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Malignant melanoma: Claims and controversies

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Abstract

Malignant melanoma is a common cancer in young people and its incidence is rising in the UK. The management of the disease is evolving, with new approaches to the treatment of locally advanced and systemic disease in particular being rapidly developed. Sentinel node biopsy is a valuable treatment option for the staging of melanoma, and completion lymphadenectomy in node-positive patients improves local disease control. However, early clearance of occult microscopic nodal disease has not been proven to confer a melanoma-specific survival advantage. Delays in the diagnosis and treatment of melanoma lead to claims being brought in negligence, but establishing causation in such cases can be difficult.

Keywords

Malignant melanoma, sentinel node biopsy, clinical negligence claims

Introduction

The treatment of patients with malignant melanoma has been revolutionised in recent years with the emergence of new BRAF (proto-oncogene) targeted drugs and the rise of immunotherapy in the fight against cancers in general. Increasing numbers of patients with stage 4 (systemic) disease are benefitting from longer survival than ever before. This article reviews the current treatment options for patients with melanoma and examines some of the variations in practice, particularly with regards to sentinel lymph node biopsy (SLNB). An understanding of the disease and its management is fundamental to the assessment of clinical negligence claims. While it is often the case that a breach of duty can be established, causation, against a backdrop of improved prospects for survival, can be more difficult to demonstrate. This article will consider some of the reasons why bringing claims in negligence for alleged mis-management of melanoma can be somewhat problematic.

Incidence and aetiology of melanoma[1,2]

Malignant melanoma is a tumour that arises from melanocytes, pigment cells that are found in the skin just above the basement membrane, which separates the upper *epidermis* from the lower *dermis*. The vast majority of melanomas, therefore, are cutaneous tumours, although in rare cases primary malignant melanoma can also arise in the eye (uveal melanoma) or the mucosa of the gastrointestinal tract. It is estimated that 13,500 people are diagnosed with melanoma in the UK each year. Malignant melanoma is the fifth most common cancer overall in the UK (excluding non-melanoma skin cancer) and the second most common cancer in people under the age of 50 years. Melanoma accounts for more cancer deaths than all other skin cancers combined. Malignant melanoma is linked to intense episodes of sun exposure in early life. Ultraviolet light, particularly UVA, is strongly associated with melanoma, which can arise either arise *de-novo* or in pre-existing moles (between 23%[3] and 42%[4] of cases), including dysplastic naevi. Acral malignant melanoma accounts for around 2–3% of all melanoma diagnoses and is associated with a worse prognosis compared with cutaneous malignant melanoma overall (5- and 10-year survival rates of 80.3% and 67.5%).[5]

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Melanoma diagnosis

Typically, patients who are diagnosed with melanoma have pale skin and a history of intermittent sun exposure, often with burning. Many patients report a change in their mole, such as an increase in size, a change in shape or bleeding. Melanomas have distinct clinical features, which include asymmetry, an irregular border, variegated pigmentation and ulceration. Increasingly, clinicians rely upon early detection of melanomas through the use of a dermatoscope, an instrument which allows for magnification of the mole using extremely bright light. The features of the mole under dermoscopy that are considered suspicious for melanoma include pigment globules, loss of the normal reticular pattern, a blue veil, radial streaks, pseudopods, regression, and asymmetry. Despite the almost universal uptake of dermoscopy by dermatologists, many plastic surgeons would be likely to excise a suspicious lesion rather than to rely upon a dermoscopy diagnosis. Dermoscopy remains an important diagnostic tool in melanoma and it is likely to increase diagnostic accuracy of skin lesions in general.[6] It remains to be seen whether the failure to diagnose a malignant melanoma could be attributed to the failure to examine a lesion with a dermatoscope, and whether that would constitute a breach of duty. It is sometimes argued that an incisional biopsy of a malignant melanoma can promote metastatic disease. However, the literature does not support that assertion.[7–9]

The treatment pathway and the role of SLNB

When a patient presents to their GP with a concerning mole, a two-week wait referral to a pigmented lesion clinic is made. The lesion is assessed and if suspicious an excisional biopsy is performed, usually at the same visit or soon thereafter. If a melanoma is confirmed on histology, it is important to know how thick it is in the skin (the Breslow thickness) and whether the lesion is ulcerated. The prognosis becomes worse with increasing thickness and in the presence of ulceration. For thin melanoma, less than 1 mm, the mitotic rate, which indicates how fast the cells are multiplying, has been (in advance of the 8th Edition of the AJCC staging system) a further prognostic indicator.

Following diagnosis and discussion in the skin cancer MDT, a wide local excision (WLE) of the biopsy scar is performed. The rationale for a wide local excision of the biopsy scar is to clear any residual disease and prevent *local* recurrence. There have been a number of studies assessing the optimum extra margin that should be obtained around primary tumours are varying thicknesses, and although there is established guidance available to clinicians[10] there is still on-going research in this area with the multi-centre MelmarT project.[11] The width of the WLE is proportional to the thickness of the tumour; recommended excision margins are provided in national guidance from the British Association of Dermatologists (BAD) and the British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS).[12]

Patients with tumours with a Breslow thickness greater than 1 mm are eligible to undergo SLNB. This allows for the identification of occult microscopic metastases in the draining lymph node basin(s). Patients with thin melanomas, less than 1 mm thick (T1 tumours), have a probability of a positive sentinel node of 5%;[13] tumours that are either ulcerated or show mitoses (T1b) are at highest risk.

A positive SLNB correlates with increasing Breslow thickness and high mitotic rate.[14] Interval nodes (such as popliteal or epitrochlear lymph nodes) are well recognised potential sentinel nodes in patients with malignant melanoma, even though they are commonly missed on lymphoscintigraphy and only detected through use of the diligent gamma probe.[15] If positive, interval SLNs are likely to be the only site of nodal metastases.[16] The failure to detect metastatic disease in interval nodes can, therefore, lead to under staging.

The rationale for SLNB is primarily to improve disease staging and loco-regional control. Following a positive SLNB, a further operation is usually recommended to remove the surrounding 'at risk' lymph nodes. This is primarily to optimise local tumour control and does not necessarily improve melanoma-specific survival.[17] However, the incidence of non-sentinel lymph node disease at completion lymph node dissection (CLND) is low, at around 14%.[18] CT staging is performed prior to a CLND; in the event of distant site disease being identified, the rationale for CLND must be re-assessed.

Early analysis of the Multicenter Selective Lymphadenectomy Trial (MSLT-1) data suggested that patients with intermediate thickness melanomas (1.2–3.5 mm) benefit from a survival advantage as a result of early detection and clearance of microscopic nodal disease by SLNB, followed by CLND, compared with those in whom the disease is allowed to become macroscopic (palpable) prior to removal.[19]

The statistical analysis of the MSLT-1 study was challenged for its failure to take into account the effect of false negative results.[20] Although the final MSLT-1 data analysis showed an improvement in 10-year disease-free survival rates in patients undergoing SLNB and CLND compared with delayed lymphadenectomy, there was no difference in overall melanoma-specific survival (81.4% and 78.3%, respectively).[21]

However, when considering node-positive patients alone, a significant 10-year melanoma-specific survival advantage *was* demonstrated in patients with intermediate thickness melanomas (62.1% vs. 41.5%), but not those with tumours >3.5 mm.

Overall, plastic surgeons have been cautious to advise that patients with intermediate thickness melanomas between 1.2 and 3.5 mm in thickness *may* benefit from a survival advantage following positive SLNB and CLND compared with un-biopsied patients who go on to develop macroscopic nodal disease necessitating therapeutic lymphadenectomy. The potential additional advantages of detecting disease early by SLNB include (1) a lengthened disease-free interval following CLND; (2) a less complication-prone completion lymphadenectomy compared with a therapeutic lymph node dissection (TLND) for palpable disease;[22] (3) early clearance of disease, reducing the risk of extranodal extension; (4) more accurate staging of disease, which facilitates entry in to clinical trials and/or adjuvant immunotherapy.

The disadvantages of SLNB include local wound complications (seroma, infection) and the risk of mild limb swelling. The performance of a SLNB also often requires the procedure to be performed under a general anaesthetic, whereas wide excision alone can often be performed under a local anaesthetic. Allergy to Patent V dye has been reported in around 1% of patients.[23] Although patients gain a psychological benefit from a negative SLNB, albeit in the short term,[24] there is a false negative rate of around 4%,[25] although the weighted average false negative rate in a large meta-analysis was 12.5%.[26] Without SLNB, the vast majority of lymph node recurrences occur within two years.[27] The failure to identify and retrieve the sentinel node at operation occurs rarely but can cause some patient anxiety. When this occurs, or when patients elect not to undergo CLND following a positive SLNB, high resolution ultrasound surveillance of the at-risk nodal basin can be used to detect early nodal recurrence.[28]

Staging melanoma

The 7th Edition of American Joint Committee on Cancer (AJCC) system for melanoma staging relies upon information about the primary tumour (Breslow thickness, number of mitoses per high power field, ulceration), in-transit or satellite disease, lymph node status and distant site disease. Microsatellites are defined as any discontinuous nest of intra-lymphatic metastatic cells >0.05 mm in diameter that is clearly separated by normal dermis (not fibrosis or inflammation) from the main invasive component of melanoma by a distance of at least 0.3 mm. Satellite and in-transit metastases are cutaneous and/or subcutaneous metastases that occur between the primary melanoma and the first echelon regional lymph nodes, which have arbitrarily been distinguished on the basis of whether they are located within (satellite) or more than (in-transit) 2 cm from the primary tumour. Clinico-pathological staging is achieved by grouping these variables together in order to derive meaningful prognostic and survival data, which is published by the AJCC and other organisations such as Cancer Research UK. Individualised melanoma-specific survival calculators are also available online.[29] Prognostic information, in terms of melanoma-specific survival, is based upon the stage of the disease at/around the time of the removal of the primary melanoma +/− SLNB. The forthcoming 8th Edition of The AJCC staging system for melanoma, to be published in January 2018, makes some important changes.[30] T1 melanomas are re-defined as T1a if less than 0.8 mm with no ulceration and T1b if less than 0.8 mm but ulcerated, or between 0.8 and 1.0 mm in thickness. Previously, mitotic rate upstaged lesions less than 1.0 mm to T1b status, but this has now been dropped. Further changes have been made to the staging of lymph nodes. The new classification affects the clinic-pathological staging groups, upon which treatment decisions are made and guidance for melanoma management will need to be re-visited. For example, it is not yet clear where the boundary for offering SLNB will be re-drawn when dealing with thin melanomas under the new system. What is clear, however, is that claims brought in negligence after the implementation of the new classification will need to have regard to the prevailing AJCC classification upon which treatment decisions were based.

Disease progression and surveillance

Many patients who develop skin-based melanoma recurrences continue to do so over a prolonged period; some patients convert to stage IV disease while in other patients the local disease is eventually controlled. Skin nodules can be surgically excised but where the number, size or extent of recurrences is such that surgical resection is no longer practically possible, consideration could also be given to other treatment modalities, such as Isolated Limb Perfusion, Electrochemotherapy[31] or intra-lesional injection of talimogene laherparepvec (T-VEC), an immunotherapy drug.[32]

New systemic cancer therapies have dramatically increased survival in some stage 4 patients with distant-site disease.[33,34] The range of immunotherapy agents and BRAF[35] inhibitors for melanoma is rapidly evolving. Although previously reserved for patients with stage 4 disease, single agent immunotherapy treatment with Nivolumab is now approved for patients with fully resected stage 3 (nodal spread) PD-1 positive

melanoma.[36] Consequently, early identification of nodal and systemic relapse becomes ever more critical. Patients considered to be at 'high risk' of disease progression (i.e. those patients with a predicted five-year survival of $\leq$50%) may elect to undergo radiological surveillance by CT; the advantages of early treatment of low-volume metastatic disease should be balanced against the risk of radiation-induced malignancy, which adds an estimated 0.6% to the lifetime cancer risk of 40% for an adult aged between 40–49 years.[37]

Late tumour recurrence

Unfortunately it is not particularly uncommon that patients return to the melanoma clinic with disseminated disease long after their follow-up period has been completed. Systemic therapy is then the mainstay of treatment, although palliative radiotherapy and/or surgery, along with symptom control in a palliative care setting, may also be required. In those patients presenting with late stage 4 disease, which has been reported to occur in 2.4% of patients with a mean Breslow thickness of 1.6mm, the source of the metastases is likely to have been the primary melanoma, with loss of late dormancy of metastatic malignant cells.[38]

Paediatric melanoma, melanocytic lesions of uncertain malignant potential, Spitz tumours and deep penetrating naevus

It is occasionally the case that melanocytic lesion can be regarded as having an 'uncertain malignant potential'. This is determined on the basis of the presenting clinical features and the histology. These tumours often arise in childhood or in adolescence (atypical Spitz tumours), and tend to be managed along melanoma pathways, including SLNB.[39–41] However, patients with Spitz tumours and SLN metastases (which are more common than in melanoma and correlate with younger age[42]) have a prognosis that is substantially better than in patients with melanoma, leading some authorities to question the value of SLNB in this context.[43]

The term 'deep penetrating naevus' (DPN) was first reported in 1989;[44] this shares some clinical and histological features with malignant melanoma in children and young adults. The accepted management of a patient with a DPN is simple excision to achieve negative margins. However, some histological features of DPN cause concern, including asymmetry of the lesion, expansile melanocytic nests in the dermis, random cytologic atypia with nuclear pleomorphism, conspicuous eosinophilic nucleolus, absence of maturation, presence of dermal mitoses, and inflammation.[45] A malignant variant of DPN has been reported,[46] with one UK centre also having reported melanoma metastatic to lymph nodes in a child diagnosed with DPN.[47]

The failure to make a clinical diagnosis

A common feature of melanoma negligence claims centres upon a perceived delay in the accurate diagnosis of a mole that the patient regards as suspicious. Given that prognosis relates to the Breslow thickness at presentation, any breach of duty in the failure to timeously diagnose a malignant melanoma is usually accompanied by cogent argument on causation. However, it can be difficult to know how thick a biopsy-proven melanoma could or would have been at a given time point upstream of the presentation, or indeed whether, at the same time point, the mole was a melanoma at all.

In one study,[48] 103 pigmented lesions observed by dermoscopy over one year or more. At 20 months most lesions were still *in situ* or early invasive with a median Breslow thickness of 0.48 mm. Only 3/103 lesions were $>$1 mm in thickness. Minor dermoscopy changes leading to excision were asymmetry of pigmentation (around 80%) or the reticular pattern of the lesion (around 60%). Major changes, such as atypical and/or negative pigment network, blue-white veil, atypical vascular pattern, irregular dots/globules, were only observed after a mean follow-up of 33 months. Hence, it seems to be the case that once moles begin to show dermoscopic evidence of becoming malignant, their rate of change is slow for around 20 months, with major signs of invasion only becoming visible after a mean of nearly three years.

Furthermore, there is also some variation in the rate of growth of melanomas, with 'type 1' thin melanomas growing slowly against a background of intermittent sun exposure and multiple naevi, and other, 'type 2' thicker, tumours showing more aggressive growth.[49]

Also, it is not the case that melanomas increase in thickness in a linear fashion.[50] However, the time when the patient first notices a significant change in the appearance of the mole correlates well with an increase in mitotic rate and Breslow thickness;[51] importantly, this is usually when a patient presents to their GP.

The failure to make a histological diagnosis

As for the failure to make the correct clinical diagnosis, the failure to accurately identify malignant melanoma in the biopsied mole denies the patient the opportunity for onward treatment. Persistence and progression of local disease, untreated by WLE, can be argued as a

potential source of distant recurrence in lymph nodes or by haematogenous spread. The Claimant will argue that the failure to identify the primary tumour, either clinically or histologically, led to lymph node metastases that could either have been avoided entirely, or that could have been identified early by SLNB, thereby avoiding the distress of macroscopic nodal recurrence and the need for TLND, which in itself is more complication-prone than CLND. Worse still, the Claimant may seek to show that earlier diagnosis could or would have prevented conversion to stage 4 disease (systemic metastases). These arguments may, however, be difficult to make unless it can be shown on the balance of probabilities, what the disease stage was at the time when it is alleged that the diagnosis should have been made.

The failure to offer SLNB

It is not mandatory to offer SLNB to patients who are eligible for it, as not all UK centres currently support SLNB services. However, SLNB is a recognised treatment option for a majority of melanoma patients, and it is therefore at least mandatory for that option to be discussed.[52] It would be difficult to argue that the failure to perform SLNB resulted in worse melanoma-specific survival, as this this would rely upon Morton's data, which remains the subject of some controversy.[53] However, in those patients where the SLNB would have been positive, a CLND ensures improved loco-regional control and a prolonged disease-free interval (DFI). This may be especially relevant with the introduction of effective adjuvant immunotherapies for patients with resected stage 3 disease. The value to patients in prolonging the DFI is evidenced by the literature, which suggests that progression-free survival correlates with an improved quality of life.[54]

Histological mis-diagnosis of the SLN

It is accepted that there is a false negative rate in the diagnosis of metastatic disease in the SLN. This can be due to a (non-negligent) failure to identify the true SLN on lymphoscintigraphy or at operation, or technical failures in the preparation of the slides. Non-malignant capsular naevus cells might also be mis-diagnosed as tumour cells. In one large UK series, capsular naevus cells were identified in 7.3% of sentinel nodes.[55] The presence of benign capsular naevus cells in sentinel lymph nodes of patients with melanoma does not influence melanoma-specific five--year survival.[56] Benign capsular naevus cells stain positively for MART-1,[57] S-100 and Melan-A but, importantly, they are negative for HMBA-45.[58,59] Intra-capsular melanoma metastases are distinguished from benign naevus cells in that they exhibit marked atypia, mitotic figures, positive HMB-45 staining and destruction of the lymph node capsule. Capsular naevus cells can be further distinguished from melanoma cells through their positive staining for p16.[60] The mis-diagnosis of capsular naevus cells as melanoma metastases can lead to an unnecessary CLND. Alternatively, the mis-diagnosis of melanoma metastases and capsular naevus cells would lead to a false negative result, under-staging and a nodal relapse.

Conclusion

Negligence claims in relation to the care delivered to patients with malignant melanoma are not uncommon. Delays in clinical diagnosis, the failure to offer SLNB and histological mis-diagnosis of the primary lesion or the sentinel node are all potential sources of litigation. An understanding of the diagnostic and treatment pathway, along with the biology of the disease, is central to determining the merits or vulnerabilities of the claim. The rapid advances made in recent years in the development of effective systemic therapies for melanoma place ever greater importance upon the detection of early distant site disease, while strengthening the causation argument for those patients in whom the diagnosis is made too late to achieve surgical and/or oncological control.

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