with each field having an area of 0.15–0.19 mm^2 (recommended field size is 0.152 mm^2).

[Level of evidence – C.]

5.2.5 Extracellular matrix patterns

On the largest tumour face, a periodic acid-Schiff (PAS) stain can be carried out, without counter stain, to assess the tumour extracellular matrix patterns.

Nine morphologic patterns of extracellular matrix deposition have been defined for ciliary body or choroidal melanomas.[39,40] Most tumours have a heterogeneous PAS distribution. The presence of extracellular ‘closed loops’ and networks (a network is defined as at least three back-to-back closed loops) is a feature strongly associated with death from metastatic disease.[40–42]

[Level of evidence – B.]

6 Non-core data items

6.1 Macroscopic data

Items include:

- size of specimen

6.2 Microscopic data

Items include:

- tumour necrosis[43]
- presence of melanin pigmentation[19]
- degree of lymphocytic infiltration[44,45]
- breach of Bruch's membrane[46]
- optic nerve extension.[47]

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

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

8 SNOMED coding

See Appendix B.

9 Reporting of small biopsy specimens

In specialist ocular oncology centres, aspiration cytology (iris, ciliary body and choroid – the latter via a trans-vitreous approach) and open-flap biopsies are usually undertaken to distinguish between a UM, metastasis or benign neoplasm, prior to treatment. Aspiration cytology specimens are handled as cytospins and cell blocks. These preparations often yield enough material for immunohistochemistry and molecular prognosis. The iris and choroid are amenable to direct biopsy. These specimens are small and require careful handling to ensure ancillary investigations such as immunohistochemistry and molecular studies are possible, to secure a firm diagnosis.

10 Reporting of frozen sections

Not applicable.

11 Specific aspects of individual tumours not covered elsewhere

11.1 Molecular testing[48–52]

Loss of chromosome 1p, monosomy 3, gain of 6p, loss of 6q, loss of 8p and gain of 8q have been linked statistically to metastatic death in UM. Monosomy 3 is at present the most significant. There are a variety of molecular and cytogenetic prognostic tests available (karyotyping, fluorescence in situ hybridisation, comparative genomic hybridisation,

microsatellite analysis, single-nucleotide polymorphism, multiplex ligation-dependent probe amplification, UM GEP). While this dataset relates to histopathological prognostic factors, it is highly recommended that pathologists reporting ciliary body and choroidal melanomas have access to some form of molecular or cytogenetic testing and, as a minimum, communicate the status of chromosome 3.

11.2 Iris cytology[53,54]

Care is required when interpreting surface aspiration cytology specimens of suspected melanoma of the iris. It is now thought that aqueous humour induces iris melanoma cells to adopt low-grade cytology, which resemble naevus cells. Finding such cells in an aspiration specimen does not exclude melanoma. In such circumstances, a formal iris biopsy is required to sample the deeper stromal melanoma cells. These deeper cells are usually more atypical and permit a secure diagnosis of melanoma to be made. The biopsy also allows for a better assessment of the architecture of the iris, and the location of any atypical cells, increasing the likelihood of achieving a definite diagnosis and differentiation between a benign or malignant melanocytic lesion.

12 Criteria for audit of the dataset

The following standards are suggested:

- completeness of histopathology core items recorded
  - standard: reports should contain 100% of the core items.

While no standards exist for the following, it is suggested that it would be beneficial to monitor:

- proportion of cases in each ‘T’ category (pTNM) and prognosis
- proportions of spindle, mixed and epithelioid tumours.

13 References

1 Palmer K, Nairn M. Management of acute gastrointestinal blood loss: summary of SIGN guidelines. *BMJ* 2008;337:1832.

2 Hammond DW, Al-Shammari NS, Danson S, Jacques R, Rennie IG, Sisley K. High resolution array CGH identifies regional deletions and amplifications of chromosome 8 in uveal melanoma. *Invest Ophthalmol Vis Sci* 2015;56:3460–3466.

3 Caines R, Eleuteri A, Kalirai H, Fisher AC, Heimann H, Damato BE *et al*. Cluster analysis of multiplex ligation-dependent probe amplification data in choroidal melanoma. *Mol Vis* 2015;21:1–11.

4 Cassoux N, Rodrigues MJ, Plancher C, Asselain B, Levy-Gabriel C, Lumbrosi-Le Rouic L *et al*. Genome-wide profiling in a clinically relevant and affordable prognostic test in posterior uveal melanoma *Br J Ophthalmol* 2014;98:769–774.

5 Onken MD, Worley LA, Ehlers JP, Harbour JW. Gene expression profiling in uveal melanoma reveals two molecular classes and predicts metastatic death. *Cancer Res* 2004;64:7205–7209.

6 Onken WD, Worley LA, Char DH, Augsburger JJ, Correa ZM, Nudleman E *et al.* Collaborative Ocular Oncology Group report 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. *Ophthalmology* 2012;119:1596–1603.

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

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

9 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.

10 Shields CL, Shields JA, Materin M, Gershenbaum E, Singh AD, Smith A. Iris melanoma: risk factors for metastasis in 169 consecutive patients. *Ophthalmology* 2001;108:172–178.

11 Rones B, Zimmerman LE. The prognosis of primary tumors of the iris treated by iridectomy. *AMA Arch Ophthalmol* 1958;60:193–205.

12 McLean IW, Foster WD, Zimmerman LE. Uveal melanoma: location, size, cell type, and enucleation as risk factors in metastasis. *Hum Pathol* 1982;13:123–132.

13 Seddon JM, Albert DM, Lavin PT, Robinson N. A prognostic factor study of disease-free interval and survival following enucleation for uveal melanoma. *Arch Ophthalmol* 1983;101:1894–1899.

14 Shields CL, Furuta M, Thangappan A, Nagori S, Mashayekhi A, Lally DR *et al.* Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. *Arch Ophthalmol* 2009;127:989–998.

15 Kujala E, Damato B, Coupland SE, Desjardins L, Bechrakis NE, Grange JD *et al*. Staging of ciliary body and choroidal melanomas based on anatomic extent. *J Clin Oncol* 2013;31:2825–2831.

16 Li W, Gragoudas ES, Egan KM. Metastatic melanoma death rates by anatomic site after proton beam irradiation for uveal melanoma. *Arch Ophthalmol 2000*; 118:1066–1070.

17 AJCC Ophthalmic Oncology Task Force. International validation of the American Joint Committee on Cancer's 7th Edition classification of uveal melanoma. *JAMA Ophthalmology* 2015;133:376–383.

18 Diener-West M, Hawkins BS, Markowitz JA, Schachat AP. A review of mortality from choroidal melanoma. II. A meta-analysis of 5-year mortality rates following enucleation, 1966 through 1988. *Arch Ophthalmol* 1992;110:245–250.

19 McLean MJ, Foster WD, Zimmerman LE. Prognostic factors in small malignant melanomas of choroid and ciliary body. *Arch Ophthalmol* 1977;95:48–58.

20 The Collaborative Ocular Melanoma Study Group. Design and methods of a clinical trial for a rare condition: the Collaborative Ocular Melanoma Study. COMS Report No. 3. *Control Clin Trials* 1993;14:362–391.

21 Collaborative Ocular Melanoma Study Group. *COMS Manual of Procedures*. Springfield, VA, USA: National Technical Information Service, 1989.

22 Shields CL, Kaliki S, Furuta M, Fulco E, Alarcon C, Shields JA. American Joint Committee on Cancer classification of posterior uveal melanoma (tumor size category) predicts prognosis in 7731 patients. *Ophthalmology* 2013;120:2066–2071.

23 Collaborative Ocular Melanoma Study Group. Histopathologic characteristics of uveal melanoma in eyes enucleated from the Collaborative Ocular Melanoma Study COMS report no. 6. *Am J Ophthalmol* 1998;125:745–766.

24 Shammas HF, Blodi FC. Orbital extension of choroidal and ciliary body melanoma. *Arch Ophthalmol* 1977;95:2002–2005.

25 Affeldt JC, Minckler DS, Azen SP, Yeh L. Prognosis in uveal melanoma with extrascleral extension. *Arch Ophthalmol* 1980;98:1975–1979.

26 Coupland SE, Campbell I, Damato B. Routes of extraocular extension of uveal melanoma: risk factors and influence on survival probability. *Ophthalmology* 2008;115:1778–1785.

27 Raoof N, Rennie IG, Salvi SM, Sisley K, Caine A, Mudhar HS. What is the significance of vortex vein invasion in uveal melanoma? *Eye (Lond)* 2009;23:1661–1667.

28 Van Beek JGM, Koopmans AE, Vaarwater J, de Rooi JJ, Paridaens D, Naus NC *et al.* The prognostic value of extraocular extension in relation to monosomy 3 and gain of chromosome 8q in uveal melanoma. *Invest Ophthalmol Vis Sci* 2014;55:1284–1291.

29 Shields CL, Shields JA, De Potter P, Cater J, Tardio D, Barrett J. Diffuse choroidal melanoma. Clinical features predictive of metastasis. *Arch Ophthalmol* 1996;114:956–963.

30 Shields CL, Kaliki S, Furuta M, Shields JA. Diffuse versus nondiffuse small (≤3 mm thickness) choroidal melanoma: comparative analysis in 1,751 cases. The 2012 F. Phinizy Calhoun lecture. *Retina* 2013;33:1763–1776.

31 Demerci H, Shields CL, Shields JA, Eagle RC Jr, Honavar S. Ring melanoma of the anterior chamber angle: a report of fourteen cases. *Am J Ophthalmol* 2001;132:336–342.

32 Demerci H, Shields CL, Shields JA, Honavar S, Eagle RC Jr. Ring melanoma of the ciliary body: report on twenty-three patients. *Retina* 2002;22:698–706.

33 Callender GR. Malignant melanotic tumors of the eye: a study of histologic types in 111 cases. *Trans Am Acad Ophthalmol Otolaryngol* 1931;36:131–142.

34 McLean IW, Zimmerman LE, Evans RM. Reappraisal of Callender's spindle a type of malignant melanoma of choroid and ciliary body. *Am J Ophthalmol* 1978;86:557–564.

35 McLean IW, Foster WD, Zimmerman LE, Gamel JW. Modifications of Callender's classification of uveal melanoma at the Armed Forces Institute of Pathology. *Am J Ophthalmol* 1983;96:502–509.

36 Damato B, Dopierala JA, Coupland SE. Genotypic profiling of 452 choroidal melanomas with multiplex ligation-dependent probe amplification. *Clin Cancer Res* 2010;16:6083–6092.

37 Angi M, Damato B, Kalirai H, Dodson A, Taktak A, Coupland SE. Immunohistochemical assessment of mitotic count in uveal melanoma. *Acta Ophthalmol* 2011;89:155–160.

38 Grossniklaus HE, Finger PT, Harbour JW, Kivëla. *Protocol for the Examination of Specimens From Patients With Uveal Melanoma.* Accessed December 2017. Available at: http://www.cap.org/ShowProperty?nodePath=/UCMCon/Contribution%20Folders/WebContent/pdf/cp-uvealmelanom-16protocol-3300.pdf

39 Folberg R, Pe'er J, Gruman LM, Woolson RF, Jeng G, Montague PR *et al*. The morphologic characteristics of tumour blood vessels as a marker of tumour progression in primary human uveal melanoma: a matched case-control study. *Hum Pathol* 1992;23;1298–1305.

40 Folberg R, Rummelt V, Parys-Van Ginderdeuren R, Hwang T, Woolson RF, Pe'er J *et al.* The prognostic value of tumor blood vessel morphology in primary uveal melanoma. *Ophthalmology* 1993;100:1389–1398.

41 Rummelt V, Folberg R, Woolson RF, Hwag T, Pe'er J. Relation between the microcirculation architecture and the aggressive behaviour of ciliary body melanomas. *Ophthalmology* 1995; 102:844–851.

42 Rummelt V, Folberg R, Rummelt C, Gruman LM, Heang T, Woolson RF *et al*. Microcirculation architecture of melanocytic nevi and malignant melanomas of the ciliary body and choroid. A comparative histopathologic and ultrastructural study. *Ophthalmology* 1994;101:718–727.

43 McClean IW, Shields JA. Prognostic value of 32P uptake in posterior uveal melanomas. *Ophthalmology* 1980;87:543–548.

44 Durie FH, Campbell AM, Lee WR, Damato BE. Analysis of lymphocytic infiltration in uveal melanoma. *Invest Ophthalmol Vis Sci.* 1990;31:2106–2110.

45 de la Cruz PO Jr, Specht CS, McLean IW. Lymphocytic infiltration in uveal malignant melanoma. *Cancer* 1990; 65:112–115.

46 Shammas HF, Blodi FC. Prognostic factors in choroidal and ciliary body melanomas. *Arch Ophthalmol* 1977;95:63–69.

47 Weinhaus RS, Seddon JM, Albert DM, Gragoudas ES, Robinson N. Prognostic factors: study of survival after enucleation for juxtapapillary melanomas. *Arch Ophthalmol* 1985;103:1673–1677.

48 Prescher G, Bornfield N, Becher R. Nonrandom chromosomal abnormalities in primary uveal melanoma. *J Natl Cancer Inst* 1990;82:1765–1769.

49 Sisley K, Rennie IG, Parsons MA, Jacques R, Hammond DW, Bell SM *et al*. Abnormalities of chromosomes 3 and 8 in posterior uveal melanoma correlate with prognosis. *Genes Chromosomes Cancer* 1997;19:22–28.

50 Onken MD, Worley LA, Char DH, Augsburger JJ, Correa ZM, Nudleman E *et al.* Collaborative Ocular Oncology Group report number 1: prospective validation of a multi-gene prognostic assay in uveal melanoma. *Ophthalmology* 2012;119:1596–603.

51 Coupland SE, Lake SL, Zeschniqk M, Damato BE. Molecular pathology of uveal melanoma. *Eye (Lond)* 2013;27:230–242.

52 Vaarwater J, van den Bosch T, Mensink HW, van Kempen C, Verdijk RM, Naus NC *et al*. Multiplex ligation-dependent probe amplification equals fluorescence in-situ hybridization for the identification of patients at risk for metastatic disease in uveal melanoma. *Melanoma Res* 2012;22:30–37.

53 Mudhar HS, Saunders E, Rundle P, Rennie IG, Sisley K. The in vivo modulatory effects of an anterior-chamber microenvironment on uveal melanoma. *Br J Ophthalmol* 2009;93:535–540.

54 Canovas D, Rennie IG, Nichols CE, Sisley K. Local environmental influences on uveal melanoma: vitreous humor promotes uveal melanoma invasion, whereas the aqueous can be inhibitory. *Cancer* 2008;112:1787–1794.

Appendix A TNM pathological staging of uveal melanoma (TNM 8th edition)[7]

Anatomical sites

Iris	C69.4
Ciliary body	C69.4
Choroid	C69.3

pT – Primary tumour

pTX Primary tumour cannot be assessed
pT0 No evidence of primary tumour

Iris

(NB: Iris melanomas originate from, and are predominantly located in, this region of the uvea. If less than half of the tumour volume is located within the iris, the tumour may have originated in the ciliary body and consideration should be given to classifying it accordingly.)

pT1: Tumour limited to the iris

- pT1a Not more than 3 clock hours in size
- pT1b More than 3 clock hours in size
- pT1c With secondary glaucoma

pT2: Tumour confluent with or extending into the ciliary body, choroid or both

- pT2a Tumour confluent with or extending into the ciliary body without secondary glaucoma
- pT2b Tumour confluent with or extending into the choroid without secondary glaucoma
- pT2c Tumour confluent with or extending into the ciliary body and/or choroid with secondary glaucoma

pT3: Tumour confluent with or extending into the ciliary body, choroid or both, with scleral extension

pT4: Tumour with extrasceral extension

- pT4a ≤5 mm in diameter
- pT4b >5 mm in diameter

Ciliary body and choroid

Primary ciliary body and choroidal melanomas are classified according to the four tumour size categories below:

Thickness (mm)

>15					4	4	4
12.1–15.0				3	3	4	4
9.1–12.0		3	3	3	3	3	4
6.1–9.0	2	2	2	2	3	3	4
3.1–6.0	1	1	1	2	2	3	4
≤3.0	1	1	1	1	2	2	4
	<3.0	**3.1–6.0**	**6.1–9.0**	**9.1–12.0**	**12.1–15.0**	**15.1–18.0**	**>18**

Largest basal diameter of tumour (mm)

pT1 Tumour size category 1

pT1a	Without ciliary body involvement and extraocular extension
pT1b	Without ciliary body involvement
pT1c	Without ciliary body involvement but with extraocular extension ≤5 mm in diameter
pT1d	With ciliary body involvement and extraocular extension ≤5 mm in diameter

pT2 Tumour size category 2

pT2a	Without ciliary body involvement and extraocular extension
pT2b	With ciliary body involvement
pT2c	Without ciliary body involvement
pT2d	With ciliary body involvement and extraocular extension ≤5 mm in diameter

pT3 Tumour size category 3

T3a	Without ciliary body involvement and extraocular extension
T3b	With ciliary body involvement
T3c	Without ciliary body involvement but with extraocular extension ≤5 mm in diameter
T3d	With ciliary body involvement and extraocular extension ≤5 mm in diameter

pT4 Tumour size category 4

pT4a	Without ciliary body involvement and extraocular extension
pT4b	With ciliary body involvement
pT4c	Without ciliary body involvement but with extraocular extension ≤5 mm in diameter
pT4d	With ciliary body involvement and extraocular extension ≤5 mm in diameter
pT4e	Any tumour size category with extraocular extension ≥5 mm in diameter

Note: When histopathological measurements are recorded after fixation, tumour diameter and thickness may be underestimated because of tissue shrinkage.

pN – Regional lymph nodes

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

pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Regional lymph node metastasis

pM – Distant metastasis

pM0	No distant metastasis
pM1	Distant metastasis
pM1a	Largest diameter of the largest metastasis ≤3 cm
pM1b	Largest diameter of the largest metastasis 3.1–8.0 cm
pM1c	Largest diameter of the largest metastasis >8 cm

Appendix B SNOMED T and M codes

Sites and subsites for description and their associated SNOMED 'T' codes

Topographical codes	SNOMED	SNOMED-CT terminology	SNOMED - CT code
Eye	TXX000 (SNOMED 2) TAA000 (SNOMED 3/RT)	Structure of eye proper (body structure)	81745001
Both eyes	TXX180 (SNOMED 2) TAA180 (SNOMED 3/RT)	Structure of both eyes (body structure)	40638003
Orbit	TY0480 (SNOMED 2) TD1480 (SNOMED 3) T-D14AD (SNOMED RT)	Entire orbital region (body structure)	39607008
Choroid	T-XX310 (SNOMED 2) T-AA310 (SNOMED 3/RT)	Choroidal structure (body structure)	68703001
Ciliary body	T-XX400 (SNOMED 2) T-AA400 (SNOMED 3/RT)	Ciliary body structure (body structure)	29534007
Iris	T-XX280 (SNOMED 2) T-AA500 (SNOMED 3/RT)	Iris structure (body structure)	41296002
Uvea	T-XX570 (SNOMED 2) T-AA570 (SNOMED 3/RT)	Uveal tract structure (body structure)	74862005

Common SNOMED 'M' codes used in uveal melanoma

Morphological codes	SNOMED	SNOMED-CT terminology	SNOMED - CT code
Melanoma	M-87203	Malignant melanoma, no International Classification of Diseases for Oncology subtype (morphologic abnormality)	2092003
Epithelioid melanoma	M-87713	Epithelioid cell melanoma (morphologic abnormality)	37138001
Spindle cell melanoma	M-87723	Spindle cell melanoma (morphologic abnormality)	68827007
Mixed spindle cell and epithelioid melanoma	M-87703	Mixed epithelioid and spindle cell melanoma (morphologic abnormality)	50813003

Morphological codes (continued)	SNOMED	SNOMED-CT terminology	SNOMED-CT code
Melanoma in melanosis	M-87413	Malignant melanoma in precancerous melanosis (morphologic abnormality)	18450009
Naevus	M-87200	Pigmented nevus, no International Classification of Diseases for Oncology subtype (morphologic abnormality)	21119008
Melanocytoma	M-87260	Magnocellular nevus (morphologic abnormality)	26325004
Metastatic melanoma	M-87206	Malignant melanoma, metastatic (morphologic abnormality)	372158004

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 uveal melanoma

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

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

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

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

MACROSCOPIC DESCRIPTION

Specimen type: Iridectomy □ Local resection of ciliary body/choroid □
Endoresection □ **Enucleation** □ **Orbital exenteration**□

Laterality: Right □ Left □

Uveal compartments involved: Iris □ Ciliary body □ Choroid □ Cannot be assessed □

Extraocular tumour extension Present □ Not identified □

If extraocular tumour extension present:

Extraocular extension, maximum tumour diameter ≤5 mm □ >5 mm □ Cannot be assessed □

Intraocular tumour size (for choroidal and ciliary body tumours only):

Largest basal diameter (mm):

≤3.0 □ 3.1–6.0 □ 6.1–9.0 □ 9.1–12.0 □ 12.1–15.0 □ 15.1–18.0 □ >18 □

Maximum height (mm):

≤3.0 □ 3.1–6.0 □ 6.1–9.0 □ 9.1–12.0 □ 12.1–15.0 □ >15 □

MICROSCOPIC DESCRIPTION

Melanoma present Yes □ No □

Uveal structures involved: Iris □ Ciliary body □ Choroid □ Cannot be assessed □

Tumour growth pattern: Focal solid mass □ Ring □ Diffuse □

Overall histological tumour type designation by cell type:

Spindle cell melanoma (>90% spindle cells) □

Mixed cell melanoma (>10% epithelioid cells and <90% spindle cells) □

Epithelioid cell melanoma (>90% epithelioid cells) □

Other □ Please specify ……

Microscopic extraocular extension: Present ≤5 mm □ Present >5 mm □ Not identified □

Mitotic count (In 40 high power fields; each field being 0.15–0.19 mm^2, ideally 0.152 mm^2)……

Closed loops and/or networks matrix patterns (for ciliary body and uveal melanoma only)

Present □ Not identified □

Comments

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

SNOMED codes **……**

Signature…… **Date**……..

Appendix D Reporting proforma for uveal melanoma in list format

Element name	Values	Implementation notes
Specimen type	Single selection value list: • Iridectomy • Local resection of ciliary body/choroid • Endoresection • Enucleation • Orbital exenteration	
Laterality	Single selection value list: • Left • Right	
Macroscopic uveal structures involved	Multi select value list (choose all that apply): • Iris • Ciliary body • Choroid • Cannot be assessed	
Macroscopic extraocular tumour extension	Single selection value list: • Present • Not identified	
Macroscopic extraocular tumour extension maximum tumour diameter	Single selection value list: • ≤5 mm • >5 mm • Cannot be assessed • Not applicable	Not applicable if macroscopic extraocular tumour extension is not identified.
Largest basal diameter	Single selection value list: • ≤3.0 • 3.1–6.0 • 6.1–9.0 • 9.1–12.0 • 12.1–15.0 • 15.1–18.0 • >18 • Not applicable	Not applicable if uveal compartments involved does not include ciliary body or choroid.

Maximum height	Single selection value list: • ≤3.0 • 3.1–6.0 • 6.1–9.0 • 9.1–12.0 • 12.1–15.0 • >15 • Not applicable	Not applicable if uveal compartments involved does not include ciliary body or choroid.
Melanoma present	Single selection value list: • Yes • No	
Microscopic uveal structures involved	Multi select value list (choose all that apply): • Iris • Ciliary body • Choroid • Cannot be assessed	
Tumour growth pattern	Single selection value list: • Focal solid mass • Ring • Diffuse	
Histological tumour type	Single selection value list: • Spindle cell melanoma • Mixed cell melanoma • Epithelioid cell melanoma • Other	
Histological tumour type, other specify	• Free text	Only applicable if 'Histological tumour type, other' selected.
Microscopic extraocular tumour extension	Single selection value list: • Present ≤ 5 mm • Present >5 mm • Not identified	
Mitotic count	Number	
Closed loops and/or networks matrix patterns	Single selection value list: • Present • Not identified • Not applicable	Not applicable if uveal compartments involved does not include ciliary body or choroid

UICC TNM version 8 pT stage	Single selection value list: • pTX • pT0 • pT1a • pT1b • pT1c • pT1d • pT2a • pT2b • pT2c • pT2d • pT3a • pT3b • pT3c • pT3d • pT4a • pT4b • pT4c • pT4d • pT4e • ypTX • ypT0 • ypT1a • ypT1b • ypT1c • ypT1d • ypT2a • ypT2b • ypT2c • ypT2d • ypT3a • ypT3b • ypT3c • ypT3d • ypT4a • ypT4b • ypT4c • ypT4d • ypT4e	

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: • M0 • pM1a • pM1b • pM1c	
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, 1
2 The health question(s) covered by the guideline is (are) specifically described	Foreword, 1
3 The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described	Foreword, 1
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	1
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, 1
12 There is an explicit link between the recommendations and the supporting evidence	5–6, 11
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	2–11
16 The different options for management of the condition or health issue are clearly presented	2–11
17 Key recommendations are easily identifiable	2–11
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	12
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