



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

Standards and datasets for reporting cancers

**Dataset for the histopathological reporting of
conjunctival melanoma and melanosis**

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CONTENTS

1	Introduction	3
2	Clinical information required on request form	4
3	Specimen receipt and preparation	4
4	Specimen handling and block selection	5
5	Core data items	6
6	Non-core data items	8
7	References	9
Appendix A	TNM classification of conjunctiva melanoma and melanosis	11
Appendix B	SNOMED ‘T’ and ‘M’ codes	12
Appendix C	Reporting proforma for conjunctival melanoma and melanosis	13

1 INTRODUCTION

These proposals for the reporting of conjunctival melanoma and melanosis should be implemented for the following reasons:

- to achieve consistency in the histological reporting of conjunctival melanoma and melanosis, with respect to report content and terminology. This will facilitate collaboration between cancer centres and cancer networks
- to provide accurate data for cancer registration
- to provide prognostic information to clinicians
- to provide prognostic information to patients
- potentially assist in selecting patients for future trials of adjuvant therapy
- to provide g data for clinical audit and effectiveness
- accurate and equitable comparison of surgical practice in different units and the comparison of patients in clinical trials
- to provide a database for research.

The synoptic proforma (Appendix C) is based on the World Health Organisation typing of tumours of the eye and its adnexa¹ and the International Union Against Cancer/American Joint Committee on Cancer TNM staging system, 6th edition.² The synoptic proforma may be used as the main reporting format or may be combined with free text.

The data have been divided into core and non-core. Core data represents a minimum standard of required for patient management and are judged, on the basis of the available published literature, to be most statistically robust. Non-core data can be included for completeness of the report, to reflect local practice. Non-core data are judged to be of lesser prognostic significance or have not been as thoroughly statistically validated as core data.

The sections on dissection technique are for guidance only and are not meant to be prescriptive. Further guidelines on how to dissect ophthalmic specimens for the diagnosis of conjunctival melanoma and melanosis can be found in the references at the end of this document.³

Conjunctival melanoma can arise *de novo*,^{4,5} from primary acquired melanosis with atypia^{4,5} and from naevi.^{4,5} There has been controversy and confusion over the natural history, histopathological appearances and histopathological terminology of the precursor lesions for conjunctival melanoma.^{6,7} The term primary acquired melanosis (PAM) was adopted by the World Health Organisation⁸ and is understood by

ophthalmologists and ophthalmic histopathologists alike. PAM with cytological atypia is a precursor of invasive melanoma.^{6,9,10} PAM is a clinical term and assumes that the lesion is acquired. The histological correlate is melanosis with or without atypia and should be reported as such by the pathologist.

2 CLINICAL INFORMATION REQUIRED ON THE REQUEST FORM

For suspected melanocytic lesions of the conjunctiva, it is essential that the following specific data items are known before histopathological reporting:

- the age of the patient (melanoma is commoner in older adults)
- racial background (racial melanosis)
- whether the lesion is congenital or acquired (if congenital, likely to be benign)
- the precise anatomical site of the lesion (lesions in the fornix and tarsal conjunctiva are more likely to be melanoma)
- any previous diagnosis of a conjunctival melanocytic lesion (retrospective review and evolution of pathology)
- any previous treatment of a conjunctival melanocytic lesion
- a detailed diagram indicating locations of multiple conjunctival mapping biopsies.

3 SPECIMEN RECEIPT AND PREPARATION

Four types of specimens are likely to be received from patients suspected of having conjunctival melanocytic lesions. These are: excisional biopsies, incisional biopsies, multiple incisional ‘mapping’ biopsies and exenterations for uncontrolled conjunctival melanoma.

Incisional and excisional biopsies are best placed flat on a piece of card or sponge by the surgeon. If not, it is recommended the specimen be flattened in this manner. This minimizes tangential section artifact that can falsely upgrade melanosis at histological interpretation¹⁰.

Exenteration specimens 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

For incisional and excisional biopsies, record the overall length, width and depth of each specimen, followed by the size of any apparent lesions. Clinically, melanosis is usually flat, brown/black and mottled, but a non-pigmented variant, so-called melanosis with atypia sine pigmentio does exist^{11,12}. Melanoma is often indicated by a firm thickening or nodule. It is good practice to paint the margins of an excisional biopsy, to aid in margin status assessment at microscopy, unless this would compromise accurate embedding of the specimen. With multiple incisional ‘mapping’ procedure, to assess the extent of melanosis, margins are not an issue as the mapping is simply establishing the extent of the lesion. Therefore these specimens do not have to be painted.

Exenteration is performed for conjunctival melanoma only after failed conservative treatment^{13,14}. The specimen can have the following measurements made: maximum antero-posterior, horizontal and vertical measurements. Any relevant external features are described. The external soft tissue margins should be painted in suitable dye for margin assessment and orientation purposes

4.2 Block taking

Incisional or multiple mapping incisional biopsies: These can be processed whole, along their longest margin if less than 3mm. If greater than 3 mm in length, they can be bread-sliced across their width.

Excisional biopsies: It is good practice to paint the margins, unless this would compromise accurate embedding of the specimen. The specimen is bread-sliced along the length (as for cutaneous melanoma excisions, see The Royal College of Pathologists’ *Dataset for Malignant Melanoma*, on www.rcpath.org/resources/pdf/skincancers2802.pdf).¹⁵ If the excision includes the limbus, the slices should ideally pass through the limbal margin, so that the lesion’s relationship to the cornea can be ascertained.

Exenterations: The optic nerve margin is taken. If bone is attached to the specimen, it should be removed, decalcified and then processed. The medial nasolacrimal duct resection margin is sampled as melanosis and melanoma can involve this margin¹⁶. Finding this margin is facilitated by probing the lacrimal puncta. The tumour in relation to the closest tissue margins is sampled, after slicing the specimen. This is often achieved by bread-slicing the specimen from side to side.

5 CORE DATA ITEMS

5.1 Macroscopic core data items

Location of tumour

For incisional and excisional biopsies, the clinical details will usually indicate the site of the biopsy. For exenterations, inspection of the specimen will indicate the site of the lesion.

Primary conjunctival melanoma located at unfavourable sites, such as the fornix, palpebral conjunctiva, caruncle, plica semilunaris and corneal stroma is associated with a higher recurrence rate and a higher rate of metastatic death, compared with favourable sites, such as the bulbar and limbal conjunctiva.^{13,14,17, 18-22}

Size of melanoma

Melanomas larger than 10 mm in greatest width²³ and those that are pathological stage pT3 and above have a greater local recurrence rate and higher death rate from metastatic tumour.²⁴

Multifocality

Multifocal primary conjunctival melanomas are associated with a higher rate of recurrence and metastatic death, than unifocal tumours, principally at favourable site locations.¹⁷

5.2 Microscopic core data

Melanosis

Melanosis occurs with and without melanocyte cytological atypia.

Melanosis without atypia is diagnosed under two circumstances:

1. Melanin overproduction without melanocyte hyperplasia. The melanin is usually taken up by the basal keratinocytes.
2. A basal layer confined hyperplasia of non-atypical melanocytes.^{4,6,9,10}

The current evidence suggests that melanosis without atypia carries a nearly 0% chance of progression to invasive melanoma.^{4,6,9,10} Some authors have used the term 'benign acquired melanosis (BAM)' for melanosis without cytological atypia.

Mildly atypical melanocytes tend to be polyhedral, with round nuclei and scant/imperceptible cytoplasm.¹⁰ Moderately/severely atypical melanocytes are epithelioid, dendritic or spindle shaped.¹⁰ These atypical melanocytes can be distributed as purely basilar or in a pattern other than basilar, i.e. occupying the mid to higher epithelium.^{9,10}

Many ophthalmic pathologists often equate atypical melanosis that has replaced the full thickness of the conjunctival epithelium as in-situ melanoma (unpublished). The assessment of the extent of involvement of the epithelium by atypical melanocytes, can be facilitated by immunohistochemistry with markers against Melan A, S100 and HMB45 proteins.

When diagnosing melanosis with atypia, consideration is given to the cytological and architectural changes. The evidence suggests that melanosis with atypia containing epithelioid cells has a 75% chance of progressing to invasive melanoma.^{6,9} Melanosis with atypia where the proliferation of atypical melanocytes (all cytological grades) occupies more than the basal layer has a 90% chance of progressing to invasive melanoma.^{6,9}

Margins of excision should be commented on for attempted excisions of melanosis with atypia. Incompletely excised melanosis with atypia does recur as melanosis with atypia and in some cases as invasive melanoma.^{4,9}

Invasive melanoma

There appears to be no significant difference in prognosis between melanomas arising *de novo*, from melanosis with atypia or from naevi.⁵

Thickness of invasive melanoma

The thickness of invasive melanoma is measured from the top of the conjunctival epithelium to the deepest invasive melanocyte (Jakobiec modification of the Breslow thickness).²⁵ It is recorded in millimeters to the first decimal point (as for cutaneous melanoma). Tumour thickness can be measured using a microscope vernier scale or an eye-piece graticule.²⁵

The thickness of invasive melanoma has prognostic significance.^{5,19,23} The literature states several critical tumour thickness cut-off points that determine prognosis (0.8 mm,^{5,19} 1 mm,¹⁷ 1.5 mm²⁰ and 2 mm^{14,23,24}). This dataset avoids this controversy by not mentioning a specific critical thickness. However the most recent pTNM pathological classification² for primary conjunctival melanoma does state a critical thickness of 0.8 mm. A pT2 tumour is no more than 0.8 mm affecting the bulbar conjunctiva; a pT3 tumour is thicker than 0.8 mm.²

Since metastatic potential is related to tumour thickness, histologically determined invasive tumour thickness could play an important part in triaging patients for sentinel lymph node biopsies.²⁶⁻²⁹

Occasionally, areas of substantia propria inflammation can obscure foci of invasion. Under these circumstances, application of immunohistochemistry with melanocytic markers is often successful at allowing the visualization of the invasive melanoma cells, originally obscured by the inflammation.

Cell types within the invasive melanoma

Tumours with an epithelioid cell component exhibit a higher recurrence rate and a higher tumour-related mortality compared to those composed of pure spindle cells.^{5,17,23,30} This is partly influenced by tumour thickness and site (favourable versus unfavourable).¹⁷

Lymphatic/blood vessel invasion

Tumours exhibiting lymphatic invasion, at favourable and unfavourable sites are associated with a higher tumour metastatic death.¹⁷

Anatomical structures infiltrated

Tumours that invade the eyelid, eyeball and orbit have a greater cumulative probability of recurrence and the greater the tumour related mortality from metastatic disease.^{22,30}

Status of excision margins

Excision margins involved by melanoma are correlated with local tumour recurrence, higher risk of metastasis and greater magnitude of tumour related mortality.^{14,30}

6 NON-CORE DATA ITEMS

Some of these items have not yet been validated or there is lesser robust statistical evidence to include them in the core data.

Macroscopic

Dimensions of specimen

Colour of lesion

Microscopic

For invasive melanoma: ulceration, growth phase, perineural invasion, tumour regression, microsatellites, mitotic rate, tumour infiltrating lymphocytes, presence or absence of co-existing naevus.

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APPENDIX A TNM CLASSIFICATION OF CONJUNCTIVA MELANOMA AND MELANOSIS BASED ON TNM 6²

Primary tumor (pT)

- pTX – Primary tumor cannot be assessed.
- pT0 – No evidence of primary tumor
- pT1 – Tumor(s) of bulbar conjunctiva occupying 1 quadrant or less and 0.8 mm or less in thickness
- pT2 – Tumor(s) of bulbar conjunctiva occupying more than 1 quadrant and 0.8 mm or less in thickness
- pT3 – Tumor(s) of the conjunctival fornix, and/or palpebral, and/or caruncle or tumor(s) of the bulbar conjunctiva, more than 0.8 mm in thickness
- pT4 – Tumor invades eyelid, cornea, and/or orbit

Regional lymph nodes (pN)

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

Distant metastasis (pM)

- pMX – Distant metastasis cannot be assessed.
- pM0 – No distant metastasis
- pM1 – Distant metastasis

Stage group: No stage grouping is recommended at this time.

Histopathologic type: This categorization applies only to melanoma of the conjunctiva.

Histopathologic grade: This grade represents the origin of the primary tumor.

- GX – Origin cannot be assessed
- G0 – Melanosis
- G1 – Malignant melanoma arises from a nevus
- G2 – Malignant melanoma arises from melanosis
- G3 – Malignant melanoma arises *de novo*

APPENDIX B SNOMED T and M CODES

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

T-AA860	Conjunctiva
T-AA861	Plica semilunaris
T-AA862	Caruncle
T-AA880	Bulbar conjunctiva
T-AA863	Conjunctiva fornix-superior
T-AA864	Conjunctiva fornix-inferior
T-AA870	Tarsal conjunctiva

Common SNOMED 'M' codes used in conjunctiva melanoma and melanosis

M-87203	Malignant melanoma
M-87413	Melanoma arising in melanosis
M-57210	Melanosis
M-87200	Naevus
M-87206	Melanoma metastasis

APPENDIX C REPORTING PROFORMA FOR CONJUNCTIVAL MELANOMA AND MELANOSIS

Surname	Forenames	Date of Birth
Hospital	Hospital no	NHS no
Date of receipt	Date of reporting	Report no
Pathologist	Surgeon	Sex

MACROSCOPIC DESCRIPTION

Specimen type: Incisional biopsy Excisional biopsy Exenteration
 Laterality: Right Left
 Dimension of specimen(s).....
 Location of tumour : Bulbar Palpebral Fornix Caruncle
 Plica semilunaris Limbus Cornea Unspecified
 Tumour characteristics: Unifocal tumour Multifocal tumour
 Size of tumour(s).....mm
 Non-conjunctival structures involved(specify).....

MICROSCOPIC DESCRIPTION

Melanosis without atypia:	Present <input type="checkbox"/>	Absent <input type="checkbox"/>
Melanosis with atypia:	Present <input type="checkbox"/>	Absent <input type="checkbox"/>
In-situ melanoma	Present <input type="checkbox"/>	Absent <input type="checkbox"/>
Invasive melanoma:	Present <input type="checkbox"/>	Absent <input type="checkbox"/>

Maximum invasive melanoma thickness.....mm

Epithelioid cells present in invasive melanoma: yes no

Lymphatic/blood vessel invasion: yes no

Growth phase.....

Ulceration	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Mitotic rate (for invasive melanoma).....	mm ²	
Perineural invasion	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Tumour regression (for invasive melanoma)	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Microsatellites (for invasive melanoma) yes no

Tumour infiltrating lymphocytes (for invasive melanoma) yes no

Co-existent naevus (for invasive melanoma) yes no

Anatomical structures involved by invasive melanoma (specify):

EXCISION MARGINS

Distance to nearest **peripheral** margin by invasive melanoma ismm
(clear / involved)

Distance to nearest **deep** margin by invasive melanoma is.....mm
(clear / involved).

Distance to nearest **peripheral** margin by in-situ melanoma / atypical melanosis.....mm
(clear / involved).

COMMENTS

Pathological staging (excision specimens only) pT pN pM (TNM 6th Edition)
SNOMED codes T..... / M.....

Signature..... **Date**.....

Shaded items are non-core.