Sentinel Lymph Node Biopsy and Lymphadenectomy in Melanoma

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The lymphatic system is usually the first place that melanoma spreads to. The sentinel lymph node (SLN) is the first lymph node or group of nodes draining a cancer. The location of this node can be identified by injection of a combination of blue dye and radioactive tracer at the primary tumour site. The node is then found intra-operatively with a gamma probe and visualisation of the blue dye staining, and sent for histological examination.

Historically, the use of SLN biopsy was welcomed by the surgical community as a minimally invasive way to accurately identify patients with clinically occult regional lymph node metastases and as a valuable staging tool. Patients with a positive SLN then went on to have a regional lymph node dissection – termed "selective lymphadenectomy". The advantage to this technique was that it spared node-negative patients an unnecessary lymph node dissection and the significant co-morbidities associated. There are also suggestions that it may minimising the development of clinical nodal disease [1]. This technique was thus popularised as an alternative to elective lymph node dissection or nodal observation. Metastasis to regional nodes is thought to be the most important prognostic factor in patients with early-stage melanoma and has been shown to occur in approximately 20% of patients with intermediate-thickness tumours [2,3].

Criticism and the Selective Lymphadenectomy Trial (MSLT-1)

Concerns regarding the routine use of SLN biopsy in melanoma patients were raised from as early as 1999 [4]. The critics argued that a survival advantage should be demonstrated before the routine use of this procedure could be endorsed, in the absence of an effective adjuvant therapy.

Hopeful to obtain an answer to this, the first Multicenter Selective Lymphadenectomy Trial (MSLT-1) was designed to assess for a primary goal of survival difference following wide excision of a melanoma between patients randomised to either wide excision and post-operative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred, or to wide excision and sentinel node biopsy with immediate lymphadenectomy if nodal metastases were detected on biopsy. In 2006, the much anticipated results of the third of five planned interim analyses of the MSLT-1 were published [5]. This confirmed previous reports that SLN status is the most powerful independent predictor of survival but did not provide a definitive answer as to whether or not SLN biopsy provided a survival benefit.

Among 1269 patients with an intermediate-thickness (1.2 to 3.5mm) primary melanoma, the mean estimated five year disease free survival rate for the population was 78.3% in the SLNB group and 73.1% in the observation group. Five year melanoma specific rates were similar in the two groups (87.1% and 86.6% respectively). Five year survival rate was 72.3% among patients with positive SLNs and 90.2% among those with negative SLNs.

The result was surprising as two prior retrospective studies had shown a 22% and 12% advantage for early lymphadenectomy at five years [6,7]. This differnce can be explained by the teram coined as "prognostic false positivity". This is where low volume (micrometastatic) deposits in the sentinel node would lead to incorrect upstaging of a disease biology that may not have lead to regional relapse [8]. Extrapolations of the results of MSLT-1 have suggested that the incidence of prognostic false positivity is approximately 24% in patients with intermediate thickness tumours and 34% for all patients [9].

The role of ultrasound in assessment of the nodal basins

The proposed alternative to sentinel lymph node biopsy is ultrasound assessment of the at risk regional node basins. It has been reported that a third of patients ultimately found to be sentinel node positive can be found this way [10]. Positivity of the sentinel node can be then confirmed with ultrasound guided cytology. With the use of lymphoscintigraphy the ability of ultrasound to identify positive nodes increases to 50% [11].

Some have argued that high resolution ultrasound could identify deposits of melanoma as small as 3-4mm in lymph nodes and that this sufficient. However others have argued that the sensitivity of ultrasound is too limited to use it as the sole surveillance tool for early detection of clinically occult regional nodal disease [1].

In reference to the use of ultrasound, another criticism of the MSLT-1 trial was the method of calculating disease-free survival. This has been successfully challenged [14]. Contrary to what was stated in the initial protocol, almost half of the patients entered into the observation arm of MSLT-1 were investigated by lymphoscintigraphy and regular targeted high resolution ultrasound which detected nodal metastasis in some patients before it became clinically palpable, thus influencing the primary end-point of the trial. In view of this, guidance from the National Cancer Institute was issued stating that this end-point should in future be calculated either by excluding nodal recurrence as an event or by expressing the end-point as distant disease free survival.

Further analysis of the MSLT-1 data

It was anticipated that the fourth interim analysis of the MSLT-1 data would be reported around 2008, and the fifth and final analysis at 10 years' follow-up in 2011; however controversy surrounds this. Only a brief summary of the fourth interim analysis was presented at a conference in 2010 in abstract form [15], which many of its critics were unaware of. In addition, rather than including the seven year follow-up data, the researchers presented 10 year follow-up data on a small, unspecified number of patients.

Current status

Despite the above arguments against the use of sentinel node biopsy in the setting of melanoma and in the absence of any adjuvant therapies, there remains enthusiasm for the technique. In 2012, The American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology sought to provide an evidence-based guideline on the use of lymphatic mapping and sentinel lymph node biopsy in staging patients with newly diagnosed melanoma [12]. They proposed that SLN biopsy should be recommended for patients with intermediate-thickness cutaneous melanomas (breslow thickness 1-4mm) for accurate staging purposes. Due to the fact that there are relatively few studies focusing on thick melanomas (> 4mm breslow thickness), it was stated that sentinel node biopsy may be recommended for staging purposes and to facilitate regional disease control. It was identified that there was insufficient evidence to support the routine use of sentinel node biopsy with thin melanomas (< 1mm breslow thickness), although it could be considered in selected patients with high risk features, including ulceration and mitotic rate greater than or equal to 1/mm2, especially in the subgroup of patients with melanomas 0.75 to 0.99mm.

They followed this with guidance with regards to completion lymph node dissection, stating this should be performed if the sentinel node biopsy was positive, advocating it for regional disease control rather than a proven survival benefit.

Within the UK, NICE guidance published in 2006 [13] stated that as yet no published randomised controlled trial evidence confirmed that the use of sentinel node biopsy benefits patients in terms of disease free survival. They state "sentinel node biopsy should only be undertaken in centres where there is clinical experience of the procedure and normally only within the context of ethics-committee approved clinical trials. However, to maintain their already established expertise, centres may continue to offer sentinel node biopsy between trials". In 2010, The British Association of Dermatologists made recommendations for the management of clinically node negative melanoma patients. They stated SLN biopsy could be considered in stage 1B melanoma and upwards in Specialist Skin Cancer Multidisciplinary teams and that patients should be introduced to the concept of SLN biopsy as a staging procedure with no proven therapeutic value [16].

Conclusion

An honest discussion must be held between the clinician and the patient, stating that at the present time there is no clear survival benefit for the use of sentinel node biopsy. Currently, in the absence of any adjuvant therapies, its use can only really be advocated as a staging tool should the patient desire a more accurate assessment of their future risk of relapse.

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