Invasive Melanoma Histopathology Reporting Guide

International Collaboration on Cancer Reporting (ICCR)

Family/Last name

Given name(s)

Gender ☐ Male ☐ Female ☐ Intersex/indeterminate

Date of birth DD – MM – YYYY

Patient identifiers

Date of request DD – MM – YYYY

Accession/Laboratory number

Elements in **black text** are REQUIRED. Elements in **grey text** are RECOMMENDED.

Tumour site (Note 1)

Not provided ◯ Specify ▼

Specimen laterality (Note 2)

Left ◯ Midline ◯ Right ◯ Not provided ◯

Specimen type (Note 3)

Not provided ◯ Curette ◯
Excision ◯ Shave ◯
Punch ◯ Re-excision ◯
Incision ◯ Other ◯ ▼

Specimen description

Specimen orientation
(This refers to the information received from the surgeon regarding orientation of the specimen by marking sutures, clips or other techniques)

Not provided ◯ Specify (if known) ▼

Specimen dimensions

length mm x width mm x depth mm

Macroscopic primary lesion description
(The description of the lesion includes includes such features as shape, colour, border, contour, evidence of surface crusting or ulceration and proximity to resection margins)

Macroscopic primary lesion dimensions

length mm x width mm x depth mm

Indeterminate ◯ (Note: Depth is optional)

Block identification key (List overleaf or separately with an indication of the nature and origin of all tissue blocks)

Other lesion(s) (Note 4)

Not identified ◯ Present ◯ ▼

Macroscopic description of other lesion(s)
(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)

SURGICAL MARGIN/TISSUE EDGES (Note 5)

In situ component: Peripheral margin

Cannot be assessed ◯
Not involved by melanoma in situ ◯ ▼
mm Distance of melanoma in situ from closest margin
Specify location(s), if possible
Involved by melanoma in situ ◯ ▼
Specify location(s), if possible

Invasive component: Peripheral margin

Cannot be assessed ◯
Not involved by invasive melanoma ◯ ▼
mm Distance of invasive melanoma from closest peripheral margin
Specify location(s), if possible
Involved by invasive melanoma ◯ ▼
Specify location(s), if possible

Invasive component: Deep margin

Cannot be assessed ◯
Not involved by invasive melanoma ◯ ▼
mm Distance of invasive melanoma from margin
Specify location(s), if possible
Involved by invasive melanoma ◯ ▼
Specify location(s), if possible

Breslow thickness (Note 6)
(Measurement should be to a minimum of 1 decimal point and to a degree of precision as to allow accurate AJCC staging)

Specify ◯ Indeterminate ◯
At least ◯ mm

Ulceration (Note 7)

Not identified ◯ Present ◯ Indeterminate ◯

Extent of ulceration (Note 8) mm

Mitotic count (Note 9) mm^2

Satellites (Note 10)

Not identified ◯ Present ◯ Indeterminate ◯

Satellites: margins (Note 11)

Cannot be assessed ◯ Not involved by satellite ◯
Involved by satellite ◯

Clark level (Note 12)

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) ◯

Lymphovascular invasion (Note 13)

Not identified ◯ Present ◯ Indeterminate ◯

Tumour-infiltrating lymphocytes (early regression)(Note 14)

Not identified ◯ Brisk ◯ Non Brisk ◯

Tumour regression (intermediate and late) (Note 15)

Not identified ◯ Present ◯ Indeterminate ◯

Tumour regression (intermediate and late):margins(Note 16)

Cannot be assessed ◯ Not involved by regression ◯
Involved by regression ◯

Neurotropism (Note 17)

Not identified ◯ Present ◯ Indeterminate ◯

Desmoplastic melanoma component (Note 18)

Not identified ◯ Present ◯
◯ Pure >90% desmoplastic melanoma
◯ Mixed desmoplastic/ non-desmoplastic melanoma

Associated melanocytic lesion (Note 19)

Not identified ◯ Present (describe) ◯

LYMPH NODES (Note 20) (If lymph nodes are not received these elements should NOT be reported.)

Number of sentinel nodes examined

Number of positive sentinel nodes

Sentinel lymph node metastasis: extranodal extension (Note 21)

Not identified ◯ Present ◯ Indeterminate ◯

Sentinel lymph node metastasis: location of tumor within the lymph node

Subcapsular ◯
Intraparenchymal ◯
Both subcapsular and intraparenchymal ◯

Sentinel lymph node metastasis: maximum single dimension of the largest discrete metastasis mm

Total number of nodes examined
(sentinel and non-sentinel)

Total number of positive nodes examined
(sentinel and non-sentinel)

Melanoma subtype (1 or more maybe applicable) (Note 22)
(Value list modified from the WHO Classification of Tumours. Pathology and Genetics of Skin Tumours. (2005).)

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 (specify) ☐

PATHOLOGICAL STAGING (AJCC 7th edition) © AJCC

Primary tumour (T) (Note 23)

◯ 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/mm2
◯ T1b with ulceration or mitoses ≥ 1/mm2
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

Regional lymph nodes (N) (Note 24)

◯ No nodes submitted or found
◯ 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)

* 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.

Note 1 - Tumour site

Reason/Evidentiary Support:

1. Sufficient information is required to localise the lesion for subsequent therapy. A diagram or photograph can facilitate this.[1-2]
2. 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.[3-5]
3. 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]

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Note 2 - Specimen laterality

Reason/Evidentiary Support:

Specimen laterality information is needed for identification purposes and to localize the lesion for subsequent therapy.

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Note 3 - Specimen type

Reason/Evidentiary Support:

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 tumors 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.

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Note 4 - Other lesion(s)

Reason/Evidentiary Support:

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.

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Note 5 - Surgical margin/Tissue edges

Reason/Evidentiary Support:

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]

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 tumor 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]

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Note 6 - Breslow thickness

Reason/Evidentiary Support:

Breslow thickness is the single most important prognostic factor for clinically localised primary melanoma.[3] 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.

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 tumor 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 tumor 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 tumor extending beyond the depth of the main tumor 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 tumor discontinuous from the primary melanoma (probably representing local metastases) and should not be included in the measurement of tumor 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 tumor 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.

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.

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).

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Note 7 - Ulceration

Reason/Evidentiary Support:

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]

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]

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Note 8 - Extent of ulceration

Reason/Evidentiary Support:

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]

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Note 9 - Mitotic count

Reason/Evidentiary Support:

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]

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 $1mm^2$.

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 ($\leq$1.0mm thick) melanomas that impacts staging (i.e. for separating pT1a and pT1b tumors).

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).

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Note 10 - Satellites

Reason/Evidentiary Support:

A microscopic satellite is any nest of metastatic tumour cells discontinuous from the primary tumour (but not separated only by fibrosis or inflammation). 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]

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Note 11 - Satellites: Margins

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.

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Note 12 - Clark level

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.

Reason/Evidentiary Support:

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]

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Note 13 - Lymphovascular invasion

Reason/Evidentiary Support:

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]

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Note 14 - Tumour-infiltrating lymphocytes (early regression)

Reason/Evidentiary Support:

To be regarded as tumour-infiltrating lymphocytes (TILs), lymphocytes must infiltrate and disrupt tumour nests and/or directly oppose tumour cells. 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]

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Note 15 - Tumour regression (intermediate and late)

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 tumor-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.

Reason/Evidentiary Support:

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.

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Note 16 - Tumour regression (intermediate and late): margins

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.

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Note 17 - Neurotropism

Reason/Evidentiary Support:

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 tumor mass (which often represents "entrapment" of nerves in the expanding tumor) as neurotropism.

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.

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Note 18 - Desmoplastic melanoma component

Reason/Evidentiary Support:

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 tumors 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 tumor was desmoplastic", or "mixed" DM if "typical features of DM were mixed with densely cellular tumor 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]

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Note 19 - Associated melanocytic lesion

Reason/Evidentiary Support:

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] 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.

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.

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Note 20 - Lymph nodes

Reason/Evidentiary Support:

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).

Any additional relevant microscopic comments should be recorded. Tumor-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.

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Note 21 - Sentinel Lymph Nodes

Reason/Evidentiary Support:

Histologic parameters of melanoma deposits in SLNs have been shown to be predictive of the presence or absence of tumor 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, tumor 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 tumor 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 tumor 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 tumor deposits are often irregularly shaped, the limits of tumor deposits can be difficult to discern, and tumor

burden is to some degree dependent on sectioning protocols, as more extensive sectioning may reveal additional tumor deposits or demonstrate a greater dimension of deposit(s) in the deeper sections.[106]

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Note 22 - Melanoma subtype

Reason/Evidentiary Support:

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.

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.

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Note 23 - Pathological Staging (AJCC 7th edition)*- Primary tumour (T)

Reason/Evidentiary Support:

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]

* 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. Update: 1st July 2011. Copyright permission pending

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Note 24 - Pathological Staging (AJCC 7th edition)*- Regional lymph nodes (N)

Reason/Evidentiary Support:

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.

* 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. Update: 1st July 2011. Copyright permission pending

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