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Histopathological reporting of cutaneous melanoma

The aim of the histopathology report on primary cutaneous melanoma is to provide the clinician with the information necessary for the optimum management of the patient. The most important components of the report are the correct diagnosis of primary melanoma (refer Chapter 5 *Clinical Diagnosis*), the microscopic assessment of completeness of excision and the microscopic measurement of tumour thickness (Breslow), the single most important prognostic factor for primary melanoma.¹ Beyond these essential components, other features are usually included in the report, some probably with prognostic value, although less than that of tumour thickness, and others which may be more helpful for studies of epidemiology and pathogenesis, for example, associated benign melanocytic lesion, cell type, solar elastosis.

A. Macroscopic description

- Dimensions of the specimen and the melanoma (in mm)
- Description of the melanoma: contour, profile, pigmentation, borders

B. Microscopic

- Essential components
 - Diagnosis of primary melanoma
 - Breslow thickness, measured to the nearest 0.1 mm
 - Margins of excision in mm
 - (i) invasive melanoma: lateral and deep margins
 - (ii) *in situ* melanoma: lateral margins
 - Level of invasion (Clark)
 - Mitotic rate per mm²
 - Ulceration: presence and extent (in mm)
- Other components
 - Vascular invasion
 - Microsatellites
 - Lymphocytic infiltrate: presence and extent of tumour-infiltrating lymphocytes (TIL)
 - Regression: presence and extent; clearance from margins of excision
 - Desmoplasia: presence and extent (% of invasive component)
 - Neurotropism
 - Associated benign melanocytic lesion
 - Solar elastosis: degree of severity
 - Predominant cell type, for example, epithelioid, spindle cell, naevoid
 - Histological growth pattern
 - Growth phase: radial, vertical
 - Immunohistochemistry

7.1 Comments on the histopathological reporting of melanoma

Assessment of completeness of excision: The entire tumour should be embedded whenever practicable. The margins need to be carefully examined not only for the presence of invasive melanoma but also for *in situ* melanoma and other atypical melanocytic proliferation. In those cases where the borders of the lesion are very poorly defined, as in some cases of melanoma in severely sun-damaged skin, the entire periphery of the specimen may be embedded for histopathological examination. Mapped serial excision has recently been recommended for the treatment of lentigo maligna (LM) and lentigo maligna melanoma (LMM) as providing a more reliable assessment of excision than the arbitrary limits of 5mm for LM and 10mm for LMM on standard histological sectioning.²

Level of invasion: Level of invasion is now included in the AJCC Clinical Staging only in the PT1 category of tumours 1 mm or less in thickness, on the basis that level of invasion is more likely to be of prognostic importance in thin melanomas.¹ Nevertheless, most clinicians expect level of invasion to be included in the report.

Mitotic rate: Some recent studies have suggested that mitotic rate (MR) is a more powerful factor than ulceration.³⁻⁶ For consistency and reproducibility in assessing mitotic rate, counting needs to begin in a zone within the invasive tumour of obvious mitotic activity ('hot spot') and on an area of one square millimetre.⁷

Ulceration: Ulceration is an integral component of the AJCC/UICC staging system.¹ The standard method for measurement of tumour thickness in ulcerated lesions, however, 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.

Vascular invasion: Vascular invasion as identified by the demonstration of melanoma cells within the lumina of blood vessels, and/or lymphatics, is an uncommon finding in the excision specimens of primary CM, but it is generally regarded as a marker of poor prognosis.⁸ Extravascular migratory metastasis, also termed angiotropism in cutaneous melanoma, has recently been proposed as a means of metastasis and therefore may be an important prognostic factor.⁹

Microsatellites, in-transit metastases, and local metastases (at the primary excision site): These are probably biologically identical with the same prognostic implications. Microsatellites and in-transit metastases are included in the same prognostic group by the AJCC.¹ Correct classification of these tumours is important for accurate recording by cancer registries, for correlation with the initial method of treatment and for assessment of prognosis and clinical staging.

Tumour-infiltrating lymphocytes (TIL): The assessment of TIL by distribution and density is a subjective exercise and prone to inter-observer variation, although agreement may be improved by instruction.¹⁰ Reports on the prognostic effect of TIL have varied; a recent study showed that TIL predicted sentinel lymph node positivity but were not an independent predictive factor for survival.¹¹

Regression: Regression is recognised by apparent loss of invasive tumour with associated fibrosis, lymphocytes, melanophages, and increased vascularity. Regression at a lateral

excision margin is an indication for re-excision because it implies that there may be further melanoma in the skin beyond the visible margins. Reports on the prognostic impact of regression have produced conflicting results but some have indicated that regression is an important adverse prognostic factor in thin melanoma.^{12,13}

Desmoplasia: Stromal desmoplasia underlying a melanoma should be examined for the presence of atypical spindle cells separated by collagen, as in *desmoplastic melanoma (DM)*. Extension of desmoplasia to the margins of excision is an indication for wider excision. Survival rates for patients with DM, with and without neurotropism, are similar to those for patients with other CM. A recent study reported that DM of 'pure' type (prominent desmoplasia throughout the invasive tumour) was associated with more favourable prognosis than DM of 'mixed' type (with partial desmoplasia).¹⁴

Neurotropism: Infiltration along nerve sheaths may be associated with an increased local recurrence rate.¹⁵ Neurotropism is common in desmoplastic melanoma (desmoplastic neurotropic melanoma), but may occur in other forms of melanoma.

Associated benign melanocytic lesion: 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 epidemiologic and genetic studies.^{16,17}

Solar elastosis: The relationship between patterns of sun exposure and site distribution of melanoma is fundamental to the understanding of the pathogenesis of melanoma. The reporting of solar elastosis as an index of prolonged sun exposure may be valuable, therefore, mainly for research purposes.^{16,17}

Predominant cell type: Melanoma composed predominantly of spindle cells has been associated with a better prognosis than those composed of epithelioid cells in some studies, but this has not been a consistent finding.¹⁸

Histological growth pattern: The classification of melanoma by Wallace Clark et al¹⁹ was widely accepted for many years on the basis of epidemiological studies that have indicated possible aetiological differences between some subtypes and on the didactic value of recognising a variety of growth patterns as an aid to diagnosis. This classification, however, has little if any prognostic value independent of tumour thickness, and its interpretation is very subjective and prone to inter-observer variation.²⁰ Recent epidemiological studies have emphasised the importance of site and different patterns of sun exposure as important determinants of melanoma growth patterns.¹⁶ This concept is supported by recent genetic studies that have indicated distinct genetic pathways in the development of melanoma at different sites and with different levels of sun exposure, but which did not demonstrate any genetic features of a separate entity for nodular melanoma.¹⁷

Growth phase: The histological criteria for recognition of the growth phases are very subjective and prone to inter-observer variation.²¹ The presence of vertical growth phase in thin tumours may be an indication of the possibility of metastasis from 'thin' melanoma.²²

Immunohistochemistry: S100 protein is expressed by most melanomas; although not specific for melanocytes, its presence is especially helpful in assessing the extent of inconspicuous infiltration by spindle cell melanomas, especially desmoplastic melanoma. Immunostaining for HMB-45 is less likely to be helpful in these problem tumours but it may

be helpful in distinguishing between melanoma and atypical naevi, by virtue of retention of HMB-45 positivity in the deep component of melanoma, more so than in naevi. Melan-A (Mart 1) is a very helpful marker of melanocytes but it is not usually expressed by spindle cells, as in desmoplastic melanoma; MITF (microphthalmia transcription factor) is also a sensitive marker of melanocytic differentiation. Studies of cell kinetics in melanoma have produced conflicting results²³ but a recent report suggested that Ki67 expression (assessed by the MIB-1 antibody) is an independent prognostic factor for thin melanomas ($\leq 1.00\text{mm}$ thick).²⁴

Primary melanoma versus metastatic melanoma: 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 proliferation²⁵ (see Table 5). *Epidermotropic* metastasis may mimic primary melanoma.

Local recurrence may be due to either persistence of incompletely excised primary melanoma or cutaneous metastasis. Clinically 'recurrent' melanoma in or adjacent to the scar or graft should be examined carefully for the histological criteria of persistent primary melanoma versus metastatic melanoma, and classified accordingly²⁶ (see Table 5). Persistent primary melanoma is most commonly the result of incomplete excision of *in situ* melanoma in sun-damaged skin, or diffusely invasive melanoma, for example, desmoplastic melanoma.^{26,27} Clinicopathological correlation is important.

Clinicopathological correlation: The clinician and the pathologist should discuss any pathology report that does not accord with the clinical diagnosis. In cases of doubt, an expert opinion should be sought. Spitz naevi, for instance, usually have benign clinical features resembling haemangioma or pyogenic granuloma, whereas their histological features may lead to misdiagnosis as melanoma.

7.2 Pathology request form

The following clinical information needs to be provided on the pathology request form.

Age and sex of patient

Anatomical site of melanoma

Clinical diagnosis

Description of type of specimen, for example, excision, biopsy (punch, incisional, shave)

Primary excision or re-excision. If re-excision, a copy of the previous report should be provided

History

- Present melanoma (duration, signs of malignancy, size of lesion)
- Previous melanoma(s)
- Family history
- Pregnancy
- History of lesional trauma, irritation or treatment with topical agent

Clinical photograph, if possible

Diagram of excision specimen with markers for orientation

Table 5 The histological features of persistent primary melanoma versus local metastasis of melanoma

	Persistent primary melanoma	Local metastasis of melanoma
Epidermal component	Usually present, with or without a dermal component	A. Absent in most cases B. Epidermotropism. The dermal component usually extends beyond a zone of epidermotropism when present. Sometimes the epidermotropic component is more extensive, simulating primary melanoma
Dermal growth pattern	The full range of patterns associated with primary melanoma: nodular, plaque-like, single cells, small groups of cells, diffuse, desmoplastic, neurotropic	A. Single or multiple symmetrical dermal and/or subcutaneous nodules B. Diffuse small groups and strands of atypical melanocytes (this pattern occurs in the smallest and presumably earliest metastases)
Inflammation	Lymphocytic inflammation usually present	Absent or sparse
Vascular invasion	Sometimes present	Present in many cases
Mitotic rate	Variable	High (usually > 6mm ²)
Cell type	The full range of cell types seen in primary melanoma, frequently including a mixture of cell types	Usually monomorphic atypical melanocytic population of epithelioid, spindle or small (naevoid) cells
Associated naevus	Commonly present	Rare (coincidental)
Necrosis	Uncommon	Often present in the centres of the nodules
Epidermal collarette	Uncommon	Usually present when nodules of metastatic melanoma are in the superficial dermis
Fibrosis	Frequently present in zones of regression and in desmoplasia	Little or no fibrosis in the stroma of the tumour
Scarring	Present in the dermis and often also in the subcutis	Present when the metastasis occurs at the primary excision site

Note: In cases of persistent primary melanoma, histological review of the primary excision specimen confirms the presence of *in situ* or invasive melanoma (or both) at a margin of excision. Melanoma metastatic to the scar of primary excision shows the same features as distant cutaneous metastasis with the additional feature of scarring from the previous surgery.

7.3 Recommended terminology and synonyms for cutaneous melanoma

Recommended terminology	Synonyms
Melanoma of common type	
Melanoma, <i>in situ</i>	Lentigo maligna (Hutchinson's melanocytic freckle) Superficial spreading melanoma <i>in situ</i> Acral lentiginous melanoma <i>in situ</i>
Melanoma, invasive	Lentigo maligna melanoma Superficial spreading melanoma Acral lentiginous melanoma Nodular melanoma Unclassified melanoma
Uncommon Variants	
Desmoplastic melanoma	
Others (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)	
Primary dermal melanoma	

7.4 Format of the report

The format can be either descriptive or synoptic (tabulated). It is suggested that both formats may be used.

7.4.1 Descriptive

The descriptive report on CM needs to refer to all the histological features of possible importance for individual cases. The accurate description of atypical cytologic features and growth patterns provide the reader, either another pathologist or a clinician, with an insight into the reasons for the pathologist's decision to make the diagnosis of malignant melanoma. In particular, an accurate description in problem cases, such as spitzoid tumours, alerts the clinician to the difficulty in reaching a definitive diagnosis, suggesting that alternative diagnoses may be considered and that further opinion(s) should be sought. The synoptic report is not a substitute for the descriptive report – it should be an easily readable, succinct, appendage.

7.4.2 Synoptic

Synoptic reports present the histological features of the tumour in a tabulated form to provide essential information for the assessment of prognosis and the planning of treatment.^{28,29,30} The report should emphasise the most important components which are:

1. the correct diagnosis of primary melanoma
2. Breslow thickness
3. accurate assessment of margins of clearance of both invasive and *in situ* melanoma. In addition the synoptic report should include those histological features thought to be of prognostic importance, especially mitotic rate, ulceration and level of invasion and other features possibly relevant to the aetiology and pathogenesis of melanoma (see 7.4.3). Accurate synoptic reports are especially valuable for research data bases and cancer registries.

7.4.3 Example of a synoptic histopathology report

Diagnosis: Melanoma, invasive	
Histological features	
Tumour thickness*	2.3mm
Margins of excision*	
A. Invasive component – nearest peripheral margin	3.7mm
B. <i>In situ</i> component – nearest peripheral margin	1.4mm
C. Deep margin	5.0mm
Mitotic rate (per mm²)*6	
Ulceration (diameter in mm)*	Present (2.0mm)
Level of invasion (Clark)*	4
Vascular invasion	Absent
Microsatellites	Absent
Regression	Absent
Neurotropism	Absent
Desmoplasia (% of invasive tumour)	Absent
Solar elastosis	Present Severe
Tumour-infiltrating lymphocytes (TIL)	
• Distribution: focal or diffuse	Focal
• Density: sparse or dense	Sparse
Associated benign melanocytic lesion	Compound naevus
Predominant cell type	Epithelioid
Growth phase	
• Radial	
• Vertical	Vertical
Intraepidermal growth pattern (e.g. pagetoid, lentiginous, mixed)	Pagetoid
* Essential components.	

Evidence summary	Level	References
Breslow thickness, margins of excision (microscopic), mitotic rate, level of invasion, and ulceration are strong predictors of outcome for melanoma patients and so are regarded as essential components of a histopathological report	II/III-3	1-7
Microsatellites, in-transit and local metastases are uncommon but are strong predictors of outcome and should always be reported	II/III-3	1
Vascular invasion, although uncommonly recognised, is a marker of poor prognosis and should always be reported when present	II/III-3	8, 9
Other components, such as tumour-infiltrating lymphocytes, regression, desmoplasia, neurotropism associated benign melanocytic lesion, solar elastosis, predominant cell type histological growth pattern, growth phase and immunohistochemistry may be of prognostic or diagnostic importance or of value regarding aetiology and pathogenesis	II/III-3	10-24
The important distinction between persistent primary melanoma and local metastasis is made on histological criteria, review of the primary melanoma, and clinicopathological correlation	III-3	25-27
The descriptive and synoptic report remains essential. Although the demand for synoptic reports is increasing, their use remains optional	III-2	28, 29

Recommendations

	Grade
1. The essential components of a histopathological report: <ul style="list-style-type: none"> • Breslow thickness • margins of excision (microscopic) • mitotic rate/mm² • level of invasion (Clark) • ulceration 	A
2. The following components of a histological report are of prognostic or other value: <ul style="list-style-type: none"> • vascular invasion, local metastases, microsatellites and in-transit metastases, tumour-infiltrating lymphocytes, regression, desmoplasia, neurotropism, associated benign melanocytic lesion, solar elastosis, predominant cell type, histological growth pattern, growth phase and immunohistochemistry 	C

continued over...

Recommendations continued...

	Grade
3. Histological criteria, review of the primary melanoma and clinicopathological correlation be used for distinguishing between persistent primary melanoma and local metastasis	C
4. The synoptic report be used in conjunction with, but not as a replacement for, the descriptive report	C

7.5 Pathology report on sentinel and non-sentinel lymph nodes

The optimal histopathological protocol for examining sentinel lymph nodes (SLN) is unclear at present. The protocol must balance the accuracy of the result against the labour and costs involved. Most authorities recommend evaluation of multiple sections from each half of the SLN, including sections stained with haematoxylin-eosin (H&E) and sections stained immunohistochemically for melanoma-associated antigens (usually S100 and HMB-45 and/or MelanA and/or tyrosinase). It is unclear from the currently available evidence what is the most appropriate number of sections to examine, at what levels these should be cut from the tissue blocks and the most appropriate number and combinations of immunostains that should be assessed. A number of studies have assessed the detection rate of metastatic melanoma in SNs using different pathologic sampling protocols.³¹⁻³⁴ Most of these studies have shown that increased histopathological sampling of SLNs from melanoma patients detects more melanoma, although the extent of the increase in detection rates reported have differed in the various studies. Furthermore, the significance of small tumour deposits detected by extensive sampling remains unclear. Routine frozen section examination of SLNs from melanoma patients is not recommended.

The presence or absence of melanoma metastases should be documented in the histopathology report. Melanoma metastases should be distinguished from clusters of small banal naevus cells which are usually located in the capsule and radial trabeculae of lymph nodes.

Recent evidence suggests that the location and extent of tumour deposits within SLN provides important prognostic information.³⁵⁻³⁸ If there are only a few metastatic cells in the subcapsular sinus of the SLN, the prognosis is relatively good and the chance of finding additional metastatic disease in a completion lymph node dissection CLND specimen is extremely small. If, on the other hand, there are multiple large foci of tumour, extending deeply into the central parenchymal part of the SLN, the prognosis is much worse, and the chance of finding metastases in non-SLNs in a CLND specimen is high. However, it remains unclear which correlate of tumour burden or combination of other factors best predicts a low probability of metastatic tumour being present in non-SLN and the likelihood of further recurrence and death from melanoma. More work is necessary to define optimally the most accurate and practical method of identifying patients who have a low probability of having metastatic tumour in non-SLNs and in using this information to direct further patient management. At present it is recommended that the size of the largest metastatic focus, the tumor penetrative depth (measured using a micrometer from the inner margin

of the node capsule to the deepest tumor cell within the SN) and the percentage nodal cross sectional area involved (as measured on the slides) be recorded in the pathology report. The role and significance of molecular assessment of SLN for low volume metastases of melanoma (primarily by RT-PCR) is currently being assessed.

Non-SLNs removed during the same operative procedure as SLNs should be examined and reported in a similar manner to lymph nodes removed in lymph node dissections specimens (see below).

Evidence summary	Level	References
The microanatomic location and micromorphometric features of metastases in SLN are, according to recent studies, of prognostic importance but the optimal protocol for examination of SLN requires further study	III-3	35-38
Reporting on lymph node dissection specimens requires the accurate assessment of the number of nodes involved by metastases, the extent of that involvement, and the presence of extranodal involvement	IV	39

Recommendations	Grade
5. Pathology reports should include information from sentinel lymph biopsies, derived from multiple histological sections of sentinel nodes (including sections stained with H&E and immunohistochemically for melanoma-associated antigens including S-100)	C
6. Non-sentinel lymph nodes should be carefully examined and reported	D

7.6 Pathology report on lymph node dissection specimens³⁹

The specimen should be fixed in 10% buffered formalin for 24 hours prior to macroscopic examination. It should be dissected carefully and all lymph nodes present identified. All lymph nodes should be submitted in their entirety for microscopic examination, except that representative sections of macroscopically involved lymph nodes may be evaluated instead of the entire lymph node.

The histopathological report should indicate:

1. the number of lymph nodes found
2. the number of lymph nodes containing metastases
3. the size of any deposit of melanoma identified macroscopically.

If present, the following should be noted in the report:

1. the presence and size of aggregates of matted lymph nodes
2. the size of the largest metastasis
3. The presence and extent (in mm) of extranodal extension of tumour.

Other issues that need further consideration:

- minimal number of lymph nodes in regional clearance specimens from different sites
- definition and measurement of extent of extranodal spread.

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