COLLABORATION BETWEEN CLINICIANS AND PATHOLOGISTS: A NECESSITY FOR THE OPTIMAL MANAGEMENT OF MELANOMA PATIENTS

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Abstract

Pathological assessment of a tissue biopsy is a critical aspect in the multidisciplinary management of melanoma patients because it not only establishes a definite diagnosis in most cases but also provides information that to a major extent influences patient prognosis and directs initial further management. For the pathological report to be as accurate as possible, it is important that the clinician provides the pathologist with an adequate tissue sample and appropriate clinical details. If circumstances permit, an excision biopsy with narrow clearance margins is the most appropriate biopsy of a melanocytic tumour. This will enable an accurate assessment and allow definitive treatment to be planned appropriately if a diagnosis of melanoma is confirmed. Incomplete biopsies (such as shave, punch or curetting biopsies) may impair the accuracy of pathological diagnosis and the assessment of some important parameters and should be avoided if possible. Clinical factors that influence pathological assessment of melanocytic tumours include patient age and sex, the site of the lesion and others factors (such as prior biopsy, other trauma, surface irritation, pregnancy, topical treatment and recent strong sunlight exposure) should be communicated to the pathologist. The latter features may induce atypical pathological features and lead to a misdiagnosis of melanoma. The prognosis for patients with localised primary cutaneous melanoma depends principally on tumour thickness, but other factors such as the presence or absence of ulceration, mitotic rate, Clark level, anatomical site, age and sex are also important. The distance of the tumour from the excision margins and the presence of desmoplasia, neurotropism, regression, satellites or vessel involvement are other features that may affect prognosis and management. It is therefore important that the pathology report details all these factors. The use of a synoptic format pathology report can facilitate this.

Cutaneous melanoma is a major public health problem in European-derived populations around the world. In such countries, the incidence of melanoma has increased by about 5% per year over the past 40 years.[1] In 2003 in New South Wales, melanoma was the second most common cancer for both men and women.[2] Mortality from melanoma is lower than for other common cancers and is stable or declining slowly, but it has a disproportionately heavy impact on productive years of life because melanoma is the commonest cancer in young adults.[2] For these reasons, those involved in the diagnosis and treatment of patients with melanocytic lesions need to know the optimal methods for diagnosis, potential pitfalls in diagnosis and the important features that influence prognosis and direct management.

Patients with primary cutaneous melanocytic lesions rely on the knowledge, skills and experience of both their treating clinician and their pathologist for accurate diagnosis and appropriate management. Especially if the clinical diagnosis of a skin lesion is uncertain or suspected to be malignant, pathological assessment of a tissue biopsy is necessary. In such circumstances it is important that the clinician provides the pathologist not only with an adequate tissue sample, but also with clinical details that will assist in establishing a diagnosis. For patients with melanoma, their prognosis and further management will depend to a major extent not only on the pathological diagnosis, but also on other pathologically assessed/measured parameters. These parameters include the thickness, ulcerative state, Clark level of invasion and dermal mitotic rate of the tumour, as well as its microscopically measured proximity to the resection margins. Clinicians should know the important factors that should be included in every pathology report of a melanoma and ensure that their pathologist provides this information. The use of a synoptic format for pathology reporting of melanomas can facilitate this.

Biopsy techniques for cutaneous melanocytic lesions

If there is concern about the nature of a skin lesion and the possibility of melanoma cannot be excluded clinically, the lesion should be entirely excised for histopathological examination, with a 2mm clearance margin, when circumstances permit.[1] Such excision biopsy is recommended for reliable pathological diagnosis and to allow definitive treatment to be planned appropriately if a diagnosis of melanoma is confirmed. For melanomas, pathological examination of the specimen will provide details of the thickness of the primary tumour and any unfavourable prognostic features such as ulceration or a high dermal mitotic rate. Even if a confident clinical diagnosis of melanoma is made, it is important to perform an initial excision biopsy with narrow margins, so that subsequent definitive treatment options are not compromised. If an excessively wide margin is taken, or if complex flap reconstruction is undertaken, subsequent wider excision with adequate margins might be difficult to plan and lymphatic mapping (with a view to sentinel lymph node biopsy or simply to guide follow-up) may be inaccurate.[1]

Following excision, the specimen should be placed in 10% neutral buffered formalin for approximately 24 hours for adequate fixation prior to tissue processing. Small biopsies can be allowed less fixation time if the result is required urgently. Cytology and frozen sections for the diagnosis of primary cutaneous melanocytic lesions should be avoided because the risk of misdiagnosis is unacceptably high and changes induced by these techniques will compromise subsequent pathological assessment.

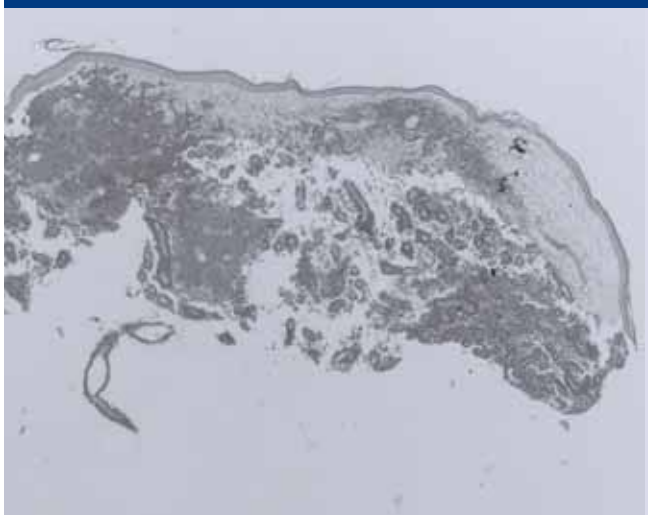
For large lesions, particularly those on cosmetically sensitive areas such as the face, or for lesions at sites that are difficult to biopsy (such as a subungual location), incision biopsy or punch biopsy may be performed with an aim of establishing a definite diagnosis. While clinical reasons dictate the need for this approach, it is important that clinicians are aware of the limitations of such procedures and the potential for misdiagnosis with the use of incomplete biopsies of melanocytic lesions. Incomplete biopsies, particularly punch biopsies, may provide unrepresentative sampling of a heterogeneous lesion so that a focal area of melanoma may be missed by the biopsy. Because the pathological diagnosis of melanocytic lesions relies on assessment of a range of architectural and cytological features of the lesion, including those at its deep edge and peripheral margins, incomplete biopsy specimens of melanocytic lesions may cause difficulties in diagnosis. In addition, for a lesion in which a definite diagnosis cannot be made on the initial partial biopsy, the assessment of a subsequent complete excision specimen may be compromised by reparative and regenerative changes in the lesion. Residual banal naevi may regenerate following incomplete removal and display pathological features mimicking those of melanoma ("pseudomelanoma").[3,4] For this reason, the use of such limited biopsies may lead to misdiagnosis by pathologists. The risk of misdiagnosis is greater if the pathologist is unaware of this phenomenon, is inexperienced or is not informed of the prior biopsy by the clinician. Even if a diagnosis of melanoma is established with confidence on the basis of a shave or punch biopsy, it may be impossible to establish the true thickness of the lesion (Figure 1). Knowledge of the thickness of the lesion is currently critical in determining appropriate definitive management, such as the width of excision margins[5] and the appropriateness of sentinel lymph node biopsy[1]. It is also an important prognostic feature. The potential for misdiagnosis when assessing incomplete biopsies is also highlighted by the fact that in one recent study it was found that up to 80% of medical malpractice claims in relation to melanoma involved incomplete biopsy specimens.[6]

Clinical information necessary for optimal pathological assessment of melanocytic tumours

A definitive pathological diagnosis of a primary cutaneous melanocytic lesion should not be made without knowledge of the age and sex of the patient and the site of the lesion. The age of the patient is important in determining the significance of any atypical features such as the occurrence of dermal mitoses. Naevi occurring in unusual sites, such as the external genitalia or acral locations, may resemble melanomas pathologically and if the site of the lesion is not identified they are readily misdiagnosed. A lack of awareness of the other clinical details may also result in misdiagnosis in a variety of situations because some factors may induce changes in naevi that are usually associated with melanomas. Such factors include prior biopsy (Figure 2), other trauma, superficial irritation, pregnancy, recent strong sunlight exposure, topical treatments or co-existent blistering disorders.[3,7-10] A pathologist unaware of such clinical scenarios may misdiagnosis a naevus as a melanoma. Alerting the pathologist to unusual or changing foci, such as light or dark areas is also important. Light areas may represent regression and while most dark areas represent benign foci of hyperpigmentation, a small percentage represent melanoma.[11] The presence of the dark foci should prompt the pathologist to examine deeper tissue sections of the specimen if the cause of these foci is not identified microscopically in the initial tissue sections.

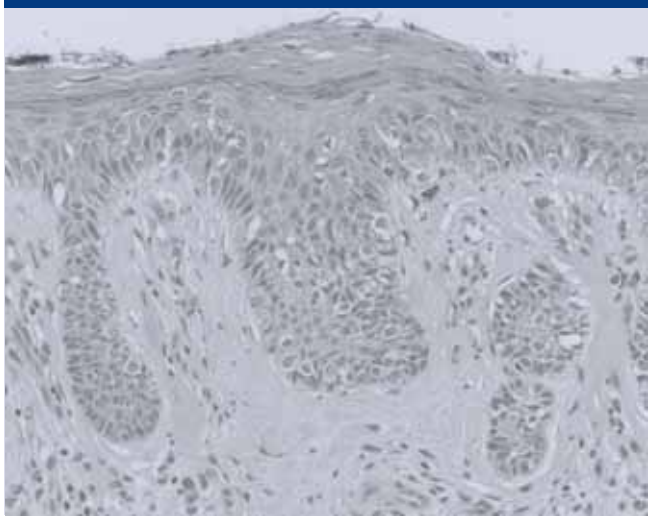
For wide excision specimens, it is also important for pathologists to be made aware of the histological subtype of a

Figure 1:



It is not possible to accurately determine the thickness of the melanoma in this ragged superficial biopsy specimen as the deep aspect of the tumour is not included. Knowledge of the depth of the tumour is critical in determining appropriate definitive management, such as the width of excision margins and the appropriateness of sentinel node biopsy. Incomplete biopsies of melanocytic lesions may at times compromise the accuracy of pathological diagnosis and should be avoided if at all possible.

Figure 2:



Pagetoid epidermal invasion (upward extension within the epidermis) of melanocytes induced by surface irritation from scratching in a junctional naevus. Pagetoid epidermal invasion in melanocytic lesions is usually associated with a diagnosis of melanoma, but may sometimes occur in other settings (see text and reference 10 for a more detailed discussion of causes). By providing the pathologist with an appropriate clinical history, such as a history of previous biopsy or irritation to the lesion, the clinician may assist in establishing the correct diagnosis.

previously biopsied melanoma and involvement of the margins in any previous biopsy, since these factors may influence how the specimen is examined pathologically and therefore the accuracy of the pathology report. For example, the pathological features of a desmoplastic melanoma may be extremely subtle and difficult to distinguish from scar tissue.[12] Very careful microscopic assessment of the tissue sections, including sections stained immunohistochemically for S100 protein are usually necessary for accurate diagnosis.

For those lesions in which assessment of surgical margins is critical in determining the need for further surgery, or its extent, orientating specimens with marking sutures (or other techniques) at the time of surgery can be very useful. In such circumstances, the pathologist can assist the clinician by providing a specimen diagram or photograph that illustrates the extent of the tumour and its proximity to the resection margins. Photography can also be very useful when assessing clinically heterogenous lesions by enabling the clinician to direct the pathologist to any areas of particular concern. Careful clinicopathological correlation in this manner may be especially helpful in the develoment of new techniques for clinical diagnosis or when clinicians are acquiring new skills, such as dermoscopy.[11]

Predictors of prognosis for patients with primary cutaneous melanoma

In the absence of detectable metastatic disease, the prognosis for a patient with a primary cutaneous melanoma depends principally on the thickness of the primary tumour. Other features, such as the presence or absence of ulceration, dermal mitotic rate, Clark level of invasion and the anatomical site of involvement and patient characteristics, such as age and gender, are also important.[13] To enable an accurate estimate of prognosis to be made, it is important that the pathology report details all these factors.

The 6th edition of the American Joint Committee on Cancer (AJCC) staging system for melanoma was introduced in 2002 and an outline of it is presented in Table 1.[14] It was based on the details of 17,600 patients from 13 melanoma treatment centres around the world.[13] The staging system is used to define risk groups with regard to metastatic risk and survival rates, criteria for patient stratification and reporting of clinical trials, to allow comparison of treatment results from different centres and as a valuable tool for clinical decision making. It is important that pathology reports include all the information necessary for accurate staging of patients.

Although not included in the recent AJCC melanoma staging system, mitotic rate (MR) is a powerful prognostic factor for melanoma patients, both by its influence on overall survival[15-19] and its influence on SN positivity[20,21] and positivity of non-SNs in completion lymph node dissection specimens (Sydney Melanoma Unit (SMU), unpublished data). One of the aforementioned studies was an SMU analysis of 3661 patients,[18] in which it was found that MR was more important than ulceration and ranked second only to Breslow thickness in prognostic significance.[18] In that study, highly statistically significant differences in patient survival were found between each MR group ($p < 0.0009$), irrespective of whether the MR was grouped according to either of two methods (method A : 0, 1-4, 5-10, and >11 mitoses/mm^2 or method B: 0-1, 2-4, and >5 mitoses/mm^2). In a subsequent SMU study, the prognostic significance of MR was determined in a separate series of 1317 patients in whom the primary lesion pathology had been assessed by the late Dr Vincent McGovern.[22] In these patients,

Table 1: Outline of the 2002 AJCC staging system for melanoma

Stage	Criteria
0	Melanoma in situ
IA	Tumour thickness ≤1.0 mm without ulceration and Clark level II/III.
IB	Tumour thickness ≤1.0 mm with ulceration or Clark level IV/V, or tumour thickness 1.01-2.0 mm without ulceration.
IIA	Tumour thickness 1.01-2.0 mm with ulceration, or tumour thickness 2.01-4.0 mm without ulceration.
IIB	Tumour thickness 2.01-4.0 mm with ulceration, or tumour thickness >4.0 mm without ulceration.
IIC	Tumour thickness >4.0 mm with ulceration.
IIIA	Any tumour thickness with no ulceration and 1-3 microscopically positive LNs.
IIIB	Any tumour thickness with ulceration and 1-3 microscopically positive LNs or any tumour thickness without ulceration and 1-3 macroscopically involved LNs or any tumour thickness with or without ulceration and either satellite(s)/ in transit metastasis(es) without metastatic node(s).
IIIC	Any tumour thickness with ulceration and either 1-3 macroscopically involved LN(s) or satellite(s)/ in transit metastasis(es) without metastatic LN(s) or any tumour thickness with 4 or more metastatic LNs or satellite(s)/ in transit metastasis(es) with metastatic LN(s).
IV	Any tumour thickness, any number of involved LNs and any distant skin, subcutaneous, nodal or visceral metastases.

Abbreviations: LN = lymph node

stage (according to the 2002 AJCC Staging System) was found to be the most predictive factor for survival ($p<0.0001$). However, MR still proved to be an important independent predictor of survival ($p=0.008$). The methods used to determine the MR pathologically were different in these two recent SMU studies and this may explain why MR was a somewhat less powerful independent predictor of survival in the latter study. In our initial study,[18] MR was assessed as the total number of mitoses per mm^2 in the dermal area of the tumour with the highest MR (as per recommendations of the 1982 International Pathology Workshop),[23] whereas the method used by Dr McGovern was to determine the average number of mitoses in at least 10 high power (x300) fields across the entire lesion and to express MR as the average number of mitoses per high power field (HPF) (as per the 1972 recommendations of the International Pigment Cell Conference).[24] In contrast to the method used to determine the MR in our initial study and current recommendations, no endeavour was made by Dr McGovern to find the area with the highest MR.

In view of these results, we recommend that the MR of a melanoma should be determined by commencing the mitotic count in the microscopic field with most mitoses and then counting in successive fields (over a 1mm^2 area). As the number of mitotic figures often varies greatly between different parts of a tumour, unless a standardised method is used to determine the MR, there is likely to be poor interobserver reproducibility between pathologists in their assessment of MR. As the field diameter of different

Table 2: An example of a synoptic pathology report for a primary cutaneous melanoma

Pathologic Feature	Example
Sex	Male
Site	Left shoulder
Diagnosis	Melanoma
Histological subtype	Superficial spreading
Vertical growth phase	Present
Breslow thickness	2.4mm
Ulceration (diameter in mm)	Present (3.6mm)
Dermal mitotic rate (per mm2)	9
Clark level	IV
Vascular or lymphatic invasion	Absent
Neurotropism	Present
Desmoplasia (% of dermal invasive tumour)	Absent
Satellites	Absent
Features of regression:	
Early (TILs)	Mild and focal (non-brisk)
Intermediate (angiofibroplasia +/- TILs)	Absent
Late (fibrosis and loss of rete ridges)	Absent
Predominant cell type	Epithelioid
Associated naevus	Dysplastic compound naevus
Nearest lateral margin to insitu component	1.2mm
Nearest lateral margin to dermal invasive component	4.2mm
Distance from tumour to deep margin	6.5mm

Abbreviations: mm = millimetres; % = percentage; TILs = tumour infiltrating lymphocytes

microscopes is known to vary greatly,[25] it is also important that the MR is expressed as mitoses per mm^2 rather than per high power microscopic field.

Given these findings, it is important that MR be assessed by a standardised method and documented for all primary cutaneous melanomas. Including MR in future revisions of the AJCC/UICC melanoma staging system may improve its accuracy and should more rigidly define risk categories for patients entering clinical trials.

The reproducibility between pathologists of important histopathological prognostic variables, including MR, is another important question. In a further study, therefore, the inter-observer reproducibility among pathologists for these variables was assessed. It was found that there was excellent inter-observer agreement for assessment and measurement of tumour thickness (intraclass correlation coefficient (ICC) = 0.96), ulcerative state (kappa score (k) = 0.83) and MR (ICC=0.76) and fair to good agreement for Clark level (k=0.60).[26] This is despite the fact that the pathologists involved in the study had widely differing experience in the assessment of melanocytic lesions and included specialist dermatopathologists and general and trainee pathologists.

Features that should be included in the pathology report of a melanoma

It is critically important that the pathology report includes information that allows the most appropriate management recommendation to be made to the patient and also allows the determination of a reliable estimate of prognosis. The latter is important not only so that the patient can be informed of this estimate, but also so that assessment of clinical trial eligibility can be determined and stratification into a risk category subgroup within the trial can be performed accurately. Ultimately the results of these trials have the potential to significantly affect the treatment and management of melanoma patients.

In addition to the important prognostic features described above, there are other features that have an important influence on patient management and therefore must be documented in the pathology report. Such features include the microscopically measured distance of the tumour from the excision margins. The recommended appropriate margin of excision for a primary cutaneous melanoma depends on the thickness of the primary tumour. Most authorities currently recommend that melanomas <1mm thick should be removed with a 1cm margin, melanomas between 1 and 2mm thick should be excised with a margin of either 1cm or 2cm and melanomas that are >2mm thick should be excised with surgical margins of 2cm.[5,27] The thickness of the tumour is also used to determine which patients are most suitable for a sentinel lymph node biopsy.[1]

The presence of neurotropism or desmoplasia in a melanoma is associated with an increased risk of local recurrence.[28,29] The presence of these features in a melanoma will usually prompt a wider margin of excision to be performed or may prompt the administration of postoperative radiotherapy. The degree of desmoplasia within a melanoma may correlate with its risk of metastasising to regional lymph nodes and with patient prognosis. Recent reports suggest that regional node field metastases are less frequent in "pure" desmoplastic melanomas and that such tumours are associated with a more favourable prognosis than non-desmoplastic melanomas.[29,30]

Other features of primary melanomas that should be included in the pathology report include its histological type, growth phase, predominant cell type, presence of lymphatic or vascular invasion, presence of satellites and any evidence of regression.

Traditionally, melanomas are classified into different histological subtypes: superficial spreading, lentigo maligna/Hutchinson's melanotic freckle, acral lentiginous and nodular.[23,24,31] Although it appears that assignment to one of these subtypes does not have significant prognostic relevance, it is recognised that they define well-known clinicopathological entities.

The concept of tumour progression is based on the assumption that a melanoma develops the potential to metastasise by going through a series of evolutionary steps. Melanomas in the "radial growth" phase have no capacity to metastasise and are therefore cured by adequate local excision. Definitions have been proposed to histologically determine the growth phase of the tumour.[15] Some studies have shown that the histologically defined growth phase correlates with the metastasising capability of the tumour.[15,32]

The presence of satellites[13] and of vascular or lymphatic invasion[15] are correlated with reduced survival in melanoma patients. A predominance of spindle cells has been associated with a more favourable prognosis in some studies.[33,34] The relationship between the presence of regression and prognosis

in melanoma patients has been the subject of some controversy. Most studies assessing the relationship have been limited by lack of standandised definitions of criteria for diagnosis, small sample sizes and limited follow up. However, some studies have shown that thin melanomas with regression are associated with a higher incidence of metastases than tumours of similar thickness not associated with regression.[35]

For every disease, it is possible to compile a list of pathological features that are of agreed importance and to incorporate them into a synoptic report format. It is our view that both the pathologist and clinician benefit from the discipline of respectively reporting and reading reports in a synoptic format, an example of which is provided in Table 2.

Conclusions

The pathological diagnosis and assessment of various pathological parameters are key initial elements in the multidisciplinary care of melanoma patients. The accuracy and reliability of diagnosis are enhanced by clinicians and pathologists who possess a sound knowledge of diagnostic criteria, an awareness of potential pitfalls and good judgement. They should also communicate appropriately with each other. The clinician should provide the pathologist with a suitable biopsy specimen and an appropriate clinical history to assist in establishing a diagnosis. The pathologist, in turn, should provide the clinician with a report containing sufficient information to allow an evidence-based management plan and a reliable estimate of prognosis to be made. The use of a synoptic report format will ensure that potentially important information is not overlooked.

References

1. Thompson JF, Scolyer RA, Kefford RF. Cutaneous melanoma. Lancet 2005; 365:687-701.
2. Tracey E, Roder D, Bishop J, Chen S, Chen W. Cancer in New South Wales: Incidence and Mortality 2003. Sydney: Cancer Institute NSW, 2005.
3. Kornberg R, Ackerman AB. Pseudomelanoma: recurrent melanocytic nevus following partial surgical removal. Arch Dermatol 1975; 111:1588-90.
4. Dymock RB, Menz J. Recurrent melanocytic naevi following partial removal (pseudomelanoma). Australas J Dermatol 1986; 27:67-9.
5. Thomas JM, Newton-Bishop J, A'Hern R, Coombes G, Timmons M, Evans J, et al. Excision margins in high-risk malignant melanoma. N Engl J Med 2004; 350:757-66.
6. Troxel DB. Pitfalls in the diagnosis of malignant melanoma: findings of a risk management panel study. Am J Surg Pathol 2003; 27:1278-83.
7. Sanchez JL, Figueroa LD, Rodriguez E. Behavior of melanocytic nevi during pregnancy. Am J Dermatopathol 1984; 6:89-91.
8. Lee HJ, Ha SJ, Lee SJ, Kim JW. Melanocytic nevus with pregnancy-related changes in size accompanied by apoptosis of nevus cells: a case report. J Am Acad Dermatol 2000; 42:936-8.
9. Glusac EJ. Under the microscope: doctors, lawyers, and melanocytic neoplasms. J Cutan Pathol 2003; 30:287-93.
10. Petronic-Rosic V, Shea CR, Krausz T. Pagetoid melanocytosis: when is it significant? Pathology 2004; 36:435-44.
11. Crotty KA, Menzies SW. Dermoscopy and its role in diagnosing melanocytic lesions: a guide for pathologists. Pathology 2004; 36:470-7.
12. McCarthy SW, Scolyer RA, Palmer AA. Desmoplastic melanoma: a diagnostic trap for the unwary. Pathology 2004; 36:445-51.
13. Balch CM, Soong SJ, Gershenwald JE, Thompson JF, Reintgen DS, Cascinelli N, et al. Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 2001; 19:3622-34.
14. Balch CM, Buzaid AC, Soong SJ, Atkins MB, Cascinelli N, Coit DG, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 2001; 19:3635-48.
15. Clark WH, Jr., Elder DE, Guerry Dt, Braitman LE, Trock BJ, Schultz D, et al. Model predicting survival in stage I melanoma based on tumor progression. J Natl Cancer Inst 1989; 81:1893-904.
16. Ostmeier H, Fuchs B, Otto F, Mawick R, Lippold A, Krieg V, et al. Can immunohistochemical markers and mitotic rate improve prognostic precision in patients with primary melanoma? Cancer 1999; 85:2391-9.
17. Retsas S, Henry K, Mohammed MQ, MacRae K. Prognostic factors of cutaneous melanoma and a new staging system proposed by the American Joint Committee on Cancer (AJCC): validation in a cohort of 1284 patients. Eur J Cancer 2002; 38:511-6.
18. Azzola MF, Shaw HM, Thompson JF, Soong SJ, Scolyer RA, Watson GF, et al. Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma. Cancer 2003; 97:1488-98.
19. Barnhill RL, Katzen J, Spatz A, Fine J, Berwick M. The importance of mitotic rate as a prognostic factor for localized cutaneous melanoma. J Cutan Pathol 2005; 32:268-73.
20. Sondak VK, Taylor JM, Sabel MS, Wang Y, Lowe L, Grover AC, et al. Mitotic rate and younger age are predictors of sentinel lymph node positivity: lessons learned from the generation of a probabilistic model. Ann Surg Oncol 2004; 11:247-58.
21. Kesmodel SB, Karakousis GC, Botbyl JD, Canter RJ, Lewis RT, Wahl PM, et al. Mitotic rate as a predictor of sentinel lymph node positivity in patients with thin melanomas. Ann Surg Oncol 2005; 12:449-58.
22. Francken AB, Shaw HM, Thompson JF, Soong SJ, Accortt NA, Azzola MF, et al. The prognostic importance of tumor mitotic rate confirmed in 1317 patients with primary cutaneous melanoma and long follow-up. Ann Surg Oncol 2004; 11:426-33.
23. McGovern VJ, Cochran AJ, Van der Esch EP, Little JH, MacLennan R. The classification of malignant melanoma, its histological reporting and registration: a revision of the 1972 Sydney classification. Pathology 1986; 18:12-21.
24. McGovern VJ, Mihm MC, Jr., Bailly C, Booth JC, Clark WH, Jr., Cochran AJ, et al. The classification of malignant melanoma and its histologic reporting. Cancer 1973; 32:1446-57.
25. Ellis PS, Whitehead R. Mitosis counting--a need for reappraisal. Hum Pathol 1981; 12:3-4.
26. Scolyer RA, Shaw HM, Thompson JF, Li LX, Colman MH, Lo SK, et al. Interobserver reproducibility of histopathologic prognostic variables in primary cutaneous melanomas. Am J Surg Pathol 2003; 27:1571-6.
27. McKinnon JG, Starritt EC, Scolyer RA, McCarthy WH, Thompson JF. Histopathologic excision margin affects local recurrence rate: analysis of 2681 patients with melanomas < or =2 mm thick. Ann Surg 2005; 241:326-33.
28. Quinn MJ, Crotty KA, Thompson JF, Coates AS, O'Brien CJ, McCarthy WH. Desmoplastic and desmoplastic neurotropic melanoma: experience with 280 patients. Cancer 1998; 83:1128-35.
29. Hawkins WG, Busam KJ, Ben-Porat L, Panageas KS, Coit DG, Gyorki DE, et al. Desmoplastic melanoma: a pathologically and clinically distinct form of cutaneous melanoma. Ann Surg Oncol 2005; 12:207-13.
30. Scolyer RA, Thompson JF. Desmoplastic melanoma: a heterogeneous entity in which subclassification as "pure" or "mixed" may have important prognostic significance. Ann Surg Oncol 2005; 12:197-9.
31. Clark WHJ. A classification of malignant melanoma in man correlated with histogenesis and biologic behaviour. Advances in the biology of the skin. Vol. VIII. New York: Pergamon Press, 1967:621-47.
32. Gimotty PA, Guerry D, Ming ME, Elenitsas R, Xu X, Czerniecki B, et al. Thin primary cutaneous malignant melanoma: a prognostic tree for 10-year metastasis is more accurate than American Joint Committee on Cancer staging. J Clin Oncol 2004; 22:3668-76.
33. Van Der Esch EP, Cascinelli N, Preda F, Morabito A, Bufalino R. Stage I melanoma of the skin: evaluation of prognosis according to histologic characteristics. Cancer 1981; 48:1668-73.
34. Sondergaard K, Schou G. Therapeutic and clinico-pathological factors in the survival of 1,469 patients with primary cutaneous malignant melanoma in clinical stage I. A multivariate regression analysis. Virchows Arch A Pathol Anat Histopathol 1985; 408:249-58.
35. Sondergaard K, Hou-Jensen K. Partial regression in thin primary cutaneous malignant melanomas clinical stage I. A study of 486 cases. Virchows Arch A Pathol Anat Histopathol 1985; 408:241-7.