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FEATURE

OVERTREATMENT

Sentinel node biopsy for melanoma: is it worth it?

Why do thousands of melanoma patients worldwide have sentinel node biopsy despite a lack of clear evidence that it will improve outcomes? **Ingrid Torjesen** investigates

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In 2006 a hotly anticipated paper on melanoma treatment was published in the *New England Journal of Medicine*. The paper unveiled the five year results of the Multicenter Selective Lymphadenectomy Trial (MSLT-I), a trial designed to determine whether using sentinel lymph node biopsy to detect early nodal spread provided a window of opportunity for wider lymphadenectomy to improve survival.[1]

The trial was seen as a ray of hope because, while other much rarer cancers had potential treatments in development, no interventions had been shown to produce a survival advantage in melanoma.

Melanoma is the fifth most common cancer in the UK and the incidence is rising—one in 60 people can expect to develop melanoma during their lifetime[2]; in the United States it is one in 50.[3] Of the seven most common cancers in the US, melanoma is the only cancer whose incidence is increasing.[3]

These figures are concerning because we still do not have effective adjuvant treatment. Early diagnosis of the primary tumour is still the best opportunity for cure by surgical resection. Five year median survival is 92% for stage I disease, 40-45% for stage III disease (when it has spread to the lymph nodes), and 5-15% with metastasis to distant organs, where median survival without treatment is 6-9 months.[3]

MSLT-I, led by Donald Morton at the John Wayne Cancer Institute in the US, was expected to show that sentinel node biopsy and early lymphadenectomy for patients with positive nodes conferred a survival advantage over observation and removal of the affected nodes once they became palpable.

A total of 2001 patients were randomised between 1994 and 2002, and the MSLT-I third interim analysis was published in the *New England Journal of Medicine* in 2006.[1] It reported the outcomes for 1269 patients with primary melanoma of intermediate thickness (1.2 -3.5 mm). The analysis found no overall survival advantage from sentinel node biopsy at five year follow-up (12.5% (96) of the 769 patients who had sentinel node biopsy died and 13.8% (69) of the 500 who did not).

After a median follow-up of 60 months, tumour cells recurred at any site in 26.8% (134) of the patients in the observation group and 20.7% (159) of those in the biopsy group. Based on this the researchers claimed that the disease-free survival was significantly improved in the biopsy group at five years.

The results proved controversial. It was not surprising, said critics, to see an improved disease-free survival in the biopsy arm as those patients whose disease was most likely to progress had had their regional nodes removed. There was bound to be a greater increase in nodal recurrence in the observation arm because regional nodes were not removed, but merely observed.

So it was hoped that the fourth interim analysis of the MSLT-I data after seven years' follow-up, which was expected around 2008, and the fifth and final analysis at 10 years' follow-up, due around 2011, would settle the question of the effectiveness of sentinel node biopsy once and for all.

The results of these analyses have not yet been published, but use of sentinel node biopsy has not stood still. The technique has been promoted by researchers and pharmaceutical and biotechnology companies, with the result that health services around the world are spending large amounts of money on it, especially in the US, where the procedure is the standard of care. In the UK—despite guidelines from the National Institute for Health and Clinical Excellence in 2006 cautioning otherwise[4]—the procedure has found its way into routine clinical practice, at a cost of millions of pounds to the NHS.

Whole professional careers and businesses have been built on sentinel node biopsy for melanoma. Professional pride and company profits are now at stake. Having a positive sentinel node is now one of the inclusion criteria for recruiting patients into clinical trials of new adjuvant treatments.

Progression theory

Two of MSLT-I's most outspoken critics are Steven Rosenberg, chief of surgery at the National Cancer Institute in Bethesda, Maryland, and J Meirion Thomas, professor of surgical oncology at the Royal Marsden Hospital and Imperial College London.

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Sentinel node biopsy

Sentinel node biopsy was developed at the John Wayne Cancer Institute in the early 1990s.[5-7] It was greeted with great excitement as the first intervention that might improve survival for some patients with melanoma.

Melanoma usually spreads through the lymphatic system, and the sentinel node is the first draining lymph node to which cancer cells are likely to spread from the primary tumour.

In sentinel node biopsy, a radioactive tracer and blue dye is injected at the site of the primary tumour to highlight the sentinel node. The site of the sentinel node is then identified using lymphoscinitigraphy and confirmed perioperatively by using a hand held gamma probe and inspection for blue staining.

Under the microscope, the node is tested for deposits of tumour cells. All patients found to have a positive sentinel node are advised to have immediate regional (completion) lymphadenectomy. These patients may then go on to have radiotherapy or adjuvant therapy, although these treatments are likely to be of only marginal benefit.

In 2008 Rosenberg wrote in *Nature Clinical Practice Oncology* that: "The survival analysis comparing patients with positive sentinel lymph nodes to patients who recurred with nodal disease is difficult to interpret since it assumes no false-positive analyses of the sentinel nodes and that all abnormal cells in the nodes would eventually form a tumour. This is not a valid assumption."[8]

Thomas agrees. He believes that many of the abnormal cells identified in a positive sentinel node biopsy specimen will be destroyed by the body's immune system in the harsh environment of the lymphatic system, making these false positive diagnoses. He wrote in the same journal in 2008: "Progression to palpable nodal disease might not have occurred even if the positive sentinel node had not been removed. Such patients are incorrectly up-staged, are given inaccurate prognostic information, and can undergo unnecessary completion lymphadenectomy and unnecessary adjuvant therapy."[9]

It has already been shown in breast cancer that axillary dissection in women with positive sentinel node biopsy specimens does not reduce local or regional recurrence at six years' follow-up.[10] This suggests that positive nodes do not necessarily progress, at least in breast cancer.

Thomas is cautious about applying those results to melanoma. He says. "Breast cancer is a completely different disease. Lots of drugs work in breast cancer, and none of them work in melanoma."

Formal challenge

In 2007 Thomas took his concerns about the appropriateness of the endpoints used in the third analysis of MSLT-I to the US National Cancer Institute, which funded the trial. Jeff Abrams, chief of the clinical investigations branch of the cancer therapy evaluation programme at the institute, accepted that it remained open to debate whether sentinel node biopsy should be standard care.

In a response seen by the *BMJ*, he said: "We agree that since a survival advantage was not seen in this study it is premature to indicate to patients that sentinel node biopsy will improve their outcome."

Neither the MSLT-I researchers nor the *New England Journal of Medicine* have issued a correction or clarification saying that the conclusions of the third analysis went too far. Nor has there been any public explanation of the delay in publication of the subsequent analyses.

Fourth and fifth analyses

A brief summary of the fourth interim analysis was presented at a conference in 2010 in abstract form.[11] But rather than including the seven year follow-up data, the researchers presented 10 year follow-up data on a small, unspecified number of patients. The obvious questions are why did the researchers not present the seven year follow-up data, and why have they so far not published their long awaited results in a peer reviewed journal?

In subsequent publications the researchers have made no reference to the results of the fourth analysis. Instead, they continue to refer to the five year data from the third analysis. As recently as June last year Morton did not mention the results of the fourth analysis in an update he wrote on the MSLT-I trial.[12]

So little attention has been shone on the fourth analysis that some of MSLT-I's fiercest critics, including Thomas, were unaware of the existence of the conference abstract. And when the *BMJ* contacted lead researcher Morton to ask about the whereabouts of the fourth analysis, he again did not refer to the seven year follow-up data. "For a trial of this type truly long term [10 years] follow-up is essential for the results to be meaningful," he said.

So what about the fifth and final analysis of the 10 year follow-up data? According to the protocol for MSLT-I, the trial has been completed and all the final 10 year follow-up data were collected by June 2012.[13] Morton said that a paper describing and analysing the 10 year data was in preparation and that distant disease-free survival would be included. However, he gave no timescale for when publication of the results could be expected.

Adverse effects of overtreatment

While awaiting these results, large numbers of patients are being exposed to sentinel node and regional lymphadenectomy for unknown benefit despite the known harms of what for many will be unnecessary surgery. It is generally accepted that only 20% of patients who have sentinel node biopsy will have positive sentinel nodes, and only 20% of those will have metastatic disease in the non-sentinel nodes.[14] Therefore 96% of patients who have sentinel node biopsy will have unnecessary surgery.[15] Postoperative complications are common. Nearly 60% of patients experience lymphoedema after regional lymphadenectomy on the lower limbs and 17.5% after this procedures on upper limbs.[16] Other postoperative complications include wound infections, cellulitis, and scarring.

Patients are becoming increasingly concerned about the adverse effects of regional lymphadenectomy. Several studies in the United States have shown that the uptake of lymphadenectomy by sentinel node positive patients is only 50-69%,[17 18] with patient refusal the most common reason for surgery not going ahead.

MSLT-II

Morton is now leading another major trial in melanoma—the Multicenter Selective Lymphadenectomy Trial II (MSLT-II). This trial, also funded by the National Cancer Institute, is

assessing the potential benefits of regional lymphadenectomy for melanoma patients with positive sentinel nodes. The trial is expected to complete in 2022.[19]

Marc Moncrieff, a consultant plastic surgeon at the Norfolk and Norwich University Hospitals Foundation Trust, which is one of the UK centres for MSLT-II, accepts that, although he would recommend immediate lymphadenectomy for patients with positive nodes, some patients are receiving surgery they don't need. "Eighty eight per cent of patients don't have any further disease in their nodal basin. It is extremely morbid at that point to then take away all the rest of the lymph nodes, I'll accept that," he says. "A lot of my patients get lymphoedema, particularly in the groin, when I clear the groin out, so if I can avoid doing that to my patients that would be fantastic."

Use of sentinel node biopsy

Given the lack of clear evidence of benefit, how has sentinel node biopsy become the standard care for melanoma patients in many developed countries? Professional enthusiasm is one possible explanation. Among the authors of the new guideline from the American Society of Clinical Oncology and the Society of Surgical Oncology, is Alastair Cochran, who was involved in developing the technique. The guideline recommends sentinel node biopsy for patients with intermediate thickness melanomas (1-4 mm) and some thicker melanomas for staging purposes, and complete dissection of lymph nodes for all patients with a positive sentinel node biopsy specimen for "good regional disease control."[20]

Another explanation for the rapid uptake of the technique is industry influence. Ten years ago, journals reported that the World Health Organization had issued a statement saying sentinel node biopsy should be considered standard of care.[21-23]

In fact, WHO never took an official position. In 1999, Natale Cascinelli, then president of WHO's melanoma programme, was reported in the journal *Oncology* as making positive comments at a conference in Paris about sentinel node biopsy "as standard of care in the management of stage I melanoma patients."[24] The comments were later reported to have been press released by the Neoprobe Corporation, a maker of intraoperative lymphatic mapping supplies.[25] The claim was also repeated in a free Schering sponsored booklet sent to US dermatologists.[25 26] Schering markets interferon alfa-2b, an adjuvant therapy for advanced melanoma, and sentinel node biopsy is used to identify suitable candidates for the drug.[27]

The *BMJ* contacted Navidea, formally the Neoprobe Corporation, and Merck, which now owns Schering, but both declined to comment.

One country where the procedure is not recommended for routine use is England. NICE guidance published in 2006 states that although sentinel node biopsy has become the standard care in several countries, "there is as yet no published randomised controlled trial evidence that this procedure benefits patients in terms of disease-free survival."[4]

It adds: "There is good evidence that sentinel node biopsy for melanoma may be useful as a staging investigation, and participation in EORTC [European Organisation for Research and Treatment of Cancer] adjuvant trials may become dependent on its availability."

A Department of Health spokesperson said: "We expect patients who need this procedure to be referred in line with NICE guidance." This states that sentinel node biopsy should be performed only in centres with expertise in the context of clinical trials, thereby ensuring that the technique will be properly evaluated.

However, data obtained by the *BMJ* from the Health and Social Care Information Centre show that at least 19 trusts in England carried out sentinel node biopsy procedures on melanoma patients between 2006 and 2011. The figures, which are not comprehensive, suggest that in 2010-11 over 1100 sentinel node biopsies could have been conducted.

Only two trials of sentinel node biopsy in melanoma are ongoing, MSLT-II and MINITUB (minimal sentinel node tumour burden), which is testing whether patients with a minimally affected sentinel node should have regional excision. MSLT-II includes patients from Guy's and St Thomas' NHS Foundation Trust and Norfolk and Norwich University Hospitals NHS Foundation Trust[19]; and only centres registered with EORTC can enter patients into MINITUB. This is likely to account for only a fraction of the 1100 biopsies.

Cost to health systems

Whether or not the procedure is effective, it is certainly expensive. In 2003, it was estimated that sentinel node biopsy cost a patient in the US between $10 096 (£6200; €7600) and $15 223, making the procedure almost 10 times more expensive than the UK standard of care—a wider excision around the site of the melanoma—which costs $1000 to $1740 as an outpatient.[28]

With an estimated 76 250 new cases of melanoma expected in the US in 2012,[29] and assuming 60% of them are intermediate or thick tumours for which patients receive sentinel node biopsy, the total cost of biopsy procedures at $15 000 each would surpass $686m. Added to this must be the cost of subsequent completion lymphadenectomy in some patients.

In 2005, a group of plastic surgeons from the Royal Free Hospital in London estimated the cost of conducting sentinel node biopsy in the UK at £1550 per patient plus £2915 for each patient who had complete lymphadenectomy.[30] Based on 6000 new melanomas occurring in the UK every year, of which 3000 were of intermediate thickness and 600 were thick,[2] they calculated that if all 3600 patients with intermediate and thick melanomas were offered sentinel node biopsy it would cost the NHS £7.6m.

They added that there was also "a significant cost in setting up a sentinel node service, including nuclear medicine staffing and probe costs."

According to figures from Cancer Research UK, the number of cases of malignant melanoma has at least doubled since then; there were 12 818 new diagnoses recorded in the UK in 2010.[31]

Sentinel node biopsy may provide more accurate staging, but with no effective treatments to offer patients and the risk of adverse effects from surgery, especially lymphoedema, it is hard to justify using such an expensive and invasive procedure simply as a staging tool.

The full and final results of MSLT-I would clarify whether sentinel node biopsy is beneficial, and what, if any, its role in melanoma should be. It is time for the funders of MSLT-1 and those responsible for overseeing research to demand prompt publication of the full and final results of MSLT-I.

Competing interests: The author has completed the ICMJE unified disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in

Trusts that carried out sentinel node biopsy or lymph node excision between 2006 and 2011 in patients with a diagnosis of melanoma

*Sentinel node biopsy**

- Barts and the London NHS Trust
- Frimley Park Hospital NHS Foundation Trust
- Guy's and St Thomas' NHS Foundation Trust
- Hull and East Yorkshire Hospitals NHS Trust
- Leeds Teaching Hospitals NHS Trust
- Norfolk and Norwich University Hospitals NHS Foundation Trust
- Oxford Radcliffe Hospitals NHS Trust
- Poole Hospital NHS Foundation Trust
- Portsmouth Hospitals NHS Foundation Trust
- Royal Devon and Exeter NHS Foundation Trust
- Royal Free Hampstead NHS Trust
- Salisbury NHS Foundation Trust
- Southampton University Hospitals NHS Trust
- St George's Healthcare NHS Trust
- St Helens and Knowsley Hospitals NHS Trust
- The Christie NHS Foundation Trust
- The Dudley Group of Hospitals NHS Foundation Trust
- The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust

Lymph node biopsy or wider lymph excision†

- Cambridge University Hospitals NHS Foundation Trust
- Countess of Chester Hospital NHS Foundation Trust
- Lancashire Teaching Hospitals NHS Foundation Trust
- Medway NHS Foundation Trust
- Mid Essex Hospital Services NHS Trust
- Royal Cornwall Hospitals NHS Trust
- Royal Surrey County Hospital NHS Foundation Trust
- University College London Hospitals NHS Foundation Trust
- University Hospitals Birmingham NHS Foundation Trust

Wider lymph node excision‡

- Bradford Teaching Hospitals NHS Foundation Trust
- Buckinghamshire Healthcare NHS Trust
- Chesterfield Royal Hospital NHS Foundation Trust
- County Durham and Darlington NHS Foundation Trust
- East and North Hertfordshire NHS Trust
- Gloucestershire Hospitals NHS Foundation Trust
- Imperial College Healthcare NHS Trust
- North Bristol NHS Trust
- Sheffield Teaching Hospitals NHS Foundation Trust
- South Tees Hospitals NHS Foundation Trust
- The Newcastle Upon Tyne Hospitals NHS Foundation Trust
- The Royal Marsden NHS Foundation Trust
- University Hospital Birmingham NHS Foundation Trust
- University Hospital of North Staffordshire NHS Trust
- University Hospitals of Leicester NHS Trust

Hospital episode statistics (HES) from the Health and Social Care Information Centre.
* Trusts carried out sentinel node biopsy.
†Trusts carried out biopsy or excision of lymph node, which may be a sentinel node biopsy.
†Trusts carried out a block excision of lymph nodes—ie, a lymphadenectomy.

the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

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