Sentinel node biopsy in malignant melanoma: is the information worth the risk?

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ABSTRACT

Malignant melanoma has a high incidence in New Zealand and Australia. Melanoma primarily spreads via the lymphatic system, and nodal metastases are an important prognostic marker. The sentinel lymph node is the first draining node in a lymphatic basin downstream of a tumour. The use of sentinel node biopsy in malignant melanoma remains controversial, with the purported benefits being widely debated. Sentinel node biopsy offers useful prognostic information in patients with 1-4mm thickness melanoma, though no therapeutic benefits have been shown when used in conjunction with completion lymph node dissection. There are few physical risks of sentinel node biopsy, which has a low complication rate. There is spare evidence addressing the psychological impacts of sentinel node biopsy, though it appears to confer some short-term benefits. Patient preferences and clinical judgement are important considerations. Sentinel node biopsy may only be useful as a prognostic indicator in patients with 1-4mm thickness melanoma. No therapeutic benefits have been shown to date. As new evidence emerges, the role of sentinel node biopsy should be reconsidered accordingly.

BACKGROUND

Malignant melanoma (MM) is increasing in incidence globally, with high rates in New Zealand and Australia.[1, 2] Although melanoma causes 75% of skin cancer-related deaths, its optimal management remains unclear.[3, 4] MM is defined as a malignant clonal expansion of melanocytes, originating in the dermis. Like many cancers, it primarily spreads via the lymphatic system, and nodal involvement is present in 20% of patients with intermediate thickness (1-4mm) melanoma.[5] Nodal metastases are an important prognostic marker in MM, and it has been hypothesised lymph node clearance may improve prognosis for patients with nodal metastases.[5] When nodal metastases are clinically palpable, the decision to proceed with lymphadenectomy is straightforward.[6] However, trials have shown routine lymphadenectomy confers no survival benefit for patients with intermediate-thickness melanoma but without palpable metastases.[7]

The sentinel lymph node is defined as the first draining node in a lymphatic basin downstream of a tumour, and can be identified intraoperatively using lymphoscintigraphy with radioisotope and blue dye.[5, 8] Sentinel node biopsy (SNB) has been suggested as a means of identifying patients with micrometastases who may benefit from lymphadenectomy.[8] Completion lymph node dissection (CLND) is then performed only if the sentinel node contains metastases.

The benefits of SNB remain controversial, despite its rapid uptake in clinical practice and guidelines. This review aims to summarise and review the current evidence addressing whether the information gained from SNB in patients with MM is worth the associated physical and psychological risks.

INFORMATION GAINED FROM SENTINEL NODE BIOPSY

The therapeutic benefits of SNB are widely debated, though its role in detecting micrometastases as a prognostic factor in MM is well established. Primary melanoma lesions can be classified as thin (≤1mm), intermediate (1-4mm), or thick (>4mm), with a progressively worsening prognosis in each group.[9] The benefits of SNB differ in each group, corresponding to an increasing risk of nodal and distant metastasis.

For melanomas >1mm thickness, sentinel lymph node status has been identified as the most important independent predictor of overall survival.[10, 11] Therefore, identification of Stage I/II (node-negative) or Stage III (node-positive) disease is an important process and may guide further surgical or adjuvant treatment.

A recent systematic review showed SNB has a false negative rate of 12.5% overall (95% CI 11%-14.2%) for the detection of micrometastases.[12] Furthermore, the post-test probability negative (proportion of patients with a negative SNB who develop nodal metastases), was calculated as 3.4% (95% CI 3.0%-3.8%).[12] Some authors have raised concerns about the prognostic false positivity rate of SNB, wherein micrometastases are detected in patients who will not progress to develop clinically significant recurrence. Data from MSLT-I, a large randomised trial, showed as many as 34% of patients with a positive SNB who consequently underwent CLND would not have developed clinical recurrence at a 5-year follow up.[13] This represents a common clinical dilemma, wherein predicting the risk of recurrence in any individual patient is a difficult task.

Thin lesions represent nearly 70% of all melanomas, and are unlikely to exhibit metastatic spread.[14] Meta-analyses have shown a pooled SNB

positivity rate of 5.6% for patients with thin melanomas, and therefore SNB provides limited information for these patients.[14, 15] Given a low pre-test probability of metastasis and a known false-negativity rate of SNB, it is unlikely SNB will reliably provide valuable prognostic information for patients with thin melanomas.

Patients with intermediate thickness melanomas have been hypothesised to have the most benefit from SNB, as they are unlikely to have distant spread, but may have nodal metastasis. Key prognostic factors for patients with intermediate and thick melanoma include nodal spread, Breslow depth and ulceration of the primary tumour; in order of decreasing hazard ratio.[16] A recent pooled analysis of 19 studies showed melanomas with a positive SNB have a 0%-47.8% risk of melanoma-related death at a 4 year follow up, compared with 0%-11.9% for those with a negative SNB.[15]

Thick melanomas are most likely to have distant metastases, and have the poorest prognosis. It has been suggested SNB may be less useful in determining prognosis in thick melanomas, given their propensity to have already metastasised to nodes and distant organs at the time of presentation.[17] Few studies have investigated thick melanomas specifically, and the prognostic value of a positive SNB has not been consistently shown in this population.[15, 18, 19]

SNB therefore offers valuable prognostic information for patients with 1-4mm thickness melanoma. If such a patient is identified as Stage III by SNB, that represents a significantly different prognosis, which may be of value for patients and clinicians when considering adjuvant treatment options, ongoing management and follow up.

THERAPEUTIC BENEFITS OF SENTINEL NODE BIOPSY

A Cochrane review from 2015 identified MSLT-I as the only randomised trial to date comparing SNB +/- immediate CLND vs. SNB and nodal observation in melanoma patients.[20-22] A 10 year follow up of this trial showed SNB +/- CLND improved disease-free survival for patients with intermediate (HR 0.76, 95% CI 0.62-0.94) and thick (HR 0.70, 95% CI 0.50-0.96) melanomas, but there was no significant difference in melanoma-specific survival between the two groups.[21] The authors have reported other sub-group analyses, but these have been widely debated and are not statistically appropriate.[23, 24] Furthermore, several retrospective studies have shown similar results to MSLT-I, supporting the conclusion that SNB has no impact on overall survival for these patients.[25-29]

Approximately 80% of patients with a positive sentinel node have no further nodal metastases.[17] Therefore SNB alone is hypothesised to provide both diagnostic and therapeutic benefits. A second randomised trial, MSLT-II, began in 2005 and is currently investigating whether all patients with a positive SNB require CLND.17 N-SNORE, a validated prognostic score, may predict the presence of positive non-sentinel nodes in patients with a positive SNB, and determine which patients may benefit from CLND.[30, 31] Until MSLT-II is completed, CLND may be discussed with patients undergoing SNB, though no clear evidence of a survival benefit exists.[21, 26, 29]

PHYSICAL RISKS OF SENTINEL NODE BIOPSY

SNB is safe, with a complication rate of 5-10%.[11, 32] Most adverse events are haematomas, seromas or wound infections, and resolve with minimal intervention. It is important to note radiolabelled colloid or dye is contraindicated in pregnant women and those with hypersensitivity.[33] Anaesthetic-related risks are also relevant when selecting surgical candidates.

Wide local excision (WLE) with SNB may have equivalent complication rates to WLE alone, and therefore SNB may not confer additional morbidity to patients not requiring CLND.[11] In contrast, CLND has a complication rate of up to 37%.[11, 32, 34] Rates of infection, haematoma, seroma and nerve injury are all significantly greater following CLND. Furthermore, lymphoedema affects 10-30% of patients and significantly diminishes quality of life.[32, 34, 35]

Appropriate use of SNB may spare patients without nodal disease from the morbidity associated with routine CLND. However, the known prognostic false positivity rate of SNB may over-diagnose metastasis in some patients, leading to additional morbidity from CLND.[13] Furthermore, patients who undergo early CLND following detection of micrometastases have been shown to have a lower lymphoedema rate when compared with CLND for clinically recurrent disease.[36] SNB is therefore a safe, low-risk procedure, which may spare selected patients from the morbidity associated with either routine or delayed CLND.

PSYCHOLOGICAL RISKS AND BENEFITS OF SENTINEL NODE BIOPSY

Ryatt et al. showed short-term psychosocial benefits of SNB, independent of the biopsy result.[37] The majority of patients (91%) believed they gained some benefit from SNB, and peace of mind was cited as the main advantage by 85%.[37] SNB was perceived positively; almost all patients (97%) were glad they had the procedure, and 98% would recommend it to others.[37] Furthermore, recurrent melanoma has been shown to increase tension, fatigue and confusion, and reduce vigour.[38] This suggests SNB +/- CLND as a means of preventing recurrence may improve long-term quality of life and well-being.

Limited evidence suggests psychosocial factors may influence outcomes in a number of cancers. Patients in denial about their breast cancer diagnosis and those who adopted a fighting spirit had improved 5-year survival than those who stoically accepted their diagnosis, or adopted a hopeless outlook.[39] Furthermore, 'Type-C' individuals, characterised by being cooperative, unassertive, patient, and compliant with external pressures, have a poor prognosis in melanoma.[40] The inverse appears to be true; in MSLT-I, patients with more vigour at baseline had longer disease-free and overall survival after adjusting for age, tumour thickness, site and ulceration status.[38]

Psychological factors and individual preferences are highly variable, and it is important to discuss with patients whether they want to know their prognosis precisely. Over-anxious, psychotic or unstable patients may need considerable counselling before comprehending the reasons for performing SNB, and may have a poorer prognosis independent of their SNB result.

DISCUSSION

Clinical judgement is paramount when considering the decision to proceed with SNB. The risks and benefits of SNB, with or without CLND, should be weighed against potential prognostic information, psychological benefits, and a modest improvement in disease-free survival if CLND is performed following a positive SNB. The tumour location and subsequent lymphatic drainage also contributes to the risk-benefit profile. Each patient's comorbidities should be considered, including the operative and anaesthetic risks, plus other potential causes of morbidity and mortality. If another disease process is advanced and more likely to contribute to mortality than melanoma, there is little utility in accurately staging metastatic disease. Discussion of SNB and the associated risks and benefits should be considered standard of care for all patients with >1mm thickness melanoma. Ultimately the physician's role in this setting is to present and explain the available options and allow the patient to make an informed decision.

The economic cost of SNB has been variably reported as this differs between individual centres and health systems. The US Medicare reimbursement rate for SNB has been reported as up to US$19,000 per patient, with 80% of these patients having negative nodes.[41] British studies report additional costs related to SNB as £1420, though there is little data from a New Zealand setting.[15, 42] The demands of routine SNB in a public health system with constrained resources need to be considered. Economic and health-system factors are likely to influence any local or national policy regarding SNB.

There are many areas for future research in this area, including determining accurate predictors of which patients may benefit most from SNB, by identifying patients at highest risk of nodal metastasis or recurrence. The impacts of SNB on quality of life (QoL) remain poorly investigated, and

warrant further attention. Ultrasound surveillance of nodal basins appears a promising alternative to SNB, and may be increasingly utilised in the future.[13] Furthermore, emerging evidence suggests tumour lymphangiogenesis may be a predictor of sentinel node status and an alternative or adjunct to SNB.[43, 44]

CONCLUSION

Despite considerable debate, SNB is a safe and effective means of detecting nodal metastasis in patients with MM. It has been shown to prolong disease-free survival in patients with intermediate and thick melanoma when used in conjunction with CLND, but no mortality benefit has been demonstrated, and concerns have been raised regarding prognostic false positivity. The psychosocial effects of SNB have not been fully elucidated, and its effect on QoL in the short- and long-term remains unknown. SNB is useful as a diagnostic and prognostic tool for selected patients, but has minimal therapeutic benefits. Discussion of SNB should be standard of care for all patients with 1-4mm thickness melanoma. Ultimately, the decision to proceed with SNB should be guided by patient preferences regarding how accurately they want to know their prognosis, whether they are prepared to proceed with CLND, and the constraints of a public health system. This decision should be continually re-evaluated as new evidence emerges regarding SNB and other novel techniques for the management of melanoma.

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