Are the physical and psychological risks of a sentinel lymph node biopsy in melanoma worth the information gained?

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BACKGROUND

Sentinel lymph node biopsy (SLNB) in melanoma is a procedure without proven overall survival benefit.[1] Like any surgery, it also has the potential to physically and emotionally harm patients. Despite this, the procedure provides regional disease control and accurate disease staging.[1] These factors can potentially ease patient suffering, increase disease-free survival and provide powerful prognostic information to patients and clinicians alike, the significance of which cannot be discounted.[2]

A sentinel node is the first lymph node to which afferent lymphatic vessels from a body site drain. Studies have proven that sentinel nodes are common initial sites of metastasis in melanoma.[3] After the administration of local anaesthesia, standard SLNB procedure involves intradermal injection of technetium-99m–labelled radioactive colloid and isosulfan blue dye around the melanoma.[3,4] This mixture then drains through the afferent lymphatic system arriving at the sentinel node 10-30 minutes later.[5] The general location of the sentinel node can then be identified trans-dermally with a gamma-sensor, and an incision made in the skin. The sentinel node is then identified by the blue colour it takes on from the isosulfan blue dye, excised, and subjected to pathological examination for any signs of melanoma metastasis.[5]

The above procedure is generally indicated if a primary melanoma is >1mm thick or has other adverse features (e.g. ulceration).[6] There is still uncertainty about the role of SLNB in thin (<1mm) or thick (>4mm) primary melanomas because such patients are already at such a low or high risk of metastatic disease respectively.[1,3] This essay will therefore focus on the advantages and disadvantages of SLNB in patients with an intermediate thickness (1-4mm) primary lesion, as this is the group in which most sentinel node biopsies are undertaken (due to international guidelines) and the most extensively researched group.

ALTERNATIVES

The alternatives to SLNB are to watchfully wait for clinically detectable nodal disease to occur, or to remove all the lymph nodes in the regional basin without checking the sentinel node first – a 'therapeutic lymph node dissection'. Studies have shown that if sentinel nodes are pathologically negative for metastatic disease, then surrounding nodes are also unlikely to contain micro-metastases.[5,6] The principles behind SLNB are thus: firstly to prove that the sentinel nodes are clear of metastasis, and spare the patient from undergoing therapeutic lymph node dissection; and secondly, to be more proactive in the staging of the melanoma than watchfully waiting for signs of clinical disease.[3] In practice, the only alternative to SLNB is observation, as therapeutic lymph node dissection is a major procedure that is not routinely undertaken without pathological or clinical evidence of nodal disease.[7]

Depending on the results, sentinel node biopsies have the potential to send patients down one of two very different pathways. If a sentinel node is found to contain metastatic deposits, the melanoma is classified as stage III disease that has a five year survival of 39-70% depending on the total number of nodes affected.[8] This is an indication for therapeutic lymph node dissection, which has been shown to significantly reduce regional disease morbidity in addition to increasing disease free survival.[5] The presence of regional node involvement is also an indication for adjuvant therapies that can involve participation in clinical trials with novel agents such as ipilimumab or treatment with high-dose interferon alpha.[8,9] Disease free survival is increased by Interferon alpha therapy, and even more encouragingly, Ipilimumab has been shown to increase the all-cause survival in stage IV melanoma and possibly earlier.[9,10] Hence if a patient failed to undergo SLNB, their access to these disease controlling and potentially life prolonging therapies could be delayed.[10]

Conversely if a node is found to be pathologically negative this is a good prognostic indicator, with one study reporting >80% survival at 5 years.[11] This same study reported a false-negative rate of 3.4%, but the outcomes for these patients were similar to those undergoing nodal observation. Aside from the physical and psychological risks discussed later, undergoing the procedure did not disadvantage them.[10] One can imagine that getting such positive prognostic information would provide significant psychological relief to patients, reducing some of the stress, anxiety and depression, which are highly prevalent in cancer patients.[12] This psychological benefit may then

even translate to physical health benefits, as a result of the reduction in stress and emotional unloading.

The best evidence for SLNB vs. observation comes from the Multicentre Selective Lymphadenectomy Trial (MSLT-I).[1] The MSLT-1 was a large, international, multi-centre randomised controlled trial. At 10 years the study showed no significant reduction in melanoma specific, or all-cause mortality after SLNB, in the entire cohort of intermediate thickness melanoma patients (Hazard Ratio (HR) =0.84; 95% CI, 0.64 to 1.09; P = 0.18).[1] This could be because only approximately 20% of patients (those with a positive sentinel node) could ever gain a benefit from surgery and in a subgroup analysis, a significant melanoma-specific survival was shown in this group (HR 0.67; 95% CI, 0.46 to 0.97; P = 0.04).[1] In addition to this, the MSLT-I showed that compared with delayed dissection after observation; therapeutic lymph node dissection after SLNB is significantly associated with a longer disease free survival.[1] The study showed that in these circumstances the recurrence at the regional basin reduced from 20-50% (Obs.) to 2-10% (SLNB) (HR=0.76; 95% CI, 0.62 to 0.94; P = 0.01).[5] Interpreted at face value, these data would prove an advantage in quality of life through disease free survival for SLNB patients. Disease free-survival is a significant outcome in melanoma, with another study showing that patients felt time spent with recurrence to be worth only 63% of time spent disease-free.[13] The same study also showed that disease free survival significantly benefitted patients from an emotional, physical and quality-of-life perspective.[13]

LIMITATIONS

One criticism of these data is that the longer disease free survival after SLNB may occur because the nodes in which you would expect to find clinical disease recurrence have been removed, causing a lead-time bias.[14] Additionally it may be that because nodes containing melanoma found with SLNB are not classified as diseased, whereas any positive nodes found in clinical observation are, there may be an artifactual increase in disease free survival in SLNB.[15] Critics also believe the subgroup survival analysis showing significant melanoma-specific survival in patients with a positive SLNB to be inherently flawed because it assumes all these nodes will become clinical nodal metastases. There is evidence to show this is not the case, and that many of these tumour cells will be "destroyed by the body's immune system in the harsh environment of the lymphatic system, making these false positive diagnoses".[14] These 'false positives' would bias MSLT-I towards intervention and lead to inaccurate increases in disease stage, unnecessary operations and adjuvant therapy regimes for patients.[15]

Further to this, it has been suggested that of the 20% of patients undergoing biopsy with a positive sentinel node, only 20% will have metastatic disease in non-sentinel nodes. This means that 16% of patients undergoing sentinel node investigation will have unnecessary therapeutic lymphadenectomy.[14] This is a procedure associated with significant morbidity, which has led to a decline in the patient uptake of this operation.[5] Despite these criticisms, the MSLT-I has shown conclusively that SLNB is a more accurate prognostic factor than standard demographic and histopathological factors.[1] This means that if the procedure is undertaken, patients can be given the most accurate information regarding their likely disease outcomes, something that is likely to be worth the risk of significant morbidity to some patients.

Metastatic disease in the sentinel node can also be significant to patients psychosocially, because nodal disease is a bad prognostic indicator in a disease that causes 80% of skin cancer related deaths.[10] Learning this news is devastating for patients and their families, but having a clear prognostic view can allow for better advance care planning.[2] The information gained in SLNB can therefore not only imbue patients a greater disease free survival, but a greater quality of life in their last months and years. This advantage comes from giving patients the knowledge they require to come to terms with their disease, put their affairs in order, and interact with palliative care at an earlier stage. While patients often fear palliative care and believe accepting it means nothing more can be done for them, the opposite is actually true. Studies show palliative care not only improves quality-of-life outcomes but also carries a substantial survival advantage if introduced at an early stage.[16] The prognostic accuracy of SLNB could thus allow patients

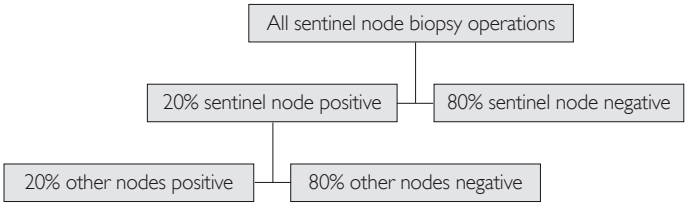

Figure 1: Epidemiologic results of sentinel lymph node biopsy in melanoma

to access this survival benefit, and have less aggressive care at the end of their lives.

To access the benefits of SLNB, patients must undergo surgery, which is not without complications. According to one study, the rate of complications in SLNB is 4.6%, with the most common issues being local haematoma, seroma or wound infection.[3] These complications are usually without long-term consequences.[3] More serious complications include nerve damage and lymphedema, the rate of which is 0.6-1%, however the absolute risk of these varies widely depending on the site of the sentinel node.[3,5] The rate of total complications and lymphedema are significantly higher in therapeutic lymph node dissection, at rates of 23.2% and 11.7% respectively; however patients will have to tolerate these risks if nodal disease is found on SLNB or clinical observation.[3] Further to this, MSLT I showed patients who had a positive SLNB specimen and underwent therapeutic lymphadenectomy had a lower incidence of lymphedema and a shorter hospital stay than those who underwent delayed lymphadenectomy for clinical nodal recurrence.[17] In summary, the rates of physical complication in SLNB are low, and the consequences usually transient. Lymphedema is a dreaded complication, but the risk is low, and outcomes in therapeutic dissection are better after SLNB. Given the context of melanoma the potential benefits of the information gained outweighs these physical risks.

Surgeons strive to reduce physical complications in surgery, however often more distressing to their patients are the psychological complications. There is one retrospective outcome study looking at such complications after SLNB in melanoma. This study reported the most common psychological complication to be concern about the histology result during the postoperative waiting period, which occurred in 85% of participants.[2] Postoperative anxiety, in 9% of patients, was the next most common psychological complication. Despite these concerns, 97% of patients felt glad they had the procedure and 98% would recommend it to other patients.[2] Patients also reported the procedure made them feel reassured and well looked after, with specific advantages being peace of mind, improved family life, and the ability to plan for the future.[2] These advantages were realised independent of the biopsy outcome.[2] Overall, this study proved that patients feel the advantages of SLNB outweigh its psychological complications and feel comforted by the information it provides, even if the biopsy comes back positive.

CONCLUSION

Current evidence would suggest SLNB does not improve melanoma-specific or all-cause survival in intermediate thickness melanoma. However, these are not the only important factors to patients, and there is proof that the procedure may improve disease free survival, which factitious or not, improves patient quality of life. In addition to this, SLNB provides the most accurate prognostic information available, and as discussed there are numerous patient-centred advantages to this, including eligibility for adjuvant therapies. Physically, the risk of complications is low in SLNB, and psychologically the procedure is more likely to relieve patient distress than create it. So, weighing the quality of life improvements gained from prognostic information against the physical and psychological risks of the procedure, it is apparent that the information gained is well worth the risks. Hence, while SLNB is not a procedure without controversy, it is still a worthwhile one and something that should continue to be discussed with patients.

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