CURRENT STRATEGIES FOR THE SURGICAL MANAGEMENT OF MELANOMA

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Abstract

Over the past 25 years, surgical strategies for the management of primary cutaneous melanoma have changed considerably. In the 1970s and 1980s, most melanomas were widely excised with 3cm-5cm margins and regional lymph nodes were often treated by elective dissection. Today, excision margins rarely exceed 2cm and elective lymph node dissection has been almost completely replaced by selective sentinel node (SN) excision, with completion lymph node dissection only in the small proportion of patients found to have micrometastatic disease in a SN. These major changes in the surgical approach to primary melanoma management have occurred because large clinical trials have indicated that little or no benefit is achieved by excising melanomas with very wide margins, or by performing elective lymph node dissections. The other important factor has been the introduction and validation of the SN biopsy procedure, guided by preoperative lymphoscintigraphy. In the absence of effective forms of systemic therapy, the place of surgery in the management of metastatic disease has become more firmly established and it has become apparent that an aggressive surgical approach in patients with apparently limited metastatic disease, even at systemic sites, is fully justified.

Management of the primary melanoma

The role of surgery in the management of melanoma begins with excision-biopsy of the suspect lesion. Even if a confident diagnosis of melanoma is made on clinical grounds, preliminary excision of the entire lesion with around 2mm clearance margins is recommended, so that appropriate definitive treatment can be planned. Details such as the thickness of the primary tumour and whether any unfavourable features are present, such as ulceration, regression or a high mitotic rate, will determine the definitive excision margins that will be recommended and whether the likelihood of metastasis to regional lymph nodes is sufficiently high to warrant sentinel node (SN) biopsy as a staging procedure. The problems associated with partial biopsies (incision, punch and shave biopsies) of melanocytic lesions are described elsewhere in this issue of Cancer Forum.

There is universal agreement that complete surgical excision of a primary cutaneous melanoma is required, but there is continuing debate about the clearance margins that should be employed. Some have argued that complete excision of the tumour is all that is necessary, whereas others have suggested that wide clearance margins are required, particularly for thick primary melanomas (>4mm). It is clear that the 5cm clearance margins generally regarded as standard treatment for all melanomas in the 1960s and 1970s can no longer be considered appropriate, because they do not affect long-term survival, nor do they achieve lower local recurrence rates than more conservative margins. Indeed, several large retrospective studies reported in the 1980s indicated that local recurrence was most uncommon in patients whose melanomas were excised with margins of 2cm or more. Rather, these studies made it clear that the risk of local recurrence was principally dependent on the thickness of the primary melanoma. In a 1985 review of the Sydney Melanoma Unit experience,7 recurrence rates in 1839 patients with five years of follow up were reported. For thick tumours (defined as ≥ 3mm) the local recurrence rate was 21% when the excision margin was <2cm and 9% when the excision margin was ≥2cm. For thin tumours (defined as 0.1-0.7mm in thickness), the recurrence rates were two% when excision margins of <2cm were used and less than 1% when excision margins of ≥2cm were used. Because of continuing uncertainty about the excision margins that were necessary to minimise the risk of local recurrence and to avoid an adverse effect on survival outcome, several large, prospective, randomised trials were undertaken. One of these trials, undertaken by members of the World Health Organisation (WHO) Melanoma Group,1 compared results for patients with primary melanomas <2mm in Breslow thickness who had their tumours excised with margins of either 1cm or 3cm. For the 612 patients in this study, disease-free and overall survival rates did not differ for the two groups, but it was clear that melanomas ≤1mm in thickness were adequately treated by excision with a 1cm margin. Another important study was undertaken in the United States, in which patients with intermediate thickness melanomas (1-4mm) were randomised to be treated with either 2cm or 4cm excision margins. For the 486 patients in this study, local recurrence rates were similar for the two groups and there was no significant difference in overall five year survival. As expected, however, treatment morbidity and length of hospital stay were significantly greater in the 4cm margin group.

Two subsequent European trials compared the results of treating primary melanomas with 2cm and 5cm excision margins. One of these, undertaken by the Swedish Melanoma Study Group, involved 989 patients with melanomas 0.8-2.0mm in thickness. The other, undertaken by the French Group for Research on Malignant Melanoma, involved 326 patients with primary melanomas <2.1mm in Breslow thickness. Both these studies failed to produce any evidence that 5cm margins reduced the local recurrence rate or improved survival outcome. The most recently reported large trial examining the question of excision margins was a 900 patient study undertaken in Britain. Excision margins of 1cm and 3cm were compared for patients with melanomas ≥2mm in Breslow thickness. It was found that a 1cm margin was associated with a slightly greater risk of local recurrence than a 3cm margin, but with a median follow-up period of 60 months there was no difference in survival outcome for the two groups.

What conclusions can be reached about excision margins on the basis of all the information currently available? For invasive melanomas that are ≤1mm in Breslow thickness, a 1cm minimum clearance margin should be adequate and there is
general consensus about this. For tumours between 1mm and 2mm in thickness, there is some evidence that excision margins greater than 2mm in Breslow thickness, available evidence suggests that an excision margin of at least 2cm is required, to minimise the risk of local recurrence, but whether this margin is adequate or a margin of 3cm is required remains uncertain, because the appropriate trials have not been conducted. A further consideration is that most of the available clinical trial evidence has been based on patients with tumours located on the trunk or a proximal extremity, with exclusion of patients who have melanomas in the head and neck area or on a distal extremity. It is possible that different guidelines are required for the management of primary tumours in these sites.

Surgical morbidity and cosmetic implications must also be considered. Even if excision margins of ≥2cm do achieve slightly lower local recurrence rates for patients with intermediate thickness and thick melanomas, this small benefit must be weighed against the increased surgical morbidity and disfigurement that will inevitably be associated with wider excision margins. It could be argued that it is better to accept a slightly higher risk of local recurrence and avoid the additional morbidity and cosmetic deformity that a wider margin will produce, because if local recurrence does occur, it can usually be managed by simple surgical removal. Even though local recurrence is associated with a reduced survival outcome, it is scientifically inappropriate to assume that the process of performing a wider excision with the intention of reducing the risk of local recurrence will necessarily improve survival. Indeed, careful evaluation of all the available evidence suggests that it is tumour biology rather than the extent of local treatment that determines ultimate outcome. Some compromise on excision margins therefore seems reasonable in situations where the risks of surgical morbidity and cosmetic deformity are high.

Management of regional lymph nodes

During the 1970s and 1980s, there was ongoing controversy about the value of elective lymph node dissection (ELND) for patients with intermediate thickness melanomas who presented with no clinical evidence of regional node metastasis. Although retrospective studies appeared to indicate a survival benefit, randomised trials did not do so. Particularly for patients with primary melanomas of the lower limb, the long-term morbidity of ELND was considerable and in any case only approximately 20% of patients were found to have metastatic disease in the regional nodes when ELND was performed.

A potential solution was proposed at a meeting of the Society of Surgical Oncology in 1990 by Donald Morton and his associates from the John Wayne Cancer Institute. They suggested that it was possible to assess the status of regional lymph nodes with confidence by performing lymphatic mapping to identify a sentinel node in each patient and then remove that node for histological examination. Technical details of the procedure were published in 1992 and it was proposed that SN biopsy would allow ELND to be avoided in 80% of patients, but identified the 20% of patients most likely to benefit from the procedure. Within three years of that initial publication describing SN biopsy, confirmation of its accuracy in identifying regional node metastases was provided by studies undertaken in the United States and at the Sydney Melanoma Unit. In both these studies lymphatic mapping and SN biopsy were performed, but with immediate completion ELND so that all remaining nodes in the node field could be assessed histologically. The results of the two studies were remarkably similar to those that had been reported by Morton and his colleagues and established conclusively that the sentinel node hypothesis was valid. In other words, if no evidence of micrometastatic disease was found in SNs, metastatic disease was not likely to be present in other nodes in that node field. Other validation studies with similar results were reported subsequently and all confirmed that SN status accurately reflects the status of the entire node field in patients with melanoma.

Although the practical clinical importance of the SN concept had not been fully appreciated until the early 1990s, the SN concept was not new. Indeed, it had been very clearly described by the pathologist Virchow in the mid 19th Century. The SN concept is remarkably simple. Lymph draining from a tumour passes first to a SN before passing onwards to other nodes in the regional node field. If tumour cells enter lymphatic collectors, they are thus most likely to be found in the SN. In the early studies undertaken by Morton and his colleagues, blue dye was injected intradermally at a primary melanoma site and blue-stained afferent lymphatics were traced to a blue-stained SN in the regional node field. This was a tedious and quite invasive process, but it soon became apparent that preoperative lymphoscintigraphy could not only provide valuable information preoperatively, but could also facilitate SN identification by intraoperative use of a hand-held gamma probe. A report from the Sydney Melanoma Unit was the first to suggest that it was possible to use residual radioactivity in the SN after preoperative lymphoscintigraphy for intraoperative SN identification with a gamma probe. It was quickly recognised that the most rapid and confident identification of SNs was achieved if all three methods were used, ie. a preoperative lymphoscintigram, blue dye injection at the primary melanoma site immediately preoperatively and use of a gamma probe intraoperatively.

Knowledge of a patient's SN status has important prognostic implications and the results of several large studies confirming this have now been reported. Irrespective of other prognostic variables, the five-year survival probability for melanoma patients who are SN positive is much lower than the five-year survival for those who are SN negative. Results for 991 patients treated at the Sydney Melanoma Unit are typical and are shown in Figure 1; the five-year survival rate for patients who were SN positive was 56%, whereas for those who were SN negative it was 90%.

**Figure 1:**

Disease-specific survival in sentinel node positive patients (n = 139) versus sentinel node negative patients (n = 836). (p < 0.001)
A detailed account of the technical details of SN biopsy is beyond the scope of this article, but full descriptions are given elsewhere.²⁰,²¹ It is important to note that although the SN concept is simple, the process of identifying and removing SNs can be technically challenging, particularly when more than one SN is present in a node field, as is often the case in patients with primary melanomas in the head and neck region.²² The value of the technique clearly depends upon accurate identification and removal of every SN in each patient. It has become clear that metastatic disease can be present in any node that is truly a SN and not just in the hottest SN, or the SN that is most intensely stained with blue dye. False negative rates as high as 25% have already been reported,²²,²³ where a false negative result is defined as recurrence in a node field following removal of a SN or SNs reported to be negative. Although some of these false negative results are likely to have been due to incorrect interpretation of the lymphoscintigram by the nuclear medicine physician and others are likely to have been due to failure by the pathologist to detect micrometastatic disease that was actually present, there can be no doubt that failure by the surgeon to identify and remove the correct node or nodes was responsible for the false negative result in some cases.²⁴

Although it is abundantly clear that SN assessment provides valuable prognostic information, there is no evidence at the present time that removal of these nodes, with complete regional node field dissection if a positive SN is found, will improve survival outcome. The results of large multicentre randomised trials will be required to answer this question. Preliminary results of one such trial, the Multicenter Selective Lymphadenectomy Trial²⁵,²⁶ were presented recently²⁷ but have not yet been published. After a median follow-up period of 54 months, there was no statistically significant difference in overall survival between patients treated by wide excision only and those treated by wide excision plus SN biopsy, with immediate completion lymph node dissection if a positive SN was found. However, the survival outcome for patients who were found to be SN positive and who had an immediate completion lymph node dissection was much better than the survival outcome for patients who were initially treated by wide excision only and who subsequently developed clinical disease in the regional node field and had a therapeutic lymph node dissection at that time. Further results of this trial, after a longer period of follow-up, are awaited with great interest.

The next important question that will need to be answered is whether it is always necessary to perform a completion regional node field dissection when a positive SN is found. This question is of importance because no more than 20% of patients will be found to have metastatic disease in non-sentinel lymph nodes. A new multicentre, international trial (MSLT II) has recently been commenced to examine this question. SN-positive patients who enter the study will be randomised to receive standard treatment, ie. completion regional lymph node dissection, or to have no further surgery, but to have their regional nodes checked regularly both by clinical examination and using high-resolution ultrasound.

Preoperative lymphoscintigraphy has now been performed in over 4000 Sydney Melanoma Unit patients and has provided important new insights into cutaneous lymphatic drainage pathways.²⁸,²⁹ These studies have shown that many long-held beliefs about cutaneous lymphatic drainage pathways, some dating back to the work of Sappey and his associates in the mid 19th Century,²⁸ are incorrect. It has been found, for example, that lymphatic drainage across the midline is common and that drainage to previously unrecognised lymph node sites such as the triangular intramuscular space on the back, just lateral to the scapula, can occur.³¹ From the upper limb, direct drainage not only to the axilla but also to supraclavicular SNs can occur, as well as drainage to epitrochlear SNs and to interval SNs in the arm. From the lower limb, drainage can occur not only to popliteal SNs and interval SNs in the thigh, but also directly to external iliac and obturator SNs, as well as to SNs in the femoral triangle. Sometimes, drainage from the lower back to SNs that are retroperitoneal and paravertebral can occur, and occasionally drainage is exclusively to these sites, with no drainage to the groin or axilla. Normal and abnormal lymphatic drainage patterns in patients with melanoma are discussed in greater detail elsewhere.³²,³³

The present role of sentinel node biopsy

Even if the results of clinical trials do not show a survival benefit for patients treated by SN biopsy, the value of the technique in providing prognostic information will remain. Knowledge of SN status provides a patient with the most reliable estimate of prognosis that is currently available and allows more accurate stratification for entry into adjuvant therapy trials. If effective adjuvant therapies are found, knowledge of SN status will be required to identify those at greatest risk of recurrence and therefore most in need of adjuvant therapy.

It has been suggested that the SN biopsy procedure should not be performed because it increases the risk of in transit metastasis.³⁴-³⁶ However, no increased risk of in transit metastasis was found in two large single centre series³⁷,³⁸ and the recently presented results of the Multicenter Selective Lymphadenectomy Trial demonstrate conclusively that the in transit metastasis rate is not increased in patients who have a SN biopsy procedure.³⁹ It seems likely that primary tumour biology alone determines the risk of in transit metastasis.³²,³³

Nevertheless, the concept of obtaining information about SN status in minimally invasive and non-invasive ways is already being investigated. For example, studies undertaken at the Sydney Melanoma Unit have already shown that rapid and accurate results can be obtained by examination of fine needle aspiration biopsies from SNs, using magnetic resonance spectroscopy.⁴⁰ This technology is discussed in another contribution to this edition of Cancer Forum. Studies are currently in progress to confirm the feasibility of completely non-invasive SN assessment, using surface coils to obtain magnetic resonance spectra from underlying SNs, which have been identified and localised by preoperative lymphoscintigraphy and ultrasound examination.

Surgical treatment of locally recurrent, in transit and nodal metastases

A detailed consideration of the role of surgery in the management of local melanoma recurrence. In transit disease and regional node disease is beyond the scope of this article. The important principle, however, is that whenever recurrent disease is localised and can be resected with an acceptably low risk of serious morbidity, this is the treatment of choice because it is likely to be the most effective way of preventing or relieving symptoms and may also extend survival.³² It is a sad fact that presently available forms of systemic therapy rarely achieves complete disease remission. Therefore systemic therapy is generally reserved for patients with symptomatic or rapidly progressive metastatic disease. However, surgical techniques such as isolated limb perfusion and isolated limb infusion, in which high dose regional chemotherapy is administered to patients with extensive recurrent disease confined to a limb, can achieve complete remission rates.
exceeding 50%, with a low risk of serious side effects. These techniques and the results of treatment using them are described elsewhere.58,59

Surgical treatment of systemic metastases

More than 85% of melanoma patients who present with AJCC Stage IV disease have demonstrable metastases confined to a single organ site such as the lung or the gastro-intestinal tract, although metastases sometimes appear later at other sites. In recent years positron emission tomography (PET) scanning has been used to confirm that systemic metastases are genuinely isolated. When considering surgical resection of systemic metastases, several facts must be borne in mind. It has been shown, for example, that the most powerful predictor of survival in melanoma patients with systemic metastases is the number of organs or tissues containing metastases.60-62 For patients with metastatic disease identified at only one site, median survival is around seven months, for two sites it is four months, and for three or more sites it is only two months.63

Consideration of these facts has led to a re-appraisal of the value of surgical resection in the management of patients with Stage IV melanoma. Complete surgical removal of a metastatic deposit can render patients disease free and substantially improve their survival probability. Even if survival time is not extended, resection of isolated systemic metastases can provide excellent palliation of symptoms and can also prevent the development of problems at a later date. In recent series, five-year survival rates of 20-27% have been reported following complete resection of lung metastases64,65 and five-year survival rates of 20-27% have been reported in recent series.64,65

Stage IV melanoma. Complete surgical removal of a metastatic deposit can render patients disease free and substantially improve their survival probability. Even if survival time is not extended, resection of isolated systemic metastases can provide excellent palliation of symptoms and can also prevent the development of problems at a later date. In recent series, five-year survival rates of 20-27% have been reported following complete resection of lung metastases64,65 and five-year survival rates of 28-41% following complete resection of metastases in the gastrointestinal tract.66-68 Even patients with melanoma metastases in the liver can survive for prolonged periods after surgical resection; in a combined series of patients treated at the Sydney Melanoma Unit and the John Wayne Cancer Institute, the five-year survival was 29%.69 Even when multiple systemic metastases have been resected, long-term survival has sometimes been achieved. Present evidence suggests that complete or near complete cytoreduction by surgery improves survival by reducing the overall tumour burden, allowing the host’s immunological defence mechanisms to function more efficiently. The other systemic site where surgical removal of an apparently isolated metastasis can be highly effective in relieving symptoms is in the brain, where surgical treatment alone was associated with a median survival of 7.1 months and surgery plus adjuvant postoperative radiotherapy a median survival of 9.2 months.70

References

3. Veronesi U, Cascinelli N. Narrow excision (1-cm margin). A safe technique and the results of treatment using them are described elsewhere.58,59


