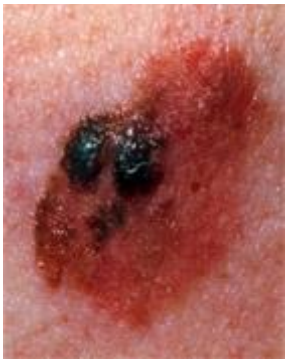
Melanoma Research

Sentinel lymph node biopsy in malignant melanoma

Is unnecessary as clinically important micrometastases can be identified by ultrasound.

When melanoma spreads, it invariably does so by the lymphatic system. The first lymph node to be affected is called the sentinel node, and this node can be identified by injecting dye and a radioactive tracer at the primary tumour site. During sentinel lymph node biopsy, the sentinel node is located by a hand held γ probe and confirmed as the sentinel node using blue dye staining; it is then removed for histology. About 80% of patients have no melanoma in the sentinel node. In the remaining patients, the tumour burden varies from tiny deposits of melanoma in the subcapsular sinus to complete replacement of several sentinel nodes with extracapsular spread. Patients who are sentinel node negative have a better prognosis than those who are sentinel node positive, and the prognosis worsens as the tumour burden increases. But evidence is accumulating that some tiny deposits of melanoma in the sentinel node have no prognostic relevance and will not progress or disseminate further as determined by the patient's immune system and other host factors. Attributing a poorer prognosis to the presence of these tiny deposits in the sentinel node is called prognostic false positivity. This can lead to patients being mistakenly upstaged, given inaccurate prognostic information, undergoing unnecessary completion lymphadenectomy and unnecessary adjuvant therapy, or inappropriately being entered into trials of adjuvant therapy.



So what does the evidence say about the therapeutic advantage of sentinel lymph node biopsy? The multicenter selective lymphadenectomy trial (MSLT-1) randomised 2001 patients with clinically localised primary melanoma either to the control arm where they were treated by delayed lymphadenectomy if they developed palpable regional node metastases or to the biopsy arm, where they were treated by early lymphadenectomy if the sentinel node was positive for metastatic melanoma. No significant difference in melanoma specific survival was seen between the groups at five years.[1] This result was surprising because two retrospective studies had shown a 22% and a 12% survival advantage for early lymphadenectomy at five years.[2] [3] In otherwise matched patients, these two studies compared the survival of sentinel node positive patients having early lymphadenectomy with those having delayed

lymphadenectomy for palpable nodal recurrence. This large difference in survival between a randomised controlled trial and two similar but non-randomised studies can be explained by prognostic false positivity within the sentinel nodes of patients in the non-randomised studies.

Other evidence exists for prognostic false positivity. Firstly, studies have reported that patients with tiny deposits of melanoma within the sentinel node—such as those that can be detected by immunohistochemistry only or deposits in the subcapsular sinus alone that are smaller than 0.1 mm—have a similar prognosis to patients who are sentinel node negative.[4] [5] Secondly, the incidence of sentinel node positivity decreases with increasing age even though the incidence of melanoma and mortality from melanoma increase with age, as do tumour thickness and ulceration, which are both adverse prognostic factors. For instance, in a study of 3075 patients undergoing sentinel lymph node biopsy,6 the incidence of sentinel node positivity was 23.1% in patients under 30 but only 12% in patients aged 61-70 ($P<0.001$). Meanwhile, mortality from melanoma rises from about 3 per 100 000 to 33 per 100 000 population between these ages. In the absence of evidence that melanomas spread more readily in the bloodstream of older patients, prognostic false positivity in younger patients is the most likely explanation, with some micrometastases being eliminated by the more competent immune systems of younger patients.[6] Thirdly, extrapolations of the results of MSLT-1 suggested that the incidence of prognostic false positivity is about 24% in patients with intermediate thickness tumours and 34% for all patients.[7] If early lymphadenectomy has no therapeutic advantage, and in the absence of effective adjuvant therapy, is it justified to continue with sentinel lymph node biopsy for its prognostic value, other than perhaps to identify patients for entry into trials of adjuvant therapy? If the answer is no then do viable alternatives exist? The greatest challenge to sentinel lymph node biopsy comes from ultrasound assessment of the at-risk regional node basins, which can identify up to a third of patients ultimately found to be sentinel node positive.[8] Positivity of the sentinel node can be confirmed by ultrasound guided cytology. The ability of ultrasound to identify positive sentinel nodes rises to 50% (with 100% specificity) if the sentinel node has been located by lymphoscintigraphy.[9] Sentinel lymph node biopsy was well established before it was realised that high resolution ultrasound (which can also identify neovasculature) could identify deposits of melanoma as small as 3-4 mm in lymph nodes.[10] Ultrasound assessment of regional node basins is a neglected technique and is not used routinely to screen at risk nodal basins at the time of diagnosis of the primary tumour. It has never been shown that sentinel node status has any prognostic value in ultrasound negative patients. Another alternative to sentinel lymph node biopsy is the use of algorithms of histological factors relating to the primary tumour, which is almost as accurate at determining prognosis as sentinel node status.[11]

So how does the evidence relate to clinical practice? Other national guidelines vary but in the UK, the National Institute for Health and Clinical Excellence guidelines on skin cancer state, "Sentinel lymph 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 lymph node biopsy between trials."[12] In reality, sentinel lymph node biopsy is increasingly practised in the UK outside the context of clinical trials and on a "postcode" basis. In some regions, the procedure is offered as routine treatment by enthusiastic dermatologists and surgeons, and in other regions, not at all. Few British patients have been entered into randomised controlled trials as envisaged by NICE.

The sentinel lymph node biopsy procedure offers no survival advantage and no systemic adjuvant therapy is available that can benefit sentinel node positive patients. It is therefore difficult to justify the surgical morbidity incurred. Ultrasound screening and surveillance will identify clinically relevant micrometastases before they become palpable. Extrapolating from the results of MSLT-1, patients do not seem to be disadvantaged by this alternative method of management. On the contrary, patients with prognostically false positive sentinel nodes will be protected from unnecessary lymphadenectomy.

References

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