PRIMARY CUTANEOUS MELANOMA STRUCTURED REPORTING PROTOCOL

(2nd Edition 2014)

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- AJCC Cancer Staging Manual 7th edition (including errata corrected with 5th reprint 10th Aug 2010).

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Scope

This protocol contains standards and guidelines for the preparation of structured reports for primary cutaneous invasive melanoma.

Structured reporting aims to improve the completeness and usability of pathology reports for clinicians, and improve decision support for cancer treatment. This protocol provides the framework for the reporting of any melanoma, whether as a minimum data set or a comprehensive report.

Abbreviations

AJCC	American Joint Committee on Cancer
ICCR	International Collaboration on Cancer Reporting
LDH	lactate dehydrogenase
LIS	laboratory information system
LYVE-1	lymphatic vessel endothelial receptor-1
MITF	microphthalmia-associated transcription factor
NHMRC	National Health and Medical Research Council
RCPA	Royal College of Pathologists of Australasia
TIL	tumour-infiltrating lymphocyte
TNM	tumour–node–metastasis
UICC	International Union Against Cancer
WHO	World Health Organization

Definitions

The table below provides definitions for general or technical terms used in this protocol. Readers should take particular note of the definitions for 'standard', 'guideline' and 'commentary', because these form the basis of the protocol.

Ancillary study	An ancillary study is any pathology investigation that may form part of a cancer pathology report but is not part of routine histological assessment.
Clinical information	Patient information required to inform pathological assessment, usually provided with the specimen request form. Also referred to as 'pretest information'.
Commentary	Commentary is text, diagrams or photographs that clarify the standards (see below) and guidelines (see below), provide examples and help with interpretation, where necessary (not every standard or guideline has commentary). Commentary is used to: • define the way an item should be reported, to foster reproducibility • explain why an item is included (eg how does the item assist with clinical management or prognosis of the specific cancer). • cite published evidence in support of the standard or guideline • clearly state any exceptions to a standard or guideline. In this document, commentary is prefixed with 'CS' (for commentary on a standard) or 'CG' (for commentary on a guideline), numbered to be consistent with the relevant standard or guideline, and with sequential alphabetic lettering within each set of commentaries (eg CS1.01a, CG2.05b).
General commentary	General commentary is text that is not associated with a specific standard or guideline. It is used: • to provide a brief introduction to a chapter, if necessary • for items that are not standards or guidelines but are included in the protocol as items of potential importance, for which there is currently insufficient evidence to recommend their inclusion. (Note: in future reviews of protocols, such items may be reclassified as either standards or guidelines, in line with diagnostic and prognostic advances, following evidentiary review).

Guideline	Guidelines are recommendations; they are not mandatory, as indicated by the use of the word 'should'. Guidelines cover items that are not essential for clinical management, staging or prognosis of a cancer, but are recommended. Guidelines include key observational and interpretative findings that are fundamental to the diagnosis and conclusion. Such findings are essential from a clinical governance perspective, because they provide a clear, evidentiary decision-making trail. Guidelines are not used for research items. In this document, guidelines are prefixed with 'G' and numbered consecutively within each chapter (eg G1.10).
Predictive factor	A *predictive factor* is a measurement that is associated with response or lack of response to a particular therapy.
Prognostic factor	A *prognostic factor* is a measurement that is associated with clinical outcome in the absence of therapy or with the application of a standard therapy. It can be thought of as a measure of the natural history of the disease.
Macroscopic findings	Measurements, or assessment of a biopsy specimen made by the unaided eye.
Microscopic findings	In this document, the term 'microscopic findings' refers to histo-morphological assessment.
Standard	Standards are mandatory, as indicated by the use of the term 'must'. Their use is reserved for core items essential for the clinical management, staging or prognosis of the cancer and key information (including observations and interpretation) which is fundamental to the diagnosis and conclusion. These elements must be recorded and at the discretion of the pathologist included in the pathology report according to the needs of the recipient of the report. The summation of all standards represents the minimum dataset for the cancer. In this document, standards are prefixed with 'S' and numbered consecutively within each chapter (eg **S1.02**).
Structured report	A report format which utilises standard headings, definitions and nomenclature with required information.
Synoptic report	A structured report in condensed form (as a synopsis or precis).

Synthesis	Synthesis is the process in which two or more pre-existing elements are combined, resulting in the formation of something new. The Oxford dictionary defines synthesis as "the combination of components or elements to form a connected whole". In the context of structured pathology reporting, synthesis represents the integration and interpretation of information from two or more modalities to derive new information.

Introduction

Summary of cancer type

Melanoma is a major public health problem in many countries, particularly those with a predominance of individuals of European origin. Australia and New Zealand have the highest incidences of melanoma in the world. Melanoma is the 3rd most common cancer in both men and women in Australia and both incidence and mortality rates are increasing. Because melanoma is the most common cancer in patients aged in the 15–45 years age group it has a disproportionate effect on the most productive years of life.

Importance of histopathological reporting

Pathological assessment of a tissue biopsy is a critical aspect in the multidisciplinary management of melanoma patients. Such assessment establishes a definite diagnosis in most cases and provides information that, to a major extent, influences patient prognosis and directs the next stages of management.[1]

Accurate assessment and documentation of important pathological variables are important in influencing the management of melanoma patients. However, of even greater importance is the need to accurately determine whether a cutaneous melanocytic lesion is benign or malignant (ie a melanoma).[2] For this reason, pathology reports of melanocytic lesions should both:

- document the key diagnostic criteria on which the diagnosis was based
- provide the pathological prognostic and other parameters important for patient prognosis and treatment.[3]

Benefits of structured reporting

This structured reporting protocol provides a framework for the assessment and documentation of all the pathological features of any given case. Consistency and speed of reporting is improved by the use of discrete data elements recorded from the checklist. However, the pathologist is encouraged to include free text or narrative to document any other relevant issues, to give reasons for coming to a particular opinion and to explain any points of uncertainty. The evidence for prognostic markers may change over time, and a structured reporting template must be regularly updated to be of maximal value.

Diagnostic certainty

The ability to use descriptive text is especially important for a lesion that is difficult to classify (i.e. whether or not it is a melanoma).[4-7] The approach to such lesions should be to present the evidence for and against the particular diagnoses, and give a preferred diagnosis, but also to express the degree of uncertainty.[8-10] Where there is genuine doubt about the correct diagnosis, it may be appropriate to seek a further opinion from one or more experienced colleagues.

If a diagnosis of melanoma is favoured but not certain, the structured report may still be completed. The report may be prefaced with comments such as 'if melanoma, the lesion would have the following features: …'. Individual centres can tailor this structured reporting template to their needs.[11]

Design of this protocol

This protocol defines the relevant information to be assessed and recorded in a pathology report for melanoma. Mandatory elements (standards) are differentiated from those that are not mandatory but are recommended (guidelines). Also, items suited to tick boxes are distinguished from more complex elements requiring free text or narrative. The structure provided by the following chapters, headings and subheadings, describes the elements of information and their groupings, but does not necessarily represent the format of either a pathology report (Chapter 7) or checklist (Chapter 6). These, and the structured pathology request form (Appendix 1) are templates that represent information from this protocol, organised and formatted differently to suit different purposes.

Key documentation

- *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols* [12]
- *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand* [3]
- *Pathology And Genetics of Skin Tumours (WHO Classification of Tumours)*[13]
- *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers*[14]
- A*JCC Cancer Staging Manual,7th edition* [15]

Changes since last version

- Rework of chapter 1 and appendix 1 in line with new framework
- Removal of numbering for specimen handling in Ch 2, with subsequent renumbering
- Addition of CS2.03a
- Inclusion of a new S5.02 and subsequent renumbering of this chapter
- Edits to G6.01
- Addition of G6.03
- Rework of the checklist in Ch 6.
- Inclusion of ICCR agreed REQUIRED and RECOMMENDED elements as follows:
    - Tumour site
    - Specimen laterality
    - Specimen type
    - Specimen description
    - Specimen orientation
    - Specimen dimensions
    - Macroscopic primary lesion description
    - Macroscopic primary lesion dimensions
    - Other lesion(s)
    - Macroscopic description of other lesion(s)
    - Surgical margins/tissue edges

    - In situ Component: Peripheral Margin
    - Invasive Component: Peripheral Margin
    - Invasive component: Deep Margin
- Breslow thickness
- Ulceration
- Extent of ulceration
- Mitotic count
- Satellites
- Satellites: margins
- Clark level
- Lymphovascular invasion
- Tumour-infiltrating lymphocytes (early regression)
- Tumour regression (intermediate and late)
- Tumour regression (intermediate and late):margins
- Neurotropism
- Desmoplastic melanoma component
- Lymph nodes
    - Number of sentinel nodes examined
    - Number of positive sentinel nodes
        - Sentinel lymph node metastasis: extranodal extension
        - Sentinel lymph node metastasis: location of tumour within the lymph node
        - Sentinel lymph node metastasis: maximum single dimension of the largest discrete metastasis
    - Total number of nodes examined (sentinel and non-sentinel)
    - Total number of positive nodes examined (sentinel and non-sentinel)
- Associated melanocytic lesion
- Melanoma subtype
- Pathological Staging (AJCC 7th edition)
    - Primary tumour (T)
    - Regional lymph nodes (N)

Authority and development

This section provides details about the process undertaken in developing this protocol.

This edition of the protocol is an amalgam of two separate but interwoven processes.

a) The first edition of the Melanoma protocol was published in Feb 2010. It was developed by an expert committee as follows:

   Professor Richard Scolyer (Chair and lead author), Pathologist

   Associate Professor David Ellis, Pathologist

   Associate Professor Peter Heenan, Pathologist

   Dr Craig James, Pathologist

   Associate Professor John Kelly, Dermatologist

   Professor Stan McCarthy, Pathologist

   Associate Professor Graham Stevens, Radiation Oncologist

   Dr Sarah Swain, Pathologist

   Professor John Thompson, Surgical Oncologist

   That edition of the protocol was developed following the nine-step process set out in *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols* [12]

b) In 2011 the International Collaboration of Cancer Reporting (ICCR) was established and developed an international cancer dataset for Melanoma published to :

   www.rcpa.edu.au/Publications/StructuredReporting/ICCR.htm

   The ICCR dataset was developed by an international group of expert pathologists and clinicians. Representation of the international committee is as follows, with Professor Richard Scolyer serving as chair.

Prof John Thompson	Surgical Oncologist, Australia	
Dr Maureen Walsh	Pathologist,	The Royal College of Pathologists, UK
Dr Alan Evans	Pathologist,	The Royal College of Pathologists, UK
Dr David Frishberg	Pathologist,	The College of American Pathologists
Dr Victor Prieto	Pathologist,	The College of American Pathologists
Dr Martin Trotter	Pathologist,	The Canadian Association of Pathologists
Dr Noreen Walsh	Pathologist,	The Canadian Association of Pathologists

   The protocols developed by the ICCR member countries, including Australia's 1st edition Melanoma protocol, were used as the basis for discussion of the ICCR dataset.

This edition of the Melanoma protocol includes all of the ICCR cancer dataset elements verbatim as well as those elements and commentary from the first edition of the Melanoma protocol which complement but do not overlap with the ICCR elements. The ICCR elements are identified in each chapter with the ICCR logo placed before the

Standard or Guideline number or bullet and the ICCR element description and commentary boarded by a grey box as shown below:

G2.01	A specimen description should be recorded.

Additional commentary by the RCPA may be added to an ICCR element but is not included in the grey bordered area eg

S3.03	**The presence or absence of ulceration must be reported.**	
	CS3.03a	Ulceration is an integral component of the AJCC/UICC staging system and an independent predictor of outcome in patients with clinically localised primary cutaneous melanoma. [15-17]
	CS3.03b	Assessing the presence of ulceration may be difficult if there is only a focal loss of the epidermis; in this case, it is difficult to determine whether the epidermal deficiency is due to ulceration or sectioning artefact. Absence of fibrin or granulation tissue from putative areas of ulceration would be clues that the apparent ulceration is actually due to sectioning of only part of the epidermis.[18]
	CS3.03c	Distinguishing between iatrogenic and noniatrogenic ulceration is important because the former is of no prognostic significance.[19] Differentiation is relatively easy when a clinical history of a previous biopsy is provided or a well demarcated dermal scar is present; however, at other times it can be difficult or impossible to distinguish between the two.[20]

Stakeholders

ACT Health
Anatomical Pathology Advisory Committee (APAC)
Australasian College of Dermatologists
Australian Association of Pathology Practices Inc (AAPP)
Australian Cancer Network
Australian Commission on Safety and Quality in Health Care
Cancer Australia
Cancer Council ACT
Cancer Council NSW
Cancer Council Queensland
Cancer Council SA
Cancer Council Tasmania
Cancer Council Victoria
Cancer Council Western Australia
Cancer Institute NSW
Cancer Services Advisory Committee (CanSAC)
Cancer specific expert groups – engaged in the development of the protocols
Cancer Voices
Clinical Oncology Society of Australia (COSA)
Colorectal Cancer Research Consortium
Department of Health and Ageing
Grampians Integrated Cancer Services (GICS)
Health Informatics Society of Australia (HISA)
Independent Review Group of Pathologists
Medical Software Industry Association (MSIA)
National Breast and Ovarian Cancer Centre (NBOCC)
National Coalition of Public Pathology (NCOPP)
National E-Health Transition Authority (NEHTA)
National Pathology Accreditation Advisory Council (NPAAC)
National Round Table Working Party for Structured Pathology Reporting of Cancer.
New Zealand Guidelines Group (NZGG)
NSW Department of Health
Peter MacCallum Cancer Institute
Queensland Cooperative Oncology Group (QCOG)
Representatives from laboratories specialising in anatomical pathology across Australia
Royal Australasian College of Physicians (RACP)

Southern Cancer Network, Christchurch, New Zealand

Southern Melbourne Integrated Cancer Service (SMICS)

Standards Australia

Sydney Melanoma Unit (SMU)

The Australia and New Zealand Melanoma Trials Group (ANZMTG)

The Australasian Dermatopathology Society (ADS)

The Medical Oncology Group of Australia

The Royal Australasian College of Surgeons (RACS)

The Royal Australian and New Zealand College of Radiologists (RANZCR)

The Royal Australian College of General Practitioners (RACGP)

The Royal College of Pathologists of Australasia (RCPA)

Victorian Cooperative Oncology Group (VCOG)

Victorian Melanoma Service

Western Australia Clinical Oncology Group (WACOG)

Secretariat

Meagan Judge, Royal College of Pathologists of Australasia

Development process

This protocol has been developed following the seven-step process set out in *Guidelines for Authors of Structured Cancer Pathology Reporting Protocols.*[12]

Where evidence or consensus is not referenced, the authority is that of the expert group.

1 Pre-analytical

This chapter relates to information that should be recorded on receipt of the specimen in the laboratory.

The pathologist is reliant on the quality of information received from the clinicians or requestor. Some of this information may be received in generic pathology request forms, however, the additional information required by the pathologist specifically for the reporting of primary cutaneous melanoma is outlined in Appendix 1. Appendix 1 also includes a standardised request information sheet that may be useful in obtaining all relevant information from the requestor**.**

The accuracy of the pathological report may depend on the amount of tissue provided and the availability of relevant clinical details.[20] It is particularly important to record factors that may induce atypical pathological features in melanocytic naevi (eg previous biopsy, trauma, surface irritation, pregnancy, topical treatment and recent strong sunlight exposure) and may lead to a misdiagnosis of melanoma. Other clinical factors relevant to diagnosis include patient age and sex and the site of the lesion.[2,8-10,21]

S1.01 All demographic information provided on the request form and with the specimen must be recorded.

CS1.01a The Royal College of Pathologists of Australasia (RCPA) *The Pathology Request-Test-Report Cycle — Guidelines for Requesters and Pathology Providers* must be adhered to.[22] This document specifies the minimum information to be provided by the requesting clinician for any pathology test.

CS1.01b The patient's ethnicity must be recorded, if known. In particular whether the patient is of aboriginal or Torres Strait islander origin. This is in support of a government initiative to monitor the health of indigenous Australians particularly in relation to cancer.

CS1.01c The patient's health identifiers may include the patient's Medical Record Number as well as a national health number such as a patient's Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (New Zealand).

S1.02 All clinical information as documented on the request form must be recorded verbatim.

CS1.02a The request information may be recorded as a single text (narrative) field or it may be recorded atomically.

S1.03 The pathology accession number of the specimen must be recorded.

S1.04 The principal clinician involved in the patient's care and responsible for investigating the patient must be recorded.

G1.01 Any clinical information received in other communications from the requestor or other clinician should be recorded together with the source of that information.

2 Specimen handling and macroscopic findings

This chapter relates to the procedures required after the information has been handed over from the requesting clinician and the specimen has been received in the laboratory.

Specimen handling

- Pathologists may be asked to provide tissue samples from fresh specimens for tissue banking or other research purposes. The decision to provide tissue should only be made when the pathologist is sure that the diagnostic process and pathological evaluation will not be compromised. As a safeguard, research use of the specimen should be deferred until the diagnostic process is complete so that the specimen can be retrieved if needed for pathological evaluation.

- Biopsy specimens should be placed in a suitable fixative, such as 10% buffered formalin, before dissection.

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  - Frozen section or cytology examination is not recommended for the assessment of primary cutaneous melanocytic tumours. The significant artefacts caused by freezing the tissue may compromise subsequent analysis of paraffin-embedded sections.

- **The tissue block(s) must be selected to facilitate microscopic assessment of the thickest or most suspicious portion of the tumour, and determination of the relationship of the tumour to the surgical margins.**[20]

  - Tissue blocks should be taken of different portions of a heterogeneous lesion and any other separately identified lesion should also be sampled for microscopic examination.

- For partial biopsies, the entire specimen should be processed.

- In general, excision biopsies should be sequentially sliced transversely in 2–3-mm slices, including the centre, thickest or most suspicious part of the lesion.

- For lesions less than 10 mm in diameter, the entire specimen should be embedded, wherever possible.

- The skin surface and cut surfaces of wide excision specimens should be examined for macroscopic evidence of residual tumour, and then serially sectioned into 2–3-mm slices.

  - If the melanoma was completely excised and had no unusual features (including desmoplasia, neurotropism, amelanotic, satellites, LVI, angiotropism) in the original excision, and there is no suspicion of residual tumour on visual inspection, then it is probably sufficient to

submit only one or two slices from the centre of the scar for microscopic examination.[23-25]

- Guidelines for the pathological examination of lymphadenectomy specimens from melanoma patients (including sentinel lymph nodes and regional lymph node field dissections specimens) are documented in the National Health and Medical Research Council *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand*, 2008.[3]

Macroscopic findings

G2.01	A specimen description should be recorded.	
G2.02	All measurements should be recorded in millimetres.	
G2.03	The specimen dimensions should be recorded.	
	CG2.03a	Measurements should be length x width x depth.
G2.04	Any specimen orientation provided should be recorded in the pathology report.	
	CG2.04a	This refers to the information received from the surgeon regarding orientation of the specimen by marking sutures, clips or other techniques which must be included in the report whenever provided.
G2.05	The macroscopic primary lesion should be described.	
	CG2.05a	The description of the lesion includes such features as size, shape, colour, border, contour, evidence of surface crusting or ulceration and its proximity to the resection margins.
G2.06	The macroscopic primary lesion dimensions should be recorded.	
G2.07	The presence of other lesions should be recorded, and a description given if present.	
	CG2.07a	Other lesions are often naevi or other benign lesions, but it is particularly important to identify the presence of satellite metastases because these portend a worse prognosis.
	CG2.07b	The description of the lesion includes such features as shape, colour, border, contour, evidence of surface crusting or ulceration and its proximity to the primary lesion and the resection margins.

G2.08	A block identification key listing the nature and origin of all tissue blocks should be recorded.

G2.09 A descriptive or narrative field should be provided to record any macroscopic information that is not recorded in the above standards and guidelines, and that would normally form part of the macroscopic description.

3 Microscopic findings

This chapter relates to purely histological assessment. Information derived from multiple investigational modalities, or from two or more chapters, is described in Chapter 5.

G3.01 The microscopic findings should be described.

CG3.01a A description of the microscopic findings is important for clinical governance, to indicate the process of diagnostic decision making and any areas of uncertainty. The description is particularly important in complex or unusual cases, but may not be necessary in a straightforward case.

CG3.01b Histopathological features of clinically suspicious areas should be documented in the histopathology report.

CG3.01c Documentation of histopathological features in clinically suspicious areas will allow clinicopathological correlation.[8,20]

S3.01	**The Breslow thickness must be recorded.**	
	CS3.01a	Measurement should be to a minimum of 1 decimal point and to a degree of precision as to allow accurate AJCC staging.
	CS3.01b	Breslow thickness is the single most important prognostic factor for clinically localised primary melanoma.[3]
	CS3.01c	Breslow thickness is measured from the top of the granular layer of the epidermis (or, if the surface is ulcerated, from the base of the ulcer) to the deepest invasive cell across the broad base of the tumour (dermal/subcutaneous) as described by Breslow.[29,2,30]
		Deep, vertical extensions of the tumour, perpendicular to the base should be assumed to be periadnexal and should not be included in the Breslow thickness.
	CS3.01d	To promote consistency in the evaluation of the Breslow thickness the following points are worthy of note: 1. The Breslow thickness can only be evaluated accurately in sections cut perpendicular to the epidermal surface. Otherwise, a note should be included indicating that "the section is cut tangentially and an accurate Breslow thickness cannot be provided." Nevertheless, in some tangentially cut sections, it is often still possible

		to report a tangentially measured tumour thickness. The latter may be clinically useful, because it can be reasonably inferred that the true Breslow thickness must be less than this measurement, and, when appropriate, this should be stated clearly in the report. At other times, particularly when the epidermis is not visualized, no tumour thickness can be provided, and supplementary prognostic information must be obtained from other factors (including ulceration, mitotic rate, and Clark level). When sections have been tangentially cut, it may be fruitful to melt the paraffin block and reembed the tissue as it may then be possible to obtain perpendicular sections for determination of the Breslow thickness. 2. The Breslow thickness should be measured in the standard way when there is dermal regression (ie dermal regression extending to a greater thickness than the melanoma should not be included in the measurement of Breslow thickness). 3. In the case of periadnexal extension of melanoma (ie in the adventitial or extra-adventitial tissue immediately adjacent to skin appendageal structures usually apparent as an extension or "tongue" of tumour extending beyond the depth of the main tumour mass), it is uncertain from current evidence where the measurement of tumour thickness should be made to most accurately predict patient prognosis. (This does not include adnexal involvement by melanoma, which is regarded as in situ disease.) It is generally agreed that thickness measurements should not be based on periadnexal extension (either periadnexal adventitial or extra-adventitial extension), except when it is the only focus of invasion. In that circumstance, Breslow thickness may be measured from the inner layer of the outer root sheath epithelium or inner luminal surface of sweat glands, to the furthest extent of infiltration into the periadnexal dermis. The depth of extension of such foci beneath the granular layer of the epidermis may also be measured and reported (but it should be clearly stated how the measurements were obtained and that the periadnexal measurement represents the estimated "true" Breslow thickness). 4. The Breslow thickness cannot be determined if a superficial biopsy transects a melanoma and includes only its superficial portion. In such instances, the pathologist can only report the melanoma to be 'at least' a certain thickness. Correlation with the re-excision specimen is

		necessary. 5. Other problems may arise from differing interpretations of the nature of dermal cells (ie whether they represent melanoma or a pre-existing naevus) and of tumours with verruciform architecture. 6. The inclusion of neurotropic spread of melanoma in the measurement of Breslow thickness is controversial. In this instance, it is recommended that the thicknesses of the tumour including and excluding the neurotropic component be recorded in the pathology report. 7. Satellites, as discussed in detail below, are foci of tumour discontinuous from the primary melanoma (probably representing local metastases) and should not be included in the measurement of tumour thickness. 8. In some instances, particularly when a melanoma arises in association with a nevus, it may be difficult to distinguish small "nevoid" melanoma cells from nevus cells, and this may have implications for measuring tumour thickness. Careful assessment of architectural and especially cytologic features should assist in distinction, but at times this remains difficult, subjective, and prone to interobserver variability.
	CS3.01e	The standard method for measurement of tumour thickness in ulcerated lesions may lead to an underestimate of thickness, because the recommended measurement from the base of the ulcer to the base of the tumour makes no allowance for the amount of tumour lost through ulceration.
	CS3.01f	The thickness (measured from the top of the granular layer) of any zone of regression may also be recorded in the pathology report (but does not represent the Breslow thickness).
S3.02	**The pathology report must indicate whether or not the invasive or in situ melanoma involves the surgical margins / tissue margins.**	
	CS3.02a	The pathology report should document the: 1. In situ component: peripheral margin 2. Invasive component: deep margin 3. Invasive component: peripheral margin If involved, the location(s) must be specified if possible.

		If not involved the distance of the melanoma from the closest uninvolved margin must be recorded and the location(s) of the closest uninvolved margins should be recorded, if possible. Margin measurements to within the nearest 1 mm are sufficient for the purposes of directing further management. If the melanoma is within 2mm of the resection line, it is recommended that the margin measurement be recorded to within the nearest 0.1mm measurement.[16]
	CS3.02c	The standard treatment for primary melanoma is wide local excision of the skin and subcutaneous tissues around the melanoma. Such definitive treatment is not usually performed until after a pathological diagnosis of melanoma has been established. The aim is complete surgical excision of all in situ and invasive melanoma components. Involvement of the surgical margin may result in regrowth or metastasis from residual melanoma, and may adversely affect patient outcome.[17-19]
		On the basis of several randomized controlled trials (RCTs)[20-24] national guidelines from several countries have recommended wide excision margins according to the thickness of the primary cutaneous melanoma.[25-27] The trials were based on surgical margins measured clinically at the time of wide excision. Clinically measured wide excision margins are a less precise measure of the extent of excision of normal tissues surrounding the tumour than the histopathological margins. However, there is very little evidence is available for relationship between histopathological measured margin and local, in transit and regional recurrence.
		Providing data on distance of melanoma from the margins may be helpful not only to clinicians in guiding patient management but also for pathologists when examining any subsequent specimen (eg. re-excision specimen or for determining whether recurrent tumour at the primary site represents local persistence of melanoma or a metastasis). Defining the peripheral extent of the epidermal component of a melanoma may be difficult and subjective particularly for melanomas arising in chronically sun-damaged skin in which the peripheral changes merge with those related to the effects of severe chronic sun damage and also for acral (and mucosal) melanomas.[28]
S3.03	**The presence or absence of ulceration must be reported.**	
	CS3.03a	Ulceration is an integral component of the AJCC/UICC staging system and an independent predictor of outcome

		in patients with clinically localised primary cutaneous melanoma.[30-32]
	CS3.03b	Assessing the presence of ulceration may be difficult in recently biopsied lesions and in cases in which there is only a focal loss of the epidermis; in this case, it is difficult to determine whether the epidermal deficiency is due to ulceration or to sectioning artifact. Absence of fibrin or granulation tissue from putative areas of ulceration would be clues that the apparent ulceration is actually due to sectioning of only part of the epidermis.[33]
	CS3.03c	Distinguishing between iatrogenic and noniatrogenic ulceration is important because the former is of no prognostic significance.[19] Differentiation is relatively easy when a clinical history of a previous biopsy is provided or a well demarcated dermal scar is present; however, at other times it can be difficult or impossible to distinguish between the two.[20]

G3.02	The extent of ulceration should be recorded.	
	CG3.02a	Extent of ulceration (measured either as diameter or percentage of tumour width) provides more accurate prognostic information than the mere presence of ulceration.[34-37]
S3.04	**The mitotic count per square millimetre of the invasive melanoma must be recorded.**	
	CS3.04a	Multiple studies indicate that mitotic rate is an important prognostic factor for localised primary melanomas (including very large studies utilizing the methodology for mitotic count determination described below).[33,3,38-44,34,45]
	CS3.04b	The number of mitotic figures can vary greatly between different parts of a tumour. For consistency and reproducibility, a standardised method must be used to assess mitotic count.[46] It is recommended that the field diameter of a microscope be formally calibrated using a stage micrometer to determine the number of high-power fields that equates to a $1mm^2$.
	CS3.04c	In the 7th edition of the AJCC melanoma staging system, the recommended method to enumerate mitotic figures is to find an area in the dermis with obvious mitotic activity (the "hot spot"), and begin the count in this area, then extending the area counted to immediately adjacent non-overlapping high-power fields in a $1mm^2$ area. If no hot spot is identified and the mitotic figures are sparse and randomly scattered, then the count should begin in a field containing a mitosis, then

		extended to immediately adjacent non-overlapping high-power fields until a 1mm^2 area of tissue containing melanoma is assessed. When the invasive component of the tumour involves an area <1mm^2, a 1mm^2 area of dermal tissue that includes the tumour should be assessed and recorded as a number per mm^2. The number of mitotic figures should be listed as a whole number/mm^2. If no mitotic figures are identified, the mitotic count may be recorded "none identified" or "0/mm^2". This methodology for determining the mitotic count of a melanoma has been shown to have excellent interobserver reproducibility including amongst pathologists with widely differing experiences in the assessment of melanocytic tumours.[33] It is also recommended in 7th edition of the AJCC staging manual that the mitotic count should be assessed in all primary melanomas for prognostic purposes. However, it is only the presence or absence of mitotic figures in non-ulcerated thin (≤1.0mm thick) melanomas that impacts staging (i.e. for separating pT1a and pT1b tumours). The data that demonstrated the strong prognostic significance of mitotic count were obtained from the melanoma pathology reports of routinely assessed H&E stained sections. It is therefore not recommended that any additional sections be cut and examined (or immunochemical analysis be performed), in excess of those that would normally be used to report and diagnose the melanoma, to determine the mitotic count (i.e. no additional sections should be cut and examined for the purpose of determining the mitotic count; this includes the situation when no mitotic figures are identified on the initial, routinely examined sections).
S3.05	**The presence or absence of satellites must be recorded.**	
	CS3.05a	A microscopic satellite is any nest of metastatic tumour cells discontinuous from the primary tumour (but not separated only by fibrosis or inflammation).
	CS3.05b	The terms '(micro)satellites', 'in-transit metastases' and 'local metastases' probably represent biologically identical processes with identical (worse) prognostic implications.[47-50] (Micro)satellites and in-transit metastases are included in the same prognostic group by the AJCC.[30-31,50,32]
	CS3.05c	If satellites are present, margin involvement must be assessed and recorded in the pathology report. The presence of a melanoma satellite metastasis at a peripheral excision margin may be an indication for re-excision, because it implies that there may be further melanoma in the skin beyond the visible margins.

G3.03	The Clark level should be recorded.	
	CG3.03a	Clark level IV or V is referred to as a tertiary criterion for T1b in cases with no ulceration and "if mitotic count cannot be determined." Clark level should therefore be reported whenever it would form the basis for upstaging T1 lesions.
	CG3.03b	Clark level may also provide useful prognostic information if an accurate Breslow thickness cannot be determined. Most evidence suggests that the Breslow thickness of a melanoma is a more accurate prognostic indicator than the Clark level.[3] In the 2010, 7th edition of the AJCC melanoma staging system, Clark level is no longer used as a primary criterion for the definition of T1b tumours (which are now defined by the presence of a dermal mitotic count $\geq 1/mm^2$ or the presence of ulceration) except in the instance referred to above.[30,51,5]

CG3.03c Clark's levels are defined as follows:[55]

- Level I: Melanoma cells confined to the epidermis (melanoma in situ).
- Level II: Melanoma cells invade but do not fill or expand the papillary dermis.
- Level III: Melanoma cells fill and expand the papillary dermis, with extension of tumour to the papillary–reticular dermal interface. The boundary between the papillary and reticular dermis may be hard to identify, particularly if there is severe solar elastosis; it can also be hard to identify in sites such as the scalp, acral skin, mucosal or anogenital regions. The papillary dermal collagen fibres are fine and oriented vertically, whereas the reticular dermal collagen bundles are coarse and have a more horizontal orientation. This distinction can be used in polarisation microscopy because reticular dermal collagen is birefringent. Another useful landmark in separating the papillary and reticular dermis is the presence of a capillary plexus at the interface. Polypoid tumours that expand but do not fill the papillary dermis should be classified as level III.
- Level IV: Melanoma cells infiltrate into the reticular dermis.
- Level V: Melanoma cells infiltrate into the subcutaneous fat. In sites where subcutaneous fat may be absent (eg the lip or subungual regions), extension into other structures deep to the dermis (eg skeletal muscle or bone) should be recorded as Clark level V invasion.

S3.06	**The presence or absence of lymphovascular invasion must be recorded.**	
	CG3.06a	Vascular invasion is identified by the demonstration of melanoma cells within the lumina of blood vessels or lymphatics, or both. It is an uncommon finding in the excision specimens of primary cutaneous melanoma, but is generally regarded as a marker of poor prognosis.[52-53 54-55] There is a possible role for immunohistochemistry to highlight the presence of vascular invasion.[54,56]
	CG3.06b	Pathological misinterpretation may arise in the assessment of vascular invasion if a space around a tumour is regarded as retraction artefact or if a tumour completely occludes a vessel and the presence of a vessel is not recognised. The application of endothelial markers, such as CD31 and CD34, and new specific lymphatic endothelial markers, such as lymphatic vessel endothelial receptor-1 (LYVE-1) and podoplanin (D2-40), may be of assistance when there is uncertainty.[20,56-57]

G3.04	The assessment of tumour-infiltrating lymphocytes (TILs) (a marker of early regression) should be recorded.	
	CG3.04a	To be regarded as tumour-infiltrating lymphocytes (TILs), lymphocytes must infiltrate and disrupt tumour nests and/or directly oppose tumour cells.
	CG3.04b	The assessment and grading of TILs remains subjective and prone to interobserver variation, although agreement may be improved by instruction. Reports on the prognostic effect of TILs vary but most suggest the presence of 'brisk' or dense TILs is associated with a more favourable prognosis.[57,34,58] A recent report suggested a strong association between TIL infiltrates and sentinel node status and survival when utilizing a novel grading system.[59] Absent TILs predicted sentinel lymph node positivity in a number of recent studies.[60,59]
G3.05	The presence or absence of tumour regression (intermediate or late) should be recorded.	
	CG3.05a	A host immunologic response may be directed against melanoma and may result in elimination of part or all of the melanoma; this is termed regression. This phenomenon may be categorized into three temporal stages: early, intermediate and late. Early regression is signified by the presence of tumour-infiltrating lymphocytes (TILs). Intermediate and late regression result in partial or complete loss of melanoma and are characterized by immature (intermediate) and mature

		(late) dermal fibrosis, often accompanied by the presence of melanophages and effacement of the rete architecture. Most reports assessing the prognostic significance of regression have not differentially analysed intermediate and late regression.
	CG3.05b	The prognostic significance of (intermediate and late) regression is controversial.[2] Some studies report that it portends a worse prognosis (particularly in thin melanomas),[61] whereas others report that it is associated with a more favourable outcome.[2] Difficulties in interpreting such studies include lack of a standardised definition or criteria for its diagnosis, selection bias, and poor interobserver reproducibility.
	CG3.05c	Extent of regression (width and depth in millimetres) should be recorded.

G3.06	If tumour regression (intermediate or late) is present, margin involvement should be assessed and recorded in the pathology recorded.	
	CG3.06a	Regression at a peripheral excision margin is an indication for re-excision because it probably implies that there may be further melanoma in the skin beyond the visible margins.
	CG3.06b	If the margins are not involved, the clearance from margins of excision should be recorded.

S3.07	**The absence or presence of any desmoplastic melanoma component must be recorded.**	
	CS3.07a	Desmoplastic melanoma (DM) is a rare subtype of melanoma characterized by malignant spindle cells separated by prominent fibrocollagenous or fibromyxoid stroma. Primary melanomas may be entirely or almost entirely desmoplastic ("pure" DM) or exhibit a desmoplastic component admixed with a non-desmoplastic component ("mixed" DM).[70] In 2004, Busam *et al* reported a clinicopathologic study of DM patients in which subdividing the tumours into "pure" and "mixed" subtypes correlated with clinical outcome.[71] In that study, the authors classified melanomas as "pure" DM if "the overwhelming majority (≥90%) of invasive tumour was desmoplastic", or "mixed" DM if "typical features of DM were mixed with densely cellular tumour foci without fibrosis and desmoplasia" and the DM areas involved <90% and >10% of the invasive melanoma. Similar findings have since been reported by others.[62-64,66,72-73,71,74-80] Improved disease-specific survival is seen in patients with "pure" DM, when compared with patients with "mixed" DM and those with melanomas lacking a desmoplastic component.[62-64,66,72-

		[73,71,74-80] Furthermore, regional nodal metastasis (including that detected by sentinel lymph node biopsy) is less common in patients presenting with clinically localized pure DM compared with those who had mixed DM or conventional melanomas.[62-64,66,72-73,71,74-80]
	CS3.07b	A desmoplastic melanoma component is defined as spindle melanoma cells associated with and separated by stromal desmoplasia (new collagen).[64-77] A desmoplastic melanoma may show neurotropism (but not all desmoplastic melanomas are neurotropic).
	CS3.07c	In some cases of melanoma, it is impossible to be certain whether the dermal collagen around the melanoma cells is old or new and hence in such cases it is difficult to determine accurately whether a melanoma is truly desmoplastic.

S3.08	**The presence or absence of neurotropism must be recorded.**	
	CS3.08a	Neurotropism is identified by the presence of melanoma cells around nerve sheaths (perineural invasion) or within nerves (intraneural invasion).[62-64] Occasionally, the tumour itself may form neuroid structures (termed 'neural transformation'; this is also regarded as neurotropism).[62,54,56,65]. It is recommended that pathologists be cautious not to overinterpret the presence of melanoma cells around nerves in the main tumour mass (which often represents "entrapment" of nerves in the expanding tumour) as neurotropism.
	CS3.08b	Infiltration along nerve sheaths (or occasionally within the endoneurium) may be associated with an increased local recurrence rate (local persistence).[66] Neurotropism is common in desmoplastic melanoma (desmoplastic neurotropic melanoma), but may occur in other forms of melanoma.[64,67-69] The presence of neurotropism is associated with increased risk of local recurrence and may, in some cases, be treated by wider excision margins and/or adjuvant radiotherapy.
G3.07	Any associated melanocytic lesion should be recorded.	
	CG3.07a	Although of no known prognostic value, the recognition of an associated benign melanocytic lesion is relevant to the pathogenesis of melanoma, and may be important for clinicopathological correlation and epidemiological, clinical and genetic studies.[81]
	CG3.07b	Documentation of associated benign melanocytic tumour is also of relevance where there may be residual melanocytic tumour in the re-excision specimen, and when knowledge of this may assist in the interpretation

		of the residual tumour overlying a scar as pseudomelanoma/recurrent naevus, rather than melanoma.
	CG3.07c	In some instances it can be difficult or even impossible to determine whether part of the dermal component of a melanocytic tumour represents melanoma or an associated naevus. This is particularly the situation in melanoma composed of small, minimally atypical 'naevoid' cells, or in cases in which the dermal component of a melanoma 'matures' with depth.[82] Careful assessment of cytological characteristics - including the presence of mitotic figures and the identification of a second discrete cell population - may assist in some cases.

G3.08 The intra-epidermal growth pattern of the melanoma should be recorded.

CG3.08a The 2008 *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand* recommend that the intraepidermal growth pattern of the melanoma (ie pagetoid, lentiginous or mixed patterns) be recorded.[3] The recognition of the intraepidermal growth pattern is important in reaching the diagnosis of melanoma.

G3.09	The melanoma subtype should be recorded.	
	CG3.09a	The following value list is modified from the World Health Organization (WHO) *Classification of Tumours: Pathology and Genetics Skin Tumours*, published in 2005,[79] lists • superficial spreading melanoma (SSMM) • nodular melanoma (NM) • lentigo maligna melanoma (LMM) • acral-lentiginous melanoma • desmoplastic melanoma • melanoma arising from blue naevus • melanoma arising in a giant congenital naevus • melanoma of childhood • naevoid melanoma • persistent melanoma • Melanoma, not otherwise classified

		• Other (specify)
	CG3.09b	The common subtypes listed (superficial spreading melanoma, nodular melanoma, and lentigo maligna melanoma), have little if any prognostic significance independent of tumour thickness, interpretation is subjective and prone to interobserver variation,[107-109,2,110] and their use is principally for clinicopathological correlation. Nevertheless, the traditional ("Clark") melanoma histogenetic classification highlights the myriad of clinical and histological guises of melanoma, which if not recognized by clinicians and pathologists will inevitably lead to a delay in diagnosis and a concomitant adverse clinical outcome.[111] The traditional classification has been criticised because the criteria upon which it is based include clinical features (such as the site of the melanoma) and non-tumourous histopathological features (such as the character of the associated epidermis and the degree of solar elastosis) and also because of overlap in defining features, lack of an independent association with patient outcome and minimal relevance as a determinant of clinical management.
	CG3.09c	Epidemiological and molecular genetic evidence suggests that there are subgroups of melanoma that are associated with specific genetic alterations. The mutations identified in melanomas have included NRAS (15-20%), BRAF (50%), KIT (2%), and GNAQ/GNA11 (50% of uveal melanomas). There are associations between the presence of some mutations and the anatomical site of a melanoma and the degree of solar elastosis.[81,112] A comparison of the traditional clinicopathological melanoma classification with a classification based on the somatic mutation status reveals remarkable similarities. For example, melanomas associated with prominent solar damage (lentigo maligna melanomas) commonly have NRAS and sometimes KIT mutations, whereas superficial spreading melanomas that arise in the skin of intermittently sun-exposed areas often have BRAF mutations. KIT mutated melanomas most often involve acral (acral lentiginous melanoma) and mucosal sites. Nevertheless, the degree of accuracy of melanoma histogenetic subtype (or histopathological assessment) for predicting the mutation status of a melanoma is not sufficient to replace mutation testing for the purposes of patient care.
	CG3.09c	The 2008 *Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand* recommends the terminology "Melanoma, in situ" (synonyms lentigo maligna/Hutchinson's melanotic freckle, superficial spreading melanoma in situ, acral lentiginous melanoma in situ) and "Melanoma, invasive"

		(synonyms lentigo maligna melanoma, superficial spreading melanoma, acral lentiginous melanoma, nodular melanoma and unclassified melanoma) for "melanoma of common type".[3] The aforementioned guidelines also recommend the terminology desmoplastic melanoma (as an uncommon variant) and for other variants (designated as "controversial and provisional"): malignant blue naevus (melanoma resembling or arising in a blue naevus), melanoma in congenital naevus, minimal deviation (naevoid) melanoma, animal type melanoma (pigmented epithelioid melanocytoma) and primary dermal melanoma.[3]
S3.09	**Lymph node status must be recorded.**	
	CS3.09a	If lymph nodes are NOT received, this element should not be reported. If lymph nodes are submitted, the following must be recorded: • The number of sentinel nodes examined, • The number of positive sentinel nodes, • The total number of nodes examined (sentinel and non-sentinel), and • The total number of positive nodes examined (sentinel and non sentinel).
	CS3.09b	Any additional relevant microscopic comments should be recorded. Tumour-harboring status of the SLN is the strongest predictor of outcome for clinically localized primary cutaneous melanoma patients[59,83-85] There are a number of potential pitfalls in the microscopic examination of SLNs.[86] The most common diagnostic problem is distinguishing nodal nevus cells from a melanoma metastasis. This can usually be resolved by careful assessment of the location, morphologic features, and immunohistochemical staining characteristics of the cells and, in some instances, comparing the cytology of the nodal melanocytes with the cells of the primary invasive melanoma. Nodal nevi are usually located in the fibrous capsule and trabeculae of lymph nodes (but may rarely occur within the nodal parenchyma) and consist of small cytologically bland cells that are devoid of mitotic activity and, on immunohistochemistry, show strong diffuse positivity for S-100 and Melan-A, minimal staining for HMB-45, and a low (<2%) Ki-67 proliferative index. In contrast, melanoma deposits in SLNs are typically located in the subcapsular sinus or parenchyma and often comprise large, cytologically atypical cells with variably prominent nucleoli, mitotic activity, HMB-45 positivity, and Ki-67 positivity (variable but usually >2%).[87-88] Other cells that may be found within lymph nodes and that are positive for S-100 include

		interdigitating (antigenpresenting dendritic) cells, nerves, and, occasionally, macrophages. These can usually be distinguished from melanoma cells on the basis of their location, size, shape, nuclear and cytoplasmic characteristics, distribution within the node, and immunohistochemical profile.[89] Positive Melan-A/MART-1 staining of small numbers of cells in the intraparenchymal portion of lymph nodes from patients without a history of melanoma has been reported, and in our view caution should be exercised to not overinterpret isolated Melan-A/MART-1-positive (or HMB-45-positive) cells in SLNs as melanoma in the absence of other corroborative evidence (such as cytologic atypia, mitotic activity, or immunohistochemical positivity for HMB-45 and an increased high Ki-67/MIB-1 index). In our experience, the occurrence of such cells has become a more frequent diagnostic problem in recent years, presumably reflecting the utilization of more sensitive antibodies and immunohistochemical techniques.[90-91] These cells could represent nevus cells, macrophages passively carrying melanoma-associated antigens, or some other cell type carrying antigens that cross-react with Melan-A/MART-1. Similarly, weak positive staining for HMB-45 is sometimes observed in pigment-laden macrophages.
G3.10	In the presence of sentinel lymph node metastasis, the location of the tumour in the node, the presence of extranodal extension and the dimension of the maximum single dimension of the largest discrete metastasis should be recorded.	
	CG3.10a	If the submitted SLNs contain metastatic melanoma, for each involved SLN, the pathology report should document: a) the location of the tumour within the lymph node (subcapsular, intraparenchymal, or both), b) the maximum single dimension of the largest discrete metastasis, c) the presence or absence of extranodal extension.
	CG3.10b	Histologic parameters of melanoma deposits in SLNs have been shown to be predictive of the presence or absence of tumour in non-SLNs and clinical outcome.[92-105] If there are only a small number of metastatic melanoma cells in the subcapsular sinus of the SLN, the patient's prognosis is very good and the chance of finding additional metastases in a completion lymph node dissection specimen is very small. However, if there are multiple large deposits of melanoma cells that extend deeply into the central part of an SLN, the prognosis is much worse, and the chance of finding

		additional metastases in non-SLNs in a completion lymph node dissection specimen is much higher. SLN parameters predictive of non-SLN status and survival include the size of metastases, tumour penetrative depth (also known as maximal subcapsular depth and centripetal thickness and defined as the maximum distance of melanoma cells from the nearest inner margin of the lymph node capsule), the location of tumour deposits in the SLN, the percentage cross-sectional area of the SLN that is involved, and the presence of extracapsular spread. However, the power of individual features of melanoma metastases in SLNs to predict tumour in non-SLNs, as well as survival, reported in some studies has not been reported by others. The determination of some of these parameters may not always be reliable, because tumour deposits are often irregularly shaped, the limits of tumour deposits can be difficult to discern, and tumour burden is to some degree dependent on sectioning protocols, as more extensive sectioning may reveal additional tumour deposits or demonstrate a greater dimension of deposit(s) in the deeper sections.[106]

G3.11 Any additional relevant microscopic comments should be recorded.

General commentary

Angiotropism

Angiotropism is the migration of melanoma cells along the external surface of blood vessels. A more detailed proposed definition for angiotropism is as follows:

'The melanoma cells should be cuffing the external surfaces of either capillary-sized blood vessels or lymphatic channels. The melanoma cells should be present in at least two or more foci. By definition there should be no tumour present within vascular lumina. Angiotropic foci must be located either at the advancing edge of the tumour or some distance (usually within 1–2 mm) from the main tumourous mass. Structures were counted as microvessels if they appeared vascular morphologically (ie they had a lumen surrounded by endothelium)'.[84]

Angiotropism is similar to the known propensity of melanoma to spread along nerves and skin adnexal structures. It has been proposed as a mechanism for melanoma metastasis (termed extravascular migratory metastasis) and may therefore be an important prognostic factor but requires further study.[84-86]

Cutaneous metastasis

The possibility of metastatic melanoma must be considered in cases where the tumour is located completely within the dermis and/or subcutis without either attachment to the epidermis or an intraepidermal component of atypical melanocytic proliferation. Epidermotropic metastasis may mimic primary melanoma and dermal primary melanoma may mimic a metastasis.[8,87] Therefore, the importance of clinicopathological correlation for determining whether any cutaneous melanoma is primary or metastatic cannot be overemphasised and is

probably more accurate in predicting clinical behaviour of the tumour than histopathological assessment alone.

Epidermal consumption
Consumption of the epidermis is defined as thinning of the epidermis with attenuation of basal and suprabasal layers and loss of rete ridges adjacent to collections of melanocytes and is associated with melanoma.

The value of epidermal consumption as a diagnostic and prognostic marker requires further study.[88-89]

Ki67 is a proliferation marker that is often increased in melanomas (>5%) and low in naevi (<5%) and occasionally may be useful in assessing primary melanocytic tumours to determine whether they are benign or malignant. The Ki67 proliferative index of a tumour may correlate with prognosis but requires further study.

Local melanoma metastasis versus persistent primary melanoma
The pathologist should attempt to distinguish between local melanoma metastasis (when the original primary melanoma was completely excised but has recurred at or near the primary site) and persistent primary melanoma (where the primary melanoma involved a margin on the previous resection specimen and has recurred at the primary melanoma site). This may require review of the previous primary melanoma excision.[28,90]

Predominant cell type
Melanoma composed predominantly of spindle cells may be associated with a better prognosis than those composed of epithelioid cells, but this has not been a consistent finding.

Solar elastosis
The relationship between patterns of sun exposure and site distribution of melanoma is fundamental to the understanding of the pathogenesis of melanoma.[91-92] The reporting of solar elastosis as an index of prolonged sun exposure may be valuable for research purposes.[78]

4 Ancillary studies findings

There are no ancillary tests currently used on a routine diagnostic basis for primary cutaneous melanoma.

For most melanomas, immunochemistry is not required to establish a pathological diagnosis of melanoma. In cases in which there is no in situ melanoma or in cases lacking typical morphological features or melanin pigment, immunochemistry for melanocytic markers may be useful in identifying the tumour as melanocytic in origin. Immunochemistry has only a very limited role in determining whether a primary melanocytic tumour is benign or malignant.[20]

S100 protein is expressed by most melanomas; although not specific for melanocytes, its presence is helpful in assessing the extent of inconspicuous infiltration by spindle cell melanomas, especially desmoplastic melanoma. Immunostaining for HMB-45 may be helpful in distinguishing between melanoma and atypical naevi, because HMB-45 positivity is retained in the deep component of melanoma, more than in naevi. Melan-A (Mart 1) is a sensitive marker of melanocytes but it is not usually expressed in desmoplastic melanoma. Microphthalmia transcription factor (MITF) is also a sensitive marker of melanocytic differentiation.

Recent studies evaluating chromosomal aberrations of melanocytic tumours using comparative genomic hybridisation (CGH) have shown that melanomas usually harbour numerous chromosomal aberrations where as such aberrations are rare in naevi.[93] In view of these findings, attempts have been made to utilise CGH to assist in accurate classification of melanocytic tumours, particularly for primary cutaneous melanocytic tumours in which the histopathological features alone do not permit clear characterisation as benign or malignant. However, because CGH is a labourious and time-consuming technique that requires expensive technology, it is only readily accessible as an approved supplementary diagnostic method, at the present time in a few specialised centres.

An alternative technique for the study of chromosomal aberrations in tumours that can be more readily employed in routine pathologic practice is florescent in situ hybridisation (FISH). In contrast to CGH, in which the DNA is extracted from tumour samples and analysed, FISH allows direct visualisation of quantitative genetic alterations within individual tumour cells, and thereby permits the pathologist to analyse a pure tumour population. Results validating the use of this technique both to distinguish between nevi and melanomas and to classify histologically problematic melanocytic tumours have been reported recently.[94-99] Once validated in larger studies, this technique may become commonly employed as a supplementary diagnostic test in the assessment of problematic melanocytic tumours.

With the recent development and testing of new promising targeted therapies for patients with metastatic melanoma, molecular pathology mutation testing for BRAF and c-KIT has become common in many melanoma treatment centers. At the present time, BRAF testing is recommended only in patients with inoperable AJCC stage III or stage IV disease (and will therefore usually not be performed at the time of diagnosis of primary cutaneous melanoma). Mutation testing can be performed on archival paraffin-embedded melanoma tissue. The preferential choice of tissue for mutation testing is distant metastatic tissue (most recent) first, then locoregional/in-transit metastasis, and finally primary melanoma.

In 50% of melanoma patients, their tumour carries an activating mutation in the BRAF oncogene which drives proliferation and inhibits apoptosis. The mutation is targeted by two potent orally-administered inhibitors, vemurafenib and dabrafenib. The majority of patients with BRAF-mutant melanoma treated with these agents show clinical benefit, and more than 50% have objective remissions in all sites of disease, including brain.[100-101] These drugs have very few side-effects, but can cause cutaneous SCCs in patients with sun-damaged skin. Vemurafenib is FDA-approved in the United States and PBS approval in Australia is currently being sought, while dabrafenib is only available through clinical trials programs at major melanoma centres in Australia at the present time. However, promising improvements on single agent therapy are emerging from clinical trials combining dabrafenib with trametinib, which inhibits MEK, the next enzyme downstream of BRAF. This combination looks even safer than single-agent BRAF inhibition and does not induce skin SCCs.

5 Synthesis and overview

Information that is synthesised from multiple modalities and therefore cannot reside solely in any one of the preceding chapters is described here. For example, tumour stage is synthesised from multiple classes of information – clinical, macroscopic and microscopic.

Overarching case comment is synthesis in narrative form. Although it may not necessarily be required in any given report, the provision of the facility for overarching commentary in a cancer report is essential.

By definition, synthetic elements are inferential rather than observational, often representing high-level information that is likely to form part of the 'Diagnostic summary' section in the final formatted report.

S5.01	**The primary tumour T category (AJCC 7th edition) [15] must be recorded.**	
	CS5.01a	In the 7th edition of the AJCC/UICC melanoma staging system, tumour thickness and ulceration continue to define T2, T3 and T4 categories. Moreover, T1b melanomas may also be defined by dermal mitotic count $\geq 1/mm^2$ or ulceration, rather than Clark level of invasion (as in 6th edition).[32] Clark level IV or V is referred to by the AJCC as a tertiary criterion for T1b in cases with no ulceration and "if mitotic rate cannot be determined."[30] The reference document: TNM Supplement: A commentary on uniform use, 4th Edition (C Wittekind editor) may be of assistance when staging.[113]
	CS5.01b	The 2010 (7th edition) of the AJCC melanoma staging system is shown in Tables S5.01a and S5.01b, below.[15]

S5.02	**The regional lymph nodes N category (AJCC 7th edition) [15] must be recorded.**	
	CS5.02a	As per the AJCC staging recommendations, where insufficient information is available to determine the N staging subcategory at the time of reporting a primary melanoma, these should be recorded with an "X" (ie Nx). In the 7th edition AJCC/UICC Staging system, N1 and N2 categories remain for microscopic and macroscopic nodal disease respectively (with sentinel lymph node biopsy recommended for pathological staging). Lymph node positivity is defined by the presence of melanoma cells identified on haematoxylin-eosin stained sections or on sections stained by immunohistochemistry alone. Other

		criteria for the N category are satellites, intransit metastases and microsatellites. M staging continues to be determined both by site of distant metastases and serum lactate dehydrogenase (LDH), but patients with regionally isolated metastasis from an unknown primary site should be categorised as Stage III rather than Stage IV, because their prognosis corresponds to that of Stage III disease from a known primary site. The AJCC staging committee eliminated the MX designation from the 7th edition of the AJCC/UICC TNM system. Pathologic assignment of the presence of metastasis (pM1) requires a biopsy positive for cancer from a metastatic site.

Table S5.01a **7th edition of the AJCC melanoma TNM subcategories.** Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com.

T classification	**Definition**
TX	Primary Tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Melanoma *in situ*
T1	Melanomas ≤1.0 mm in thickness
T1a	Without ulceration and mitosis <1/mm^2
T1b	With ulceration or mitoses ≥ 1/mm^2
T2	Melanomas 1.01–2.0 mm
T2a	without ulceration
T2b	with ulceration
T3	Melanomas 2.01–4.0 mm
T3a	without ulceration
T3b	with ulceration
T4	Melanomas >4.0 mm
T4a	without ulceration
T4b	with ulceration
N classification	**No. of metastatic nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	1 node
N1a	micrometastasis*
N1b	macrometastasis**
N2	2–3 nodes
N2a	micrometastasis*
N2b	macrometastasis**
N2c	in transit met(s)/satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)

M classification	Site
M0	No distant metastasis
M1a	Metastases to skin, subcutaneous tissues, or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

*Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

**Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Table S5.01b **7th edition of the AJCC pathological stage grouping for melanoma.** Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springerlink.com.

Stage	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-4a	N1a	M0
	T1-4a	N2a	M0
IIIB	T1-4b	N1a	M0
	T1-4b	N2a	M0
	T1-4a	N1b	M0
	T1-4a	N2b	M0
	T1-4a	N2c	M0
IIIC	T1-4b	N1b	M0
	T1-4b	N2b	M0
	T1-4b	N2c	M0
	Any T	N3	M0
IV	Any T	Any N	M1

S5.03 The year of publication and edition of the cancer staging system used in S5.01 must be included in the report.

G5.01 The 'Diagnostic summary' section of the final formatted report should include:

a. specimen type (S1.02)
b. tumour site and laterality (S1.02)
c. tumour type (G3.09)
d. tumour pT stage (S5.01)
e. tumour pN stage (S5.02)
f. whether or not the specimen margins are involved (S3.02)

S5.04 The pathology report must include a field for free text in which the reporting pathologist can give overarching case comment if required.

CS5.04a This field may be used, for example, to:

- explain the decision-making pathway, any elements of clinicopathological ambiguity, or factors affecting diagnostic certainty
- give recommendations for further action or investigation
- document further consultation or results still pending.

It may be helpful for the clinician and the pathologist to discuss pathology reports that do not accord with the clinical diagnosis. In cases of doubt, it may be appropriate to seek further opinion from one or more pathologists experienced in the diagnosis of melanocytic tumours.[8]

CS5.04b If there is uncertainty whether or not a cutaneous tumour is a melanoma or whether a melanoma is a primary or a metastasis, the evidence for and against the particular diagnoses should be presented and a preferred diagnosis given but this should be accompanied by an expression of the degree of uncertainty.[2,9-10] Where there is genuine doubt about the correct diagnosis, it may be appropriate to seek a further opinion from one or more experienced colleagues.

If the diagnosis of primary melanoma is favoured, the structured report may be completed, even though the diagnosis is not certain. The report may be prefaced with comments such as '*if primary melanoma, the lesion would have the following features:*'.

6 Structured checklist

The following checklist includes the standards and guidelines for this protocol which must be considered when reporting, in the simplest possible form. The summation of all standards is equivalent to the 'minimum dataset for melanoma'. For emphasis, standards (mandatory elements) are formatted in bold font.

S6.01 The structured checklist provided may be modified as required but with the following restrictions:

a) All standards and their respective naming conventions, definitions and value lists must be adhered to.

b) Guidelines are not mandatory but are recommendations and where used, must follow the naming conventions, definitions and value lists given in the protocol.

G6.01 The order of information and design of the checklist may be varied according to the laboratory information system (LIS) capabilities and described in *Functional Requirements for Structured Pathology Reporting of Cancer.*[102]

CG6.01a Where the LIS allows dissociation between data entry and report format, the structured checklist is usually best formatted to follow pathologist workflow. In this situation, the elements of synthesis or conclusions are necessarily at the end. The report format is then optimised independently by the LIS.

CG6.01b Where the LIS does not allow dissociation between data entry and report format, (for example where only a single text field is provided for the report), pathologists may elect to create a checklist in the format of the final report. In this situation, communication with the clinician takes precedence and the checklist design is according to principles given in Chapter 7.

G6.02 Where the checklist is used as a report template (see G6.01), the principles in Chapter 7 and Appendix 2 apply.

CG6.02a All extraneous information, tick boxes and unused values should be deleted.

G6.03 Additional comment may be added to an individual response where necessary to describe any uncertainty or nuance in the selection of a prescribed response in the checklist. Additional comment is not required where the prescribed response is adequate.

Values in italics are conditional on previous responses.

Values in all caps are headings with sub values.

S/G	Item description	Response type	Conditional
Pre-analytical			
S1.01	**Demographic information provided**		
S1.02	**Clinical information provided on request form**	**Text** OR **Structured entry as below:**	
	Tumour site	**Not provided** OR **Text** (specify tumour site)	
	Specimen laterality	**Single selection value list:** • Left • Right • Midline • Not provided	
	Clinical or differential diagnosis	**Text**	

S/G	Item description	Response type	Conditional
	Specimen type	**Single selection value list:** • Not provided • Excision • Punch • Incision • Shave • Curette • Re-excision • Other	**If re-excision is selected then 'For re-excision specimens' questions should be considered.** **If other is selected, record the other specimen type.**
	Other specimen type	***Text***	
	For re-excision specimens:		***Required only if re-excision is selected above***
	Previous laboratory	***Text***	
	Previous laboratory accession number	***Alpha-numeric***	
	Findings in previous biopsy	***Text***	
	History and timing of lesional trauma, biopsy, irritation or treatment with topical agent	**Text**	

S/G	Item description	Response type	Conditional
	Past history of melanoma	**Single selection value list:** • Yes • No	**If yes, give details (eg site, thickness, timing, treatment)**
	Details (eg site, thickness, timing, treatment)	***Text***	
	Evidence of metastatic disease?	**Single selection value list:** • Yes • No	**If yes, describe and consider recording the serum LDH**
	Describe	***Text***	
	Serum lactate dehydrogenase	**Numeric: ___IU**	
	Other relevant history	**Text**	
	Details of specimen orientation	**Text**	
	Any clinically or dermatoscopically suspicious areas?	**Single selection value list:** • Yes • No	**If yes, describe**
	Describe	***Text***	

S/G	Item description	Response type	Conditional
	Clinical or other relevant diagnostic imaging results	**Text** Notes: Diagrams should be noted if available	
	New primary melanoma or recurrence	**Single selection value list:** • New primary • Recurrence – local • Recurrence – intransit metastasis (between primary site and regional node field) • Recurrence – regional • Recurrence – distant • Not stated	
S1.03	**Pathology accession number**	Alpha-numeric	
S1.04	**Principal clinician caring for the patient**	Text	
G1.01	Other clinical information received	Text	
Macroscopic findings			
G2.01	Specimen description	**Text**	

S/G	Item description	Response type	Conditional
G2.03	Specimen dimensions	**Numeric: __x__x__mm** Notes: length x width x depth	
G2.04	Specimen orientation	**Not provided** **OR** **Text**	
G2.05	Macroscopic primary lesion description	**Text**	
G2.06	Macroscopic primary lesion dimensions	**Numeric: __x__x__mm** Notes: length x width x depth (depth is optional) **OR** **Indeterminate**	

S/G	Item description	Response type	Conditional
G2.07	Other lesion(s)	**Single selection value list:** • Not identified • Present	**If present, a macroscopic description of other lesion(s) should be recorded.**
	Macroscopic description of other lesion(s)	***Text***	
G2.08	Block identification key	**Text**	
G2.09	Other comments	**Text**	
Microscopic findings			
G3.01	Microscopic description	**Text**	
S3.01	**Breslow thickness**	**Indeterminate** **OR** **___mm*** **OR** **At least: ___mm*** Notes: *measurement should be to a minimum of 1 decimal point and to a	

S/G	Item description	Response type	Conditional
		degree of precision as to allow accurate AJCC staging.	
S3.02	**SURGICAL MARGIN/TISSUE EDGE STATUS**		
	In situ component: Peripheral margin	**Single selection value list:** • Cannot be assessed • Not involved by melanoma in situ • Involved by melanoma in situ	**If not involved, record the distance of melanoma in situ from closest margin and specify location(s) of closest uninvolved margin if possible.** **If involved, specify the locations of involved margin if possible**
	Location(s) of involved margin (if possible)	***Text***	
	Distance of melanoma in situ from closest margin	***Numeric: ___ mm***	
	Location(s) of closest uninvolved margin (if possible)	***Text***	

S/G	Item description	Response type	Conditional
	Invasive component: Peripheral margin	**Single selection value list:** • Cannot be assessed • Not involved by invasive melanoma • Involved by invasive melanoma	**If not involved, record the distance of invasive melanoma from closest peripheral margin and specify location(s) of closest uninvolved margin if possible** **If involved, specify the locations of involved margin if possible**
	Location(s) of involved margin (if possible)	***Text***	
	Distance of invasive melanoma from closest peripheral margin	***Numeric: ___ mm***	
	Location(s) of closest uninvolved margin (if possible)	***Text***	
	Invasive component: Deep margin	**Single selection value list:** • Cannot be assessed • Not involved by invasive melanoma • Involved by invasive melanoma	**If not involved, record the distance of invasive melanoma from closest margin and specify location(s) of closest uninvolved margin if possible** **If involved, specify the**

S/G	Item description	Response type	Conditional
			locations of involved margin if possible
	Location(s) of involved margin (if possible)	***Text***	
	Distance of invasive melanoma from closest margin	***Numeric: ___ mm***	
	Location(s) of closest uninvolved margin (if possible)	***Text***	
S3.03	**Ulceration**	**Single selection value list:** • Not identified • Present • Indeterminate	**If present, G3.02 should be considered.**
G3.02	Extent of ulceration	**Numeric: ___ mm**	
S3.04	**Mitotic count**	**Numeric: ___ per mm^2**	
S3.05	**Satellites**	**Single selection value list:** • Not identified • Present • Indeterminate	**If present, record satellites: margin involvement**

S/G	Item description	Response type	Conditional
	Satellites: margins	***Single selection value list:*** • *Cannot be assessed* • *Not involved by satellite* • *Involved by satellite*	
G3.03	Clark level	**Single selection value list:** • Confined to epidermis (I) • Infiltrates but does not fill papillary dermis (II) • Fills/expands papillary dermis (III) • Infiltrates into reticular dermis (IV) • Infiltrates into subcutaneous fat (V)	
S3.06	**Lymphovascular invasion**	**Single selection value list:** • Not identified • Present • Indeterminate	

S/G	Item description	Response type	Conditional
G3.04	Tumour-infiltrating lymphocytes (early regression)	**Single selection value list:** • Not identified • Brisk • Non-brisk	
G3.05	Tumour regression (intermediate and late)	**Single selection value list:** • Not identified • Present • Indeterminate	**If present record the extent of regression, and consider recording G3.06**
	Extent of regression	***Numeric: ___x___mm*** *Notes:* *Width x depth*	
G3.06	*Tumour regression (intermediate and late): margins*	***Single selection value list:*** • *Cannot be assessed* • *Not involved by regression* • *Involved by regression*	**If not involved, record the clearance from margins of excision**
	Clearance from margins of excision	***Numeric: ___ mm***	

S/G	Item description	Response type	Conditional
S3.07	**Desmoplastic melanoma component**	**Single selection value list:** • Not identified • Present	**If present, record if pure or mixed**
	Pure / mixed	***Single selection value list:*** • Pure desmoplastic melanoma (>90% desmoplastic features) • Mixed (mixed desmoplastic / non-desmoplastic melanoma)	
S3.08	**Neurotropism**	**Single selection value list:** • Not identified • Present • Indeterminate	
G3.07	Associated melanocytic lesion	**Single selection value list:** • Not identified • Present	**If present, describe**
	Describe	***Text***	

S/G	Item description	Response type	Conditional
G3.08	Intraepidermal melanoma growth pattern	**Single selection value list:** • Pagetoid • Lentiginous • Mixed pattern	
G3.09	Melanoma subtype	**Multi-select value list (choose all that apply):** • Superficial spreading melanoma • Nodular melanoma • Lentigo maligna melanoma • Acral-lentiginous melanoma • Desmoplastic melanoma • Melanoma arising from blue naevus • Melanoma arising in giant congenital naevus • Melanoma of childhood • Naevoid melanoma • Persistent melanoma • Melanoma, not otherwise classified • Other	**If other, specify the other subtype**
	Other subtype	***Text***	

S/G	Item description	Response type	Conditional
S3.09	**LYMPH NODE STATUS**		**Note this standard is conditional on receipt of lymph nodes in the specimen. If lymph nodes are NOT received this standard should not be reported.**
	Number of sentinel nodes examined	**Numeric:** ____	
	Number of positive sentinel nodes	**Numeric:** ____	**If >1 consider reporting G3.10**
	Total number of nodes examined (sentinel and non-sentinel)	**Numeric:** ____	
	Total number of positive nodes examined (sentinel and non-sentinel)	**Numeric:** ____	
G3.10	Sentinel lymph node metastasis: location of tumour within the lymph node	**Single selection value list:** • Subcapsular • Intraparenchymal • Both subcapsular and intraparenchymal	

S/G	Item description	Response type	Conditional
	Sentinel lymph node metastasis: extranodal extension	**Single selection value list:** • Not identified • Present • Indeterminate	
	Sentinel lymph node metastasis: maximum single dimension of the largest discrete metastasis	**Numeric: ____mm**	
G3.11	Additional comment	**Text**	
Synthesis and overview			
	PATHOLOGICAL STAGING (AJCC 7TH EDITION)		
S5.01	**Primary tumour (T)**	**Single select value list:** • TX Primary tumour cannot be assessed • T0 No evidence of primary tumour • Tis Melanoma in situ • T1 Melanomas ≤1.0 mm in thickness o T1a without ulceration and mitosis <1/mm2 o T1b with ulceration or	

S/G	Item description	Response type	Conditional
		mitoses ≥ 1/mm2 • T2 Melanomas 1.01–2.0 mm o T2a without ulceration o T2b with ulceration • T3 Melanomas 2.01–4.0 mm o T3a without ulceration o T3b with ulceration • T4 Melanomas >4.0 mm o T4a without ulceration o T4b with ulceration	
S5.02	**Regional lymph nodes (N)**	**No nodes submitted or found** **OR** **Single selection value list :** • NX Regional lymph nodes cannot be assessed • N0 No regional lymph node metastasis • N1 - 1 node o N1a micrometastasis* o N1b macrometastasis** • N2 - 2–3 nodes o N2a micrometastasis* o N2b macrometastasis** • N2c in transit	

S/G	Item description	Response type	Conditional
		met(s)/satellite(s) without metastatic nodes • N3 4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s) <u>Notes:</u> * Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed). ** Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.	
S5.03	**Year and edition of staging system**	**Numeric:** year **AND** **Text:** Edition eg 1st, 2nd etc	
G5.01	Diagnostic summary Include: a. specimen type (S1.02) b. tumour site and laterality (S1.02)	**Text**	

S/G	Item description	Response type	Conditional
	a. tumour type (G3.09) b. tumour pT stage (S5.01) c. tumour pN stage (S5.02) d. whether or not the specimen margins are involved (S3.02)		
S5.04	**Overarching comment**	**Text**	

7 Formatting of pathology reports

Good formatting of the pathology report is essential to optimise communication with the clinician, and will be an important contributor to the success of cancer reporting protocols. The report should be formatted to provide information clearly and unambiguously to the treating doctors, and should be organised with their use of the report in mind. In this sense, the report differs from the structured checklist, which is organised with the pathologists' workflow as a priority.

Uniformity in the format as well as in the data items of cancer reports between laboratories makes it easier for treating doctors to understand the reports; it is therefore seen as an important element of the systematic reporting of cancer.

Please see Appendix 2 for further guidance.

Appendix 1 Pathology request information

This appendix describes the information that should be collected before the pathology test. Some of this information can be provided on generic pathology request forms; any additional information required specifically for the reporting of primary cutaneous melanoma may be provided by the clinician on a separate request information sheet. An example request information sheet is included below. Elements which are in bold text are those which pathologists consider to be required information. Those in non-bold text are recommended.

Patient information

- **Adequate demographic and request information should be provided with the specimen.**
  - Items relevant to cancer reporting protocols include:
    - patient name
    - date of birth
    - sex
    - identification and contact details of requesting doctor
    - date of request
  - The patient's ethnicity should be recorded, if known. In particular whether the patient is of aboriginal or Torres Strait islander origin. This is in support of a government initiative to monitor the health of indigenous Australians particularly in relation to cancer.
- The patient's health identifiers should be provided.
  - The patient's health identifiers may include the patient's Medical Record Number as well as a national health number such as a patient's Medicare number (Australia), Individual Healthcare Identifier (IHI) (Australia) or the National Healthcare Identifier (New Zealand).

Clinical Information

➢ 	**The tumour site should be recorded.**	
	•	Sufficient information is required to localise the lesion for subsequent therapy. A diagram or photograph can facilitate this.[2,20]
	•	When matched for other known prognostic factors, melanomas in the head and neck area, upper back and axial skeleton have a

		worse prognosis than extremity-based lesions.[26,54,103]
	•	The anatomic site of the tumour may also affect the pathologic interpretation of the histologic features observed, and this may, in turn, influence the proffered pathologic diagnosis. For example, naevi occurring on certain sites (including the palms, sole, fingers and toes, flexural sites, genitalia, the breast and ear) often display features that would be considered evidence favouring melanoma in melanocytic tumours occurring at other sites.[1-2,6-7]
➢	**The specimen laterality should be recorded.**	
	•	Specimen laterality information is needed for identification purposes and to localize the lesion for subsequent therapy.

➢ The clinical diagnosis or differential diagnosis should be recorded.

- Providing the provisional clinical diagnosis or differential diagnosis improves clinicopathological correlation and improves diagnostic accuracy.[2,20]

➢	**The specimen type should be recorded.**	
	•	Although clinical considerations are important in determining the most appropriate biopsy technique for a melanocytic tumour, the type of biopsy performed may affect the accuracy of pathological evaluation[8-9] At times partial biopsies are performed of melanocytic lesions. Possible reasons include a very low suspicion of melanoma, the melanocytic lesion being large or located in a cosmetically sensitive area, and in some instances, no clinical suspicion of the lesion being melanocytic (eg many melanocytic lesions exhibit no clinical pigment). Further, correlation of the type of procedure with the material received can be important for patient safety. For instance, if the clinician states that the procedure was a punch biopsy but the specimen examined is a skin ellipse, it is possible that there may be a misidentification of the specimen.
	•	An excision biopsy with narrow clearance margins is usually the most appropriate method of biopsy of a clinically suspicious melanocytic tumour.[10] This enables an accurate assessment and will allow definitive treatment to be planned appropriately if a diagnosis of melanoma is confirmed.
	•	Incomplete biopsies of melanocytic tumours (punch, incision, curette and some superficial shave biopsies) may contribute to pathological misdiagnosis, because of unrepresentative sampling of a heterogenous tumour (ie a partial biopsy may sample only the benign part of a lesion and miss a coexisting melanoma) or may not provide sufficient tissue for adequate assessment of the pathological criteria necessary to permit correct diagnosis.[11,9,12] Nevertheless, it remains an accepted clinical practice to partially sample melanocytic tumours in some instances, such as large pigmented lesions in surgically challenging locations—for

		example, the face or digits. Pathological diagnostic criteria for melanoma include features at the peripheral and deep aspects of the tumour, which may not be included in an incomplete biopsy. Another potential pitfall of an incomplete biopsy of a naevus is that it may regrow from residual naevocytes after incomplete removal. Regenerating naevi often display many histological features that commonly occur in melanomas (including pagetoid epidermal invasion, cytological atypia, occasional dermal mitoses and HMB45 positivity). For these reasons, such lesions have been termed 'pseudomelanomas' and are prone to overdiagnosis as melanomas.[13-15] Incomplete biopsies of melanomas may also provide inaccurate assessment of important pathological features, such as Breslow thickness. Accurate assessment of pathological features of a primary melanoma allows prognosis to be reliably estimated; it also guides selection of appropriate management (width of excision margins, appropriateness of sentinel node biopsy); inaccurate pathological assessment can lead to inappropriate (usually insufficient) therapy.

- If a partial/incomplete biopsy (such as a punch, incisional or shave biopsy) taken from a melanocytic lesion does not show diagnostic evidence of melanoma this may not rule out melanoma. A partial biopsy may be falsely negative for sampling and interpretive reasons and in this situation clinical correlation is very important. Interpretative issues may occur because of difficulty in assessing some of the features that might suggest malignancy in a small sample such overall architecture or subtle clues from the rest of the lesion. In many such instances when a partial biopsy of a melanocytic tumour does not show diagnostic evidence of melanoma, it would be appropriate to add a comment to highlight these issues in the pathology report such as: "Where a partial biopsy includes only part of a suspected melanocytic neoplasm, the biopsy may not be fully representative and melanoma cannot be excluded. Clinicopathological correlation is indicated to determine the need for lesion follow-up versus complete excision. If clinically indeterminate, complete narrow margin tumour excision is advised".

- If a re-excision specimen is received or sent, a copy of the report for the previous biopsy or excision of the lesion or details of previous pathology laboratory and case numbers or the important findings of the previous biopsy should be provided.

- The history and timing of lesional trauma, biopsy, irritation or treatment with topical agent should be recorded.

  - Following lesional trauma, biopsy, irritation or topical treatment, melanocytic naevi may display many histological features that commonly occur in melanomas (including pagetoid epidermal invasion, cytological atypia, occasional dermal mitoses and HMB45 positivity). Such regenerating naevi have been termed 'pseudomelanomas' and are prone to overdiagnosis as

melanomas. Changes typically occur within six months of a previous injury, and the pathological changes are confined to the affected area.[8,74,106,109-111]

- Pathological clues to the presence of surface irritation or trauma include the following epidermal changes: parakeratosis or hyperkeratosis, epidermal thickening and hypergranulosis.[21] Sometimes there is evidence of superficial dermal scarring.

- A history of previous primary melanoma, at this or any other site, should be recorded.

  - Previous melanoma is a significant risk factor for melanoma (approximately 10–12% of patients with primary cutaneous melanoma develop a subsequent melanoma).[1]

  - Clinical information may be important in determining whether a melanoma is a primary tumour or a metastasis.[87]

- Evidence of metastatic disease should be recorded.

  - Knowledge of the presence and site of metastases is an essential component of American Joint Committee on Cancer/ International Union Against Cancer (AJCC/UICC staging).

- In the presence of metastatic disease, serum lactate dehydrogenase (LDH) levels should be provided.

  - Serum LDH is a component of AJCC staging for melanoma.

- Other relevant history should be recorded.

  - Relevant history includes the history of the current lesion (duration, history or duration of change, signs of malignancy, size of lesion and ulceration).

  - Relevant melanoma risk factors include number of previous melanomas, presence of dysplastic naevi, total number of naevi, family history of melanoma and nonmelanoma skin cancer history.

  - Pregnancy is relevant because it may influence the interpretation and reporting of melanocytic tumours.[1,57,112-114]

- Details of specimen orientation should be recorded.

  - The specimen should be orientated if the status of specific surgical margins is critical in determining the need for, or extent of, further surgery.

  - Specimen orientation may be indicated with marking sutures or other techniques. If a specimen is orientated, the orientation should be indicated on the specimen request form (and this may be facilitated by the use of a diagram).

- Any clinically or dermatoscopically suspicious areas (often within a

pre-existing lesion) should be recorded.

- Any identified suspicious areas (often within a pre-existing lesion) should be identified, documented and marked for sectioning (eg with a suture or by superficially scoring the epidermis and superficial dermis around the area of concern, using a suitably sized punch or other technique).

- Clinically suspicious areas may suggest a melanoma developing within a pre-existing naevus (usually long standing and previously unchanged). It is important to examine such areas histopathologically, because they may represent melanoma.

➢ Clinical or other diagnostic imaging (eg dermoscopy or confocal microscopy) or a diagram should be included with the clinical request form if this information is useful to direct the pathologist to areas of particular clinical concern in the specimen, or to improve clinicopathological correlation.[115]

- Photography can be helpful when assessing clinically or dermoscopically heterogenous lesions. The clinician can use a clinical or dermoscopic image to direct the pathologist to areas of particular clinical concern, to improve clinicopathological correlation.[8,20]

- Clinical photography is not commonly performed but there are data to support the value of photographic images in aiding histological diagnosis.[8,10,115-116]

➢ **Record if this is a new primary melanoma or a recurrence of a previous melanoma, if known.**

- The term recurrence defines the return, reappearance or metastasis of cancer (of the same histology) after a disease free period.

  Recurrence should be classified as local recurrence, intransit metastasis (between the primary tumour site and regional node field), locoregional metastasis or distant metastasis.

  Local recurrence of melanoma refers to recurrence of melanoma within 5cm of the primary tumour site. Local recurrence maybe a consequence of incompletely excised primary melanoma (local persistence) or a local metastasis.

  Intransit metastasis refers to recurrence occurring beyond 5cm of the primary site and between the primary site and the draining regional node field.

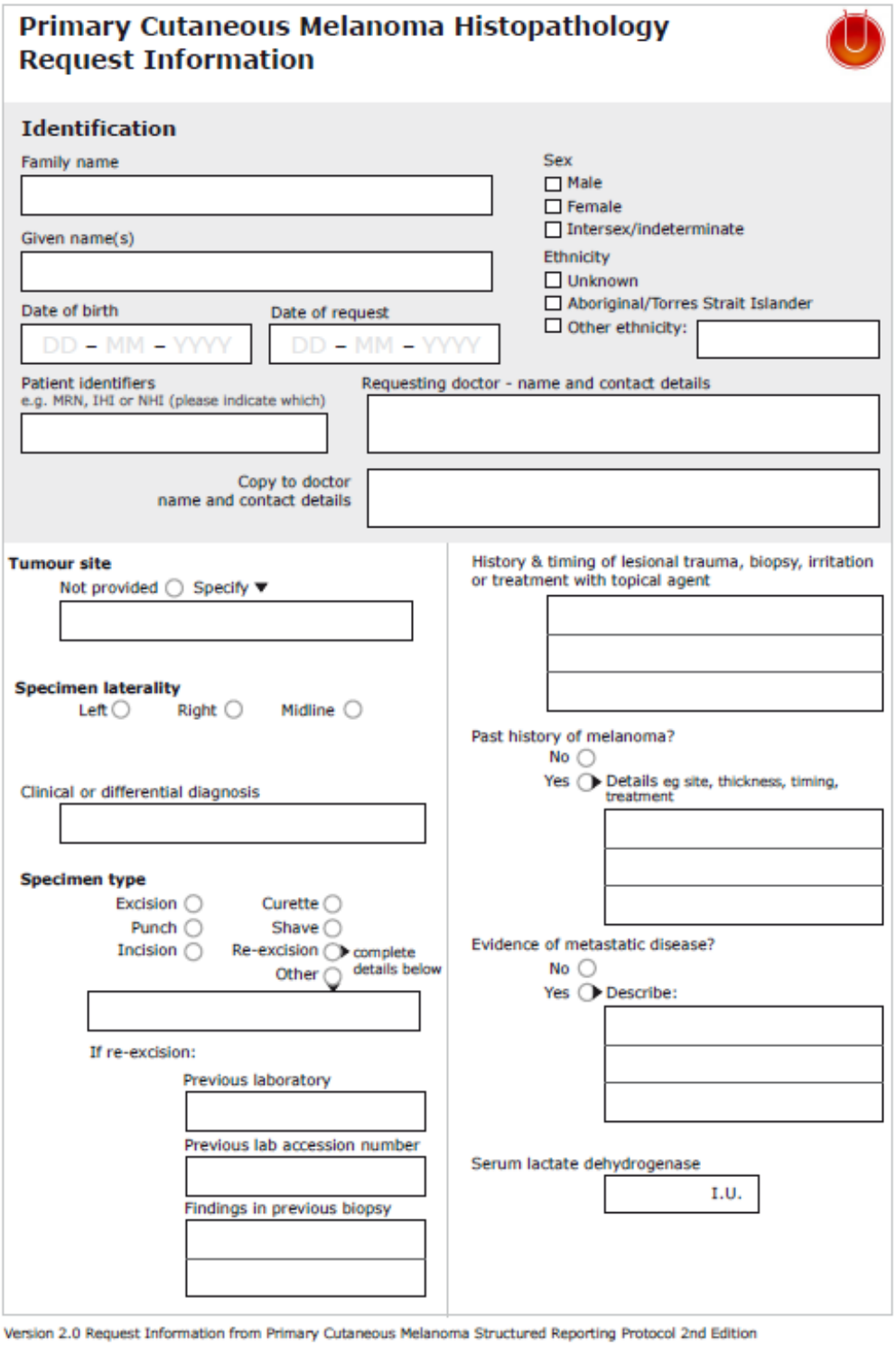
  Regional recurrence refers to the recurrence of cancer cells at the same site as the original (primary) tumour or the regional lymph nodes.

  Distant metastasis refers to the spread of cancer of the same histologic type as the original (primary) tumour to distant organs or distant lymph nodes.

- This information will provide an opportunity for previous reports to be reviewed during the reporting process, which may provide valuable information to the pathologist. This information also has implications for recording cancer incidence and evidence based research.

➢ A free text field should be included in the clinical notes section of a pathology request form so that the referring doctor can provide any relevant information that was not included in the standards and guidelines above.

Example Request Information Sheet



Primary Cutaneous Melanoma Histopathology Request Information

Identification

Family name

Given name(s)

Date of birth DD – MM – YYYY

Date of request DD – MM – YYYY

Sex
- ☐ Male
- ☐ Female
- ☐ Intersex/indeterminate

Ethnicity
- ☐ Unknown
- ☐ Aboriginal/Torres Strait Islander
- ☐ Other ethnicity:

Patient identifiers
e.g. MRN, IHI or NHI (please indicate which)

Requesting doctor - name and contact details

Copy to doctor name and contact details

Tumour site

Not provided ◯ Specify ▼

Specimen laterality

Left ◯ Right ◯ Midline ◯

Clinical or differential diagnosis

Specimen type

Excision ◯ Curette ◯
Punch ◯ Shave ◯
Incision ◯ Re-excision ◯ ▶ complete details below
Other ◯

If re-excision:

Previous laboratory

Previous lab accession number

Findings in previous biopsy

History & timing of lesional trauma, biopsy, irritation or treatment with topical agent

Past history of melanoma?

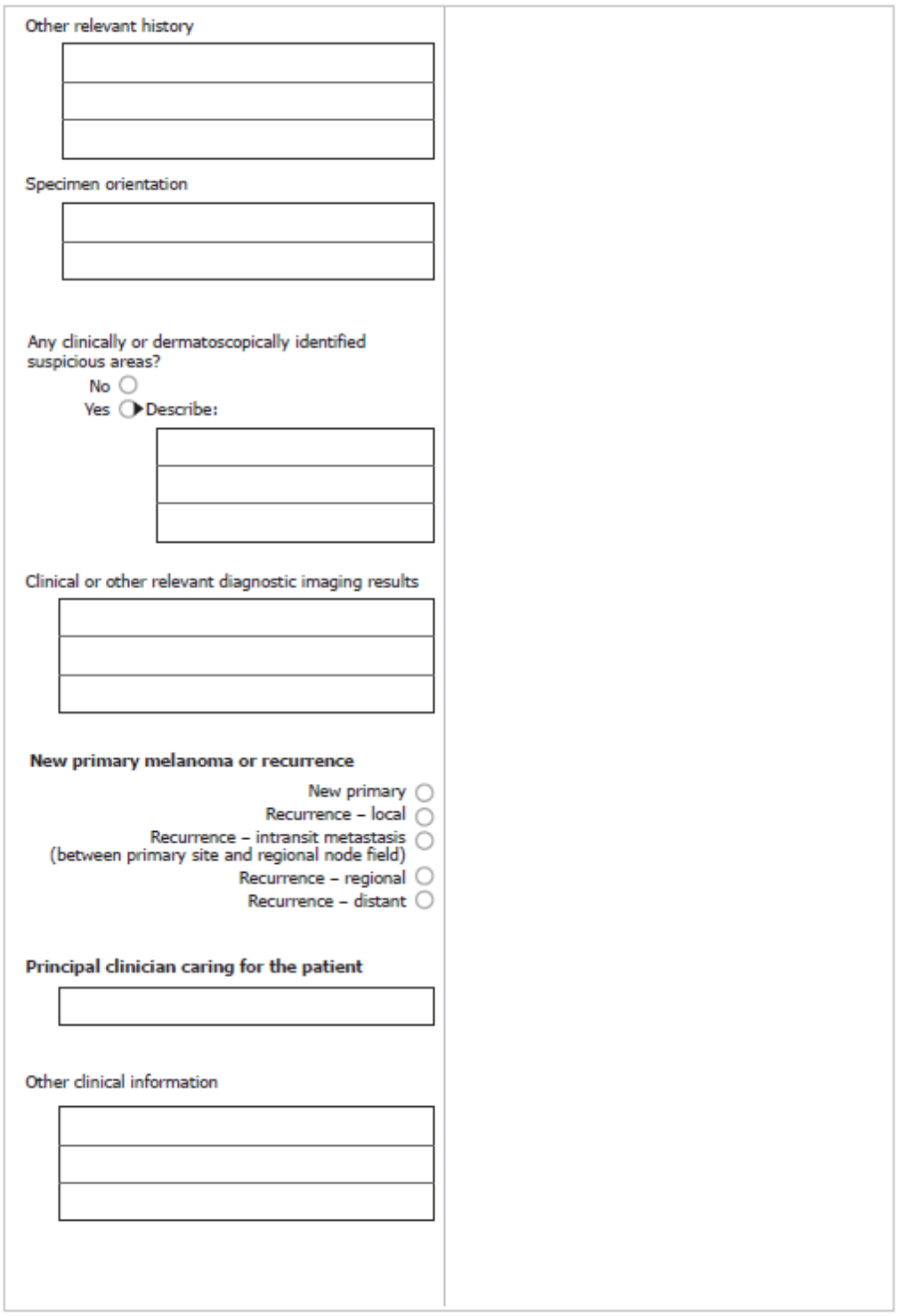
No ◯
Yes ◯ ▶ Details eg site, thickness, timing, treatment

Evidence of metastatic disease?

No ◯
Yes ◯ ▶ Describe:

Serum lactate dehydrogenase I.U.

Version 2.0 Request Information from Primary Cutaneous Melanoma Structured Reporting Protocol 2nd Edition



Version 2.0 Request Information from Primary Cutaneous Melanoma Structured Reporting Protocol 2nd Edition

The above Request Information Sheet is published to the RCPA website.

Appendix 2 Guidelines for formatting of a pathology report

Layout

Headings and spaces should be used to indicate subsections of the report, and heading hierarchies should be used where the LIS allows it. Heading hierarchies may be defined by a combination of case, font size, style and, if necessary, indentation.

Grouping like data elements under headings and using 'white space' assists in rapid transfer of information.[117]

Descriptive titles and headings should be consistent across the protocol, checklist and report.

When reporting on different tumour types, similar layout of headings and blocks of data should be used, and this layout should be maintained over time. Consistent positioning speeds data transfer and, over time, may reduce the need for field descriptions or headings, thus reducing unnecessary information or 'clutter'.

Within any given subsection, information density should be optimised to assist in data assimilation and recall. The following strategies will help to achieve this:

- Configuring reports in such a way that they 'chunk' data elements into a single unit. This will help to improve recall for the clinician.[117]
- Reducing 'clutter' to a minimum.[117] Thus, information that is not part of the protocol (eg billing information, SNOMED codes, etc) should not appear on the reports or should be minimised
- Reducing unnecessary formatting. Injudicious use of formatting elements (eg too much bold, underlining or use of footnotes) increases clutter and may distract the reader from the key information.

Where a structured report checklist is used as a template for the actual report, any values provided in the checklist but not applying to the case in question must be deleted from the formatted report.

Reports should be formatted with an understanding of the potential for the information to 'mutate' or be degraded as the report is transferred from the LIS to other health information systems.

As a report is transferred between systems:

- text characteristics such as font type, size, bold, italics and colour are often lost
- tables are likely to be corrupted as vertical alignment of text is lost when fixed font widths of the LIS are rendered as proportional fonts on screen or in print
- spaces, tabs and blank lines may be stripped from the report, disrupting the formatting
- supplementary reports may merge into the initial report.

Appendix 3 Example of a pathology report

Ng, George W.
C/O Paradise Close
Wineglass Bay
NSW, 2540

Male

DOB 1/7/1990
MRN FMC1096785

Lab Ref: **09/P28460**
Referred: 30/2/2009

Copy to: Dr G. Mannis
Rainforest Cancer Centre.
46 Smith Road,
Woop Woop, 3478

Referred by: Mr V. Button
Suite 3, AJC Medical Centre,
Bunyip Crescent
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MELANOMA STRUCTURED REPORT

Diagnostic Summary

Skin of right foot, excision biopsy:

Melanoma, pT3b, pNX, (AJCC 7th edition, 2010) margins clear.

Comment: The patient's age is noted. There is focal superficial dermal scarring, possibly a result of the recent trauma. The appearances nonetheless clearly indicate melanoma.

Supporting Information

CLINICAL

Tumour site and laterality:	Right foot
Clinical diagnosis:	? melanoma
Specimen type:	Excision biopsy
Prev. Rx / Trauma:	Trauma to the site 1 month ago
Past history of melanoma:	No
Evidence of metastastic disease:	Nil known
Other medical history:	None relevant
New primary melanoma or recurrence:	Not stated
Comment:	Suspicious area marked by scoring the surface with a 4mm punch biopsy

MACROSCOPIC

Specimen dimensions:	25mm x 12mm x 7mm
Specimen description:	An ellipse of skin.
Specimen orientation:	Unorientated.
Macro. primary lesion description:	An irregularly pigmented plaque with irregular margins and central ulceration. A 4x3mm area of increased pigmentation has been marked by scoring the surface with a punch biopsy. The lesion is one mm from the nearest superficial margin.
Macro. primary lesion dimensions:	8mm x 5mm
Other lesions:	Not identified

MICROSCOPIC

Breslow thickness:	2.3mm
Excision margins:	
Invasive -	Not involved by invasive melanoma. Closest margin 3.7mm
In-situ -	Not involved by melanoma in situ. Closest margin 1.4mm
Deep -	Not involved by invasive melanoma. Closest margin 5.0mm
Ulceration:	Present. Extent: 2.0mm
Mitotic count:	6 per mm²
Satellites:	Not identified.
Clark level:	IV
Lymphovascular invasion:	Not identified
TILs(early regression):	Non-brisk
Int. / late regression:	Not identified
Desmoplastic melanoma component:	Not identified
Neurotropism:	Not identified
Assoc. melanocytic lesion:	Present. Compound naevus
Intraepdermal growth pattern:	Mixed pattern. Lentiginous and Pagetoid
Melanoma subtype:	Acral-lentiginous melanoma

MICROSCOPIC (cont.)

Description:

The sections show acral-type skin and underlying subcutis with an asymmetrical compound melanocytic tumour. The epidermal component shows lentiginous and focally nested growth of large epithelioid melanocytes with variable intracytoplasmic pigment. There is focal single cell and nested Pagetoid epidermal invasion by large atypical cells mainly in the central part of the tumour. The dermal component shows expansile asymmetrical growth, variable, mostly poor maturation and in composed of cells with similar cytological characteristics to those of the epidermal component. Multiple mitoses are present in dermal melanocytes including two mitoses near the deep edge of the tumour. The punch biopsy scoring of the surface corresponds to the site of invasive melanoma. Focal superficial dermal scarring is also present.

Reported by Dr Samuel Wilks Authorised 4/3/2009

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