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

Dataset for histopathological reporting of uveal melanoma

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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 (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:

- 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 information used to develop this dataset was obtained by undertaking a systematic search of the PubMed database between January 2015 and July 2020, previous recommendations of the RCPath, and local guidelines in the UK. Key search terms used for electronic searches included ‘uveal melanoma’, ‘choroidal melanoma’, ‘genetic mutations’, ‘immunohistochemistry’ and ‘BAP1’. Published evidence was evaluated using modified SIGN guidance (see Appendix E).[1] 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 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 members’ attention. If members do not object to the changes, the changes 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 team, Working Group on Cancer Services and the Lay Network, and was placed on the College website for consultation with the membership from Thursday 2 September to Thursday 30 September. 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 Clinical Effectiveness team 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 fair-skinned patients. UM has a particular propensity for hepatic metastasis, which at present is incurable.[2] Most UM patients undergo conservative management of their primary tumour with radiotherapy, although some patients undergo surgery, including local tumour resection, endoresection or enucleation.[3]

Various prognostic parameters exist to predict whether the primary tumour is likely to metastasise to the liver (or not). These include the age and gender of the patient, location and size of the tumour, the presence of certain morphological features (e.g. presence of epithelioid cells, increased mitotic count, presence of closed connective tissue loops) as well as genetic alterations (copy number variations and mutations) of the UM cells.[4]

UM with monosomy 3 (M3) increase the risk of metastasis.[5–7] This metastatic risk increases even further with the combination of M3 and gains in chromosome 8q.[8–11] Tumours with disomy 3 (D3) and gains in chromosome 6p have a relatively low risk of metastasis.[11,12] 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.[13,14]

In addition, the presence of an inactivating mutation of the BRCA-associated protein 1 (*BAP1*) gene is associated with the highly metastatic UM.[15] Immunohistochemical examination of UM can provide some information about the somatic *BAP1* gene status of the tumour cells: loss of nuclear expression is typically associated with the *BAP1* gene mutation and these UM are usually M3.[16]

Further mutations have been identified in UM of prognostic relevance: in splicing factor 3B subunit 1 (*SF3B1*), and the eukaryotic translation initiation factor 1A X-linked (*EIF1AX*). While mutations in the latter gene are associated with a favourable prognosis in D3-UM, those D3-UM with a mutation in *SF3B1* are associated with a sevenfold increased risk of the metastatic disease when compared to D3-UM and wildtype for *SF3B1*.[17]

It is advisable to have access to technology that enables a genetic prognosis to be given, with this data being considered together with the clinical and histological features of the tumour to best determine metastatic risk.[4]

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

- to ascertain staging of the disease
- to provide histological 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)*[18] from the Union for International Cancer Control (UICC) and the *Cancer Staging Manual (8th edition)*[19] 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.[20]

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, rarely, orbital exenterations.

Most enucleations are sent to the pathology laboratories in 10% buffered formalin, and usually require a maximum of 24 hours of fixation prior to grossing.

However, 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.

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.

Orbital exenterations are typically sent in 10% buffered formalin and usually require 48 hours fixation before careful macroscopic description and dissection. Such exenteration specimens may be complete or limited (eyelid-sparing). 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 puncta.

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.

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 (variable in number, but usually six) 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, using a medium-sized blade. 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 in millimetres
- evidence of extraocular invasion and measured in millimetres
- growth pattern: focal solid mass, diffuse, ring. With small tumours, it is sometimes better to determine the growth pattern histologically (see section 5.2.1).
- which intraocular structures are involved by the tumour? With small UM, it is often better to determine this histologically (see section 5.1.1).
- some authorities measure the location of the tumour from the ora serrata or optic disc edge.

If the eye is fresh at cut-up, only one slice through the eye (as above) is made, as a second parallel section to the above one (on the opposite side of the optic nerve) is too difficult to undertake. The eye is allowed to fix for 24 hours and this second parallel slice is then performed, creating a central pupil-optic nerve-tumour block (PO) and two calottes.[20] A slice of the surgical margin of the optic nerve is also taken at this time.

If the eye is received in the fresh state, tumour sampling can be performed for both molecular diagnostic and research purposes (in consented cases). This is performed by undertaking a small parallel slice of the tumour only, and placing the diced tumour pieces in Eppendorf tubes for flash freezing.

4.1.5 Orbital exenteration

Exenterations are performed in rare cases of gross extraocular UM extension. The following measurements are usually taken: maximum antero-posterior, horizontal and vertical. Any relevant external features are described, e.g., whether the exenteration specimen includes eyelids or not, whether the extraocular melanoma growth is visible, its location and whether it is present within the surgical margins. The external soft tissue margins should be painted in suitable dye for margin assessment and orientation purposes. The specimen is usually 'bread-sliced' sagittally starting either at the lateral or medial side and ending at the opposite side, and the intraocular contents, along with any extraocular lesions, described as for an enucleation.

The number of slices of such specimens varies according to the size of the specimen, however it typically can be up to seven to eight slices. While the medial and lateral slices usually do not require megablock cassettes, the more central slices typically do. The surgical margin of the optic nerve is embedded separately.

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 two, five, seven and ten o'clock. However, there can be considerable variation in the number and locations of the veins.[20] 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, which thereby represents extraocular extension of the UM and increases the TNM stage. 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 Orbital 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,[21,22] with mortality rates ten-times lower than those for melanomas of other uveal sites.[23] Ciliary body melanomas behave comparatively worse than iris and choroid melanomas.[18,24–27]

[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.[25–28] The five-year mortality rates are 16%, 32% and 53% for 'small', 'medium' and 'large' tumours, respectively.[29,30] The Collaborative Ocular Melanoma Study (COMS)[31–34] 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.[18,19] It does not use the above COMS classification of tumours, rather the 7th and 8th UICC/AJCC TNM staging of UM designed a system on the basis of >3,300 tumours. The reader is referred to the appropriate texts[18,19,26] and Appendix A.

The most accurate tumour measurements are usually made pre-operatively by ultrasound by the clinical teams. 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[24,34–39] 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[38] or aqueous blood vessels.

The *TNM Classification of Malignant Tumours (8th edition)*[18] from the UICC and the *Cancer Staging Manual (8th edition)*[19] 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.[40] It grows along the choroidal plane with little focal elevation. 'Ring' (360° growth) 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 have higher metastatic rates compared to a focal or nodular solid mass.[41–43]

[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.[43–46] A histopathology report should state whether the tumour is of spindle, epithelioid or mixed cell type.

Spindle A cells exhibit a slender oval nucleus, with a characteristic longitudinal nuclear groove, fine chromatin, an indistinct nucleolus and indistinct cytoplasmic borders. Spindle A cells are considered to be naevus cells. 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[46] 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.[43–46]

The current AJCC has defined the histopathological tumour types with respect to cell types as follows:[19]

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

As the above system results in a large number of UM being classified as mixed tumours, it is recommended that the proportion of epithelioid cells is estimated in mixed cell melanomas, 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.[24,34–39] This can occur directly through the scleral collagen, perineurally, perivascularly or intravascularly into the emissary, vortex vein[39] or aqueous blood vessels.

The *TNM Classification of Malignant Tumours (8th edition)*[18] from the UICC and the *Cancer Staging Manual (8th edition)*[19] 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.[37]

[Level of evidence – B.]

5.2.4 Mitotic count[47–49]

This is independently associated with metastatic risk, with higher counts associated with shorter survival. A total of 40 high power fields (HPF) are counted with each field having an area of 0.15–0.19 mm^2 (recommended field size is 0.152 mm^2). Typically, UM with a mitotic count greater than 5/40 HPF is associated with a poorer prognosis.[48]

[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 (ECM) deposition have been defined for ciliary body or choroidal melanomas, which can be highlighted using the PAS stain.[50,51] Most tumours have a heterogeneous PAS distribution. While these ECM patterns are of interest, it has been demonstrated that only one is of prognostic significance. That is, 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.[51–53]

[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[54]
- presence of melanin pigmentation[30]

- degree of lymphocytic infiltration[55,56]
- breach of Bruch's membrane[57]
- optic nerve extension.[58]

7 TNM pathological staging (8th edition UICC)[18]

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, intraocular biopsies (iris, ciliary body and choroid – the latter via a trans-vitreous approach) and open-flap trans-scleral biopsies are usually undertaken to distinguish between a UM, metastasis or benign neoplasm, prior to treatment, or for molecular prognostication purposes.[59]

Such intraocular biopsies are handled as either cytospins stained with May–Grunwald–Giemsa and/or cell blocks. These preparations usually yield enough material for immunohistochemistry and molecular prognostication. The iris and choroid are amenable to direct biopsy.

These specimens are small and require careful handling by a trained BMS 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[5,6,14,60,61]

As mentioned above, loss of chromosome 1p, M3, gain of 6p, loss of 6q, loss of 8p and gain of 8q have been associated with risk of metastatic death in UM. M3 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. As indicated above, immunohistochemical staining for BAP1 expression provides a surrogate for the somatic *BAP1* testing (and indirectly chromosome 3) in most cases.[16] It should be noted that *BRAF* mutations occur exceptionally rarely in UM, hence it is *not* recommended that this testing is undertaken.

11.2 Iris cytology[62,63]

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 are recommended by the RCPath as key performance indicators (see Key Performance Indicators – Proposals for Implementation, July 2013):

- cancer resections should be reported using a template or proforma, including items listed in the English COSD, which are, by definition, core data items in RCPath cancer datasets. English trusts were required to implement the structured recording of core pathology data in the COSD.
  - standard: 95% of reports must contain structured data
- histopathology cases must be reported, confirmed and authorised within 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 staging of uveal melanoma (TNM 8th edition)[18]

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 extrascleral 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 With 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 category **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	COSD v8	COSD v9
Specimen type	Single selection value list: • Iridectomy • Local resection of ciliary body/choroid • Endoresection • Enucleation • Orbital exenteration		CR0760 • Iridectomy = EX • Local resection of ciliary body/choroid = EX • Endoresection = EX • Enucleation = EX • Orbital exenteration = RE	pCR0760 • Iridectomy = EX • Local resection of ciliary body/choroid = EX • Endoresection = EX • Enucleation = EX • Orbital exenteration = RE
Laterality	Single selection value list: • Left • Right		CR0820 Left = L Right = R Blank = 9	pCR0820 Left = L Right = R Blank = 9
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/40 HPF			
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 category	Single selection value list: • pTX • pT0 • pT1a • pT1b • pT1c • pT1d • pT2a • pT2b • pT2c • pT2d • pT3a • pT3b • pT3c • pT3d • pT4a • pT4b • pT4c • pT4d • pT4e		CR0910	pCR0910

	• ypTX • ypT0 • ypT1a • ypT1b • ypT1c • ypT1d • ypT2a • ypT2b • ypT2c • ypT2d • ypT3a • ypT3b • ypT3c • ypT3d • ypT4a • ypT4b • ypT4c • ypT4d • ypT4e			
UICC TNM version 8 pN category	Single selection value list: • pNX • pN0 • pN1 • ypNX • ypN0 • ypN1		CR0920	pCR0920
UICC TNM version 8 pM category	Single selection value list: • M0 • pM1a • pM1b • pM1c		CR0930	pCR0930
SNOMED Topography code	May have multiple codes. Look up from SNOMED tables.		CR6410	pCR6410
SNOMED Morphology code	May have multiple codes. Look up from SNOMED tables.		CR6420	pCR6420

Appendix E Summary table – explanation of grades of evidence

(modified from Palmer K *et al. BMJ* 2008;337:1832.)[1]

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