SURGICAL MANAGEMENT OF MELANOMA: HAVE WE MADE ANY PROGRESS IN 100 YEARS?

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Abstract

In the early 20th Century, excision of all primary melanomas with >5cm clearance margins was recommended, with amputation in selected cases – recommendations based on experience of a few patients with locally advanced disease. More recently, randomised trials showed that even thick (>4mm) primary melanomas require no more than 2-3cm clearance and thin (<1mm) and intermediate thickness (1-4mm) melanomas no more than 1-2cm margins to achieve good local control with no adverse effect on survival. The management of regional lymph nodes has also changed on the basis of clinical trial results. Elective node dissection, formerly regarded as necessary, has been abandoned. Today, most patients with intermediate thickness melanomas are offered a "sentinel" node biopsy procedure, with node dissection only if the sentinel node is positive. Sentinel node biopsy provides the most accurate staging and prognostic information currently available and achieves good local control of regional node disease. It may also confer a survival benefit in patients who are node positive but long-term results of clinical trials are awaited to confirm this. In the great majority of patients who present with thin primary melanomas, even sentinel node biopsy is generally considered unnecessary. Although substantial progress has been made over the past 100 years in defining evidence-based surgical management protocols for patients with melanoma, continuing efforts are needed to further improve surgical outcomes in the absence of reliably effective non-surgical therapies.

Treatment of the primary melanoma

In 1907, William Sampson Handley[1] reported pathways along which melanoma spread and demonstrated centrifugal lymphatic permeation – all based on a single autopsy examination of a patient with very advanced melanoma. On the basis of this slender database, he advocated wide local excision of the primary melanoma, regional lymph node dissection and amputation in selected cases. Nearly a century later, revised management policies are introduced only when they can be justified by carefully planned and well conducted large-scale randomised controlled trials. It is nevertheless instructive to review the history of melanoma management from the surgical point of view, because it highlights some of the difficulties that are inevitably encountered when management policies are based on anecdotal experiences and retrospective rather than prospective studies.

Such was the paucity of information available to guide melanoma management policies in the early 20th century that even by 1935 Sampson Handley had treated "only 8 to 10 cases, apart from hopelessly inoperable ones".[2] Hogarth Pringle in 1908 had also recommended excising tumour and adjacent skin down to and including the deep fascia.[3] These important historical documents became the basis of melanoma treatment for many subsequent decades, especially when strengthened by Olsen's report that atypical melanocytes were often found within 5cm of the primary tumour.[4] During this period excisions 10cm or more in diameter, with correspondingly large skin grafts, were regularly performed at melanoma treatment centres around the world. This radical surgical management of primary melanoma initially developed in response to the almost universal presentation of patients with locally advanced tumours.

The recommendation to always excise very widely down to and including the deep fascia, was subsequently abandoned[5, 6] and was replaced by a better defined, evidence-based policy of more limited local treatment. This change occurred primarily in response to a changing pattern of disease presentation, when it became apparent that these deforming operations did not enhance survival. In most countries the great majority of patients now present with tumours <1mm thick, rendering irrelevant the radical historical approaches for locally advanced melanoma. Two of the most recent prospective randomised trials, from France[7] and Sweden,[8] have provided further conclusive evidence that margins >2cm are generally unnecessary, even for tumours >2cm in thickness. It is currently accepted that a margin of 5mm for in situ tumours, 1 cm for all tumours ≤1mm thick and 1-2cm for all other melanomas is appropriate.

Treatment of regional lymph nodes

In his 1908 report, Pringle also emphasised that, where feasible, wide excision should be performed in continuity with regional lymph node dissection.[3] This proposal established the basis of regional lymph node treatment for 60 years. The policy was founded on the earlier premise by Snow[9] that metastatic melanoma progressed sequentially from primary site to regional lymph nodes. Eventually, however, the results of a number of major studies cast doubt on the value of elective lymph node dissection (ELND) for all patients with higher-risk tumours. Some earlier randomised but poorly stratified trials undertaken by the World Health Organization (WHO) Melanoma Program[10] and North American groups[11] failed to demonstrate an overall survival benefit for all patients with higher-risk tumours. These and several early non-randomised studies were widely

criticised, mainly because of the failure to stratify by thickness, disproportions in gender and primary tumour site and failure to accurately identify the correct regional node field for dissection. Sappey in 1874[12] had categorically stated that lymphatic drainage never crossed the midline. He later modified this to exclude sites within 5cm of each side of the original vertical and horizontal dividing lines of the body. This concept was embraced by most practitioners until quite recently, when it became obvious from preoperative lymphoscintigraphy performed in large numbers of patients that, particularly on the trunk, drainage was quite diverse and unpredictable. It was shown that up to 30% of patients may have had inappropriate node field dissections when clinical prediction of the path of lymphatic spread was used to select the dissection field.[13] Later, more carefully stratified randomised trials, the Intergroup Melanoma Surgical Trial[14] and the WHO Melanoma Program Trial[15] in which either blue dye or radio-colloid tracer were used to map the draining fields, found by multivariate analysis that routine ELND had no impact on overall survival. However, in the Intergroup trial, a small survival benefit emerged for patients 60 years of age or under. In the WHO trial, patients whose regional nodes became clinically and histologically postitive during follow-up had the poorest prognosis. The principal criticism of this latter trial was that the sample size did not allow sub-group analysis. The other crucial outcome in the WHO trial was that 36 patients with clinically negative but histologically postitive nodes who had an ELND (NO+), had a significantly better five-year survival rate (48% versus 27%; $p<0.04$) than those 25 patients with clinically negative nodes not undergoing ELND, who subsequently developed clinically and histologically overt lymph node disease (N1) (Figure 1). Thus the immediate dissection of positive but subclinical node metastases appeared to result in improved long-term survival. This clinical trial observation provided an incentive to pursue development and validation of the less invasive technique which has subsequently revolutionised the treatment of higher-risk patients – sentinel node (SN) biopsy.

Lymphatic mapping and selective "sentinel" lymph node biopsy

At a meeting of the Society of Surgical Oncology in 1990, Dr Donald Morton of the John Wayne Cancer Institute in Santa Monica suggested that it was possible to determine the status of regional lymph nodes in patients with melanoma by performing a minimally invasive procedure that has subsequently become known as SN biopsy.[16] Morton proposed that lymph draining from a primary tumour site, and potentially containing melanoma cells, drains first to a "sentinel" node before passing on to other nodes in the regional node field. He stated that it was possible to identify a SN with confidence by injecting vital blue dye at the primary melanoma site and tracing blue-stained lymphatics to the regional node field. Here, the SN (or SNs) would be blue-stained and therefore able to be identified. According to this proposal, the SN is the node most likely to contain tumour cells. If no tumour cells are present in this node, none should be present in other nodes in the node field. The publication outlining this proposal by Morton, his pathology colleague Dr Alistair Cochran and others was eventually published in 1992.[17] The paper is now a citation classic, having previously been rejected by several major surgical journals. In this report it was emphasised that the minimally invasive SN biopsy procedure would allow full regional node dissection to be avoided in approximately 80% of patients with intermediate thickness melanomas because they had negative SNs.

Confirmation of the accuracy of SN biopsy in identifying patients with metastatic disease in regional lymph nodes was quickly provided by studies undertaken in the United States[18] and Australia.[19] Both these studies involved SN biopsy with immediate complete lymph node dissection, so that all the remaining nodes in the node field could be examined. The results were remarkably similar to those that had been obtained by Morton and his colleagues. Although there had initially been great scepticism, the technique was soon taken up around the world and is now a routine procedure in most major melanoma treatment centres internationally.

Figure 1

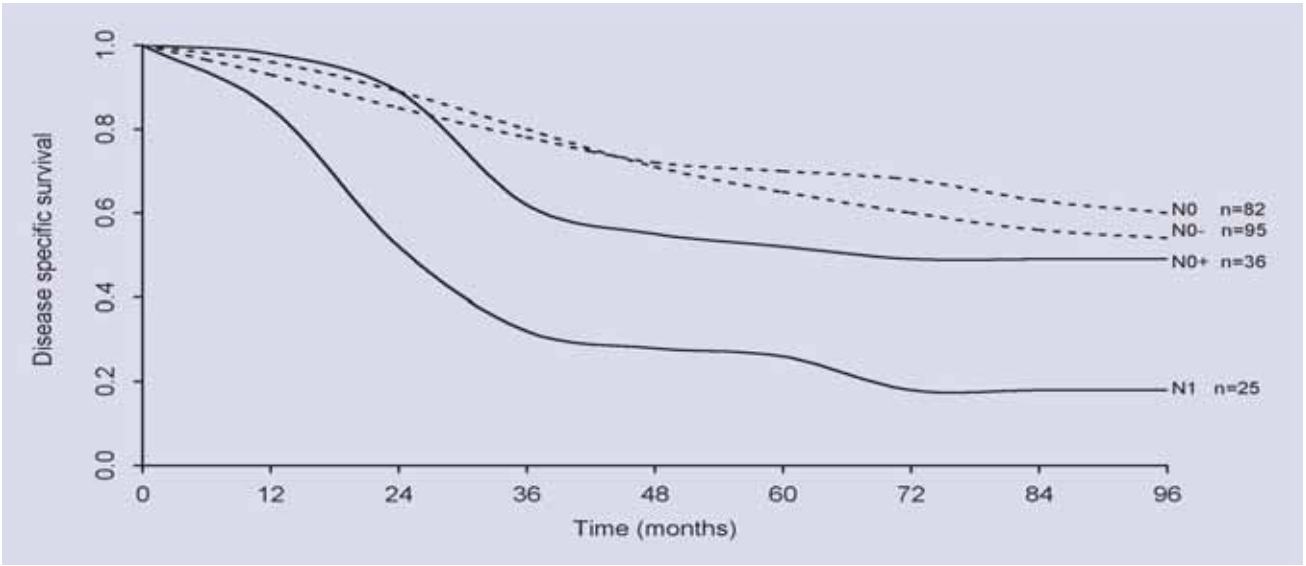
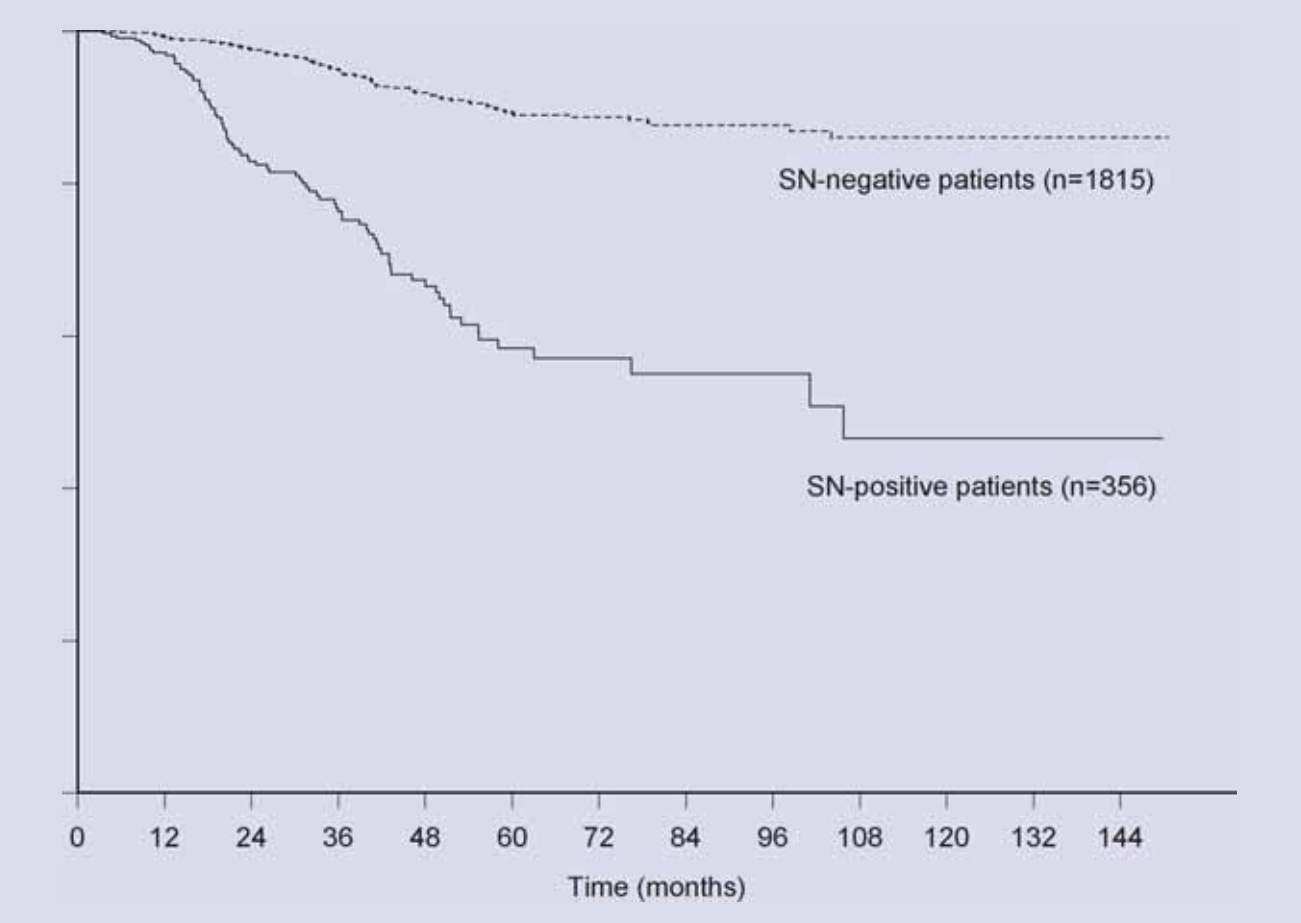


Figure 2



As already indicated, the initial studies reported by Morton's group involved only intradermal vital blue dye injection at the primary melanoma site. It was soon found however, that preoperative lymphoscintigraphy, involving injection of a radio-labelled colloid at the primary melanoma site, provided valuable information preoperatively. It also made the SN biopsy procedure easier, quicker and more accurate when a hand-held gamma probe was used intraoperatively to assist in location of the SNs. It has since become clear that SN identification is most accurate if all three methods are used – a preoperative lymphoscintigram, blue dye mapping and the use of a hand-held gamma probe intraoperatively. The Sydney Melanoma Unit (SMU) has made important contributions in improving our understanding of cutaneous lymphatic drainage pathways. This has been based on preoperative lymphoscintigraphy performed in large numbers of patients.[20, 21]

Several major studies have now shown that SN status provides the most accurate prognostic information currently available.[22-27] There is a large difference in five year disease-specific survival for patients who are SN-positive and those who are SN-negative. A recent update of an earlier SMU experience[28] has shown that in 1815 patients who were SN-negative the five-year survival rate was 89%, while in 356 patients who are SN-positive the five-year survival rate was 58% (Figure 2).

The unanswered question however, has been whether early complete regional lymphadenectomy, performed in patients who are SN-positive, improves survival outcome. Results of a large international study, the first Multicenter Selective Lymphadenectomy Trial (MSLT-I),[29,30] have recently been reported[31] at an international meeting and a paper documenting the outcome of this trial was submitted for publication in mid-February 2006. The MSLT-I results indicate that there is no significant overall survival advantage between those patients with intermediate thickness melanomas randomised to receive wide excision of their primary melanoma together with SN biopsy and those having wide excision alone. However, patients who are SN positive appear to have a significantly better survival outcome if they have an immediate completion lymphadenectomy, than patients who are observed and who have a full regional lymphadenectomy when metastatic disease becomes clinically apparent. This result is consistent with the previous WHO Melanoma Program elective node dissection study mentioned earlier (see Figure 1). Publication of the full MSLT-I results is awaited with great interest. The morbidity of the SN biopsy procedure is low[30] and the suggestion that performing an SN biopsy may increase the rate of intransit metastasis has been convincingly disproved by four large retrospective studies from the MD Anderson Cancer Center, the John Wayne Cancer Institute and the SMU,[32-35] and most recently by the MSLT-I results.[31]

The next important question to be answered is whether all patients who are found to be SN-positive require a complete regional node field clearance. It is likely that only 15-20% of patients could possibly benefit, since this is the proportion who have additional (ie. non-SN) metastases in their regional nodes. A second international multicentre trial (MSLT-II), designed to answer this question, commenced patient accrual in late 2004. In this trial patients who are found to be SN-positive are randomised to have an immediate complete node dissection (currently the standard treatment recommendation), or to be observed with regular ultrasound examination of the remaining nodes in the node field and have a complete node dissection at a late date if metastatic disease becomes apparent.

Present role of sentinel node assessment

At the third planned interim analysis of the first MSLT-I, no overall survival benefit was demonstrated for patients with intermediate thickness melanomas who had a SN biopsy procedure. When the results in SN-negative and SN-positive patients were analysed and compared with patients who did not have a SN biopsy procedure, it was found that patients who remained node negative did not benefit from having a SN biopsy, but those who were node positive benefited from early node dissection. There is a statistical difficulty with the MSLT-I results, since it was clearly not possible to pre-randomise SN-negative and SN-positive patients. However, after a median follow-up of almost five years, the proportion of patients found to be SN-positive was almost identical to the proportion of patients in the wide excision only group who subsequently developed clinically apparent disease in their regional node field. This strongly suggests that most if not all patients with a positive SN will ultimately develop clinically apparent nodal disease if early nodal intervention is not undertaken.

Thus while there is strongly suggestive evidence of a survival benefit for node-positive patients having SN biopsy, there is still no absolute proof of this. However, even if no survival benefit is ever able to be demonstrated, there are still compelling reasons to perform SN biopsy.[36,37] The procedure undoubtedly provides the most accurate staging that is currently available. It also provides the most reliable estimate of prognosis and allows patient selection and stratification for adjuvant therapy (such as with interferon alpha) and for adjuvant therapy trials.

Minimally invasive and non-invasive SN assessment

Although the morbidity of SN biopsy is low, it involves a surgical procedure with an associated inconvenience and cost. Efforts are therefore being made to assess SNs in minimally invasive or non-invasive ways. It has already been shown that examination of fine needle aspirates from SNs using magnetic resonance spectroscopy (MRS) can provide a reliable indication of SN status.[38,39] SNs containing metastatic melanoma produce spectra with characteristic peaks of taurine, choline and other metabolites that are not present in nodes not containing melanoma. The ultimate objective is to perform completely non-invasive in-vivo assessment of SNs using MRS with surface coils.[40, 41]

The role of surgery for apparently isolated metastatic disease

It has been known for many decades that local melanoma recurrences and intransit metastases are best treated by surgical excision. Some patients treated in this way are apparently cured by the procedure. It is also believed that surgery is the most effective form of treatment for macroscopic disease in lymph nodes. Long-term survival in excess of 50% can be achieved in some such patients.[25] More controversial is the role of surgery in the treatment of patients with metastases in internal organs. Five-year survival rates of up to 40% have been reported after complete resection of gastrointestinal metastases[42-44] and five-year survival rates exceeding 20% after complete resection of lung metastases.[45,46] The difficulty with these studies is that they report the results obtained in highly selected groups of patients and it would be very difficult to undertake large scale randomised trials. Nevertheless, there does appear to be the possibility of cure for some patients with systemic melanoma metastasis when complete surgical resection of those metastases can be achieved.

Summary and conclusions

Substantial progress has been made over the last 100 years in defining appropriate surgical management protocols for patients with melanoma. Desirable excision margins have been determined on the basis of randomised clinical trials and progress is being made towards defining rational management of regional lymph nodes, also on the basis of well-designed clinical trials. In the absence of reliably effective non-surgical therapies for melanoma however, continuing efforts to find ways of further improving surgical outcomes are required. □

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