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| **Institution: Queen Mary University of London (QMUL)** |
| **Unit of Assessment: A1 (Clinical Medicine)** |
| **Title of case study: Sentinel lymph node biopsy in breast cancer** |

## 1. Summary of the impact

In breast cancer surgery the major physical side effects occur as a result of surgery to the axilla. Research at Queen Mary showed significantly reduced rates of axillary clearance surgery and physical side effects, and significantly improved quality of life, in breast cancer patients managed with sentinel lymph node biopsy (SLNB) compared with patients undergoing axillary lymph node dissection. As a result, SLNB was recommended in NICE guidance and is now routine in most breast centres. Previously, only 10% of UK breast surgeons used the procedure, but by 2010 this had increased to 64%. We estimate around 3,500 patients are spared lympheodema in the UK every year as a result of this research.

## 2. Underpinning research

Because breast tumours most commonly spread first via the lymph nodes in the axilla, removing and checking these for cancer cells is essential for staging the tumour and making consequent adjuvant therapeutic decisions. Removal of tumour-positive lymph nodes may also have a therapeutic benefit, but this is not fully established. Axillary lymph node dissection (ALND) is associated with significant morbidity, including loss of arm mobility, loss of feeling and lymphoedema (arm swelling), which can be prolonged, distressing and disabling. Lymphoedema may lead to ulceration or infection if severe.

**Figure 1: Lymphoedema of the right arm following axillary lymph node dissection**

The principle of SLNB is that if the first two or three (sentinel) lymph nodes to which the tumour drains are located and have no tumour cells present, further surgery to the axilla can be dispensed with, potentially minimizing or avoiding these serious side effects. Identification is done by injecting a dye, radioisotope or both in the affected breast and identifying the nodes to which the marker substance drains. The aim of this research was to characterise and quantify physical and psychological morbidity after SLNB in the treatment of early breast cancer in a randomized controlled trial.

Between November 1999 and February 2003, 298 patients with early breast cancer (tumours measuring 3cm or less on ultrasound examination) who were clinically node-negative were recruited from three hospitals in England, and randomly allocated to undergo ALND (control group)

or SLNB followed by ALND if subsequently found to be lymph node positive (study group). A detailed assessment of physical and psychological morbidity was performed on trial participants during a one-year period postoperatively.

The main findings from this trial were:

1. Significant reduction in postoperative arm swelling, rate of seroma formation, numbness, and loss of sensitivity to light touch and pinprick in the intervention group compared with controls.
2. Quality of life and psychological morbidity scores were significantly better in the intervention group in the immediate postoperative period, with fewer long-term differences.
3. The odds of arm lymphoedema were reduced by 75% at six months in the study group as a whole, and by 82% in those who were node negative. **At six months, 21% of participants receiving axillary clearance had lymphoedema compared with 7% in those receiving sentinel lymph node biopsy.**
4. Incidence of seroma formation was reduced from 21% in the control group to 14% in the intervention group. In the node-negative cases, the difference was greater, at 24% vs 11%. (The effect is greatest in the node-negative cases, as these are the cases who do not go on to further axillary surgery.)

This trial, published in the *Journal of Clinical Oncology* in 2005, concluded that SLNB in patients undergoing surgery for breast cancer results in a statistically and clinically significant reduction in physical and psychological morbidity [1]. Downstream research within the same study identified factors predictive of further tumour cells in the axilla in sentinel node positive patients [2]; and showed that in those undergoing axillary clearance surgery, those at most risk of arm lymphoedema were the node-negative patients [3]. This is of particular importance as it is the node-negative patients who will have axillary clearance avoided as a result of sentinel node biopsy.

Stephen Duffy, Professor of Cancer Screening at QMUL, was a co-applicant on the trial grant, designed the trial, carried out the randomisation and supervised the statistical analysis [1]. A research associate at QMUL, JP Myles, carried out the primary statistical analysis under Duffy's supervision [1]. A research associate at QMUL, OF Agbaje, and honorary research associate at QMUL, P Chou, carried out secondary analyses under Duffy's supervision [2, 3].

## 3. References to the research


1. Purushotham AD, Upponi S, Klevesath MB, Bobrow L, Millar K, **Myles JP, Duffy SW**. Morbidity after sentinel lymph node biopsy in primary breast cancer: Results from a randomized controlled trial. *Journal of Clinical Oncology* 2005; 23: 4312-21.
2. Pal A, Provenzano E, **Duffy SW**, Pinder SE, Purushotham AD. A model for predicting non-sentinel lymph node metastatic disease when the sentinel lymph node is positive. *British Journal of Surgery* 2008; 95: 302-9.
3. Purushotham AD, Bennet Britton TM, Klevesath MB, **Chou P, Agbaje O, Duffy SW**. Lymph node status & breast cancer-related lymphoedema. *Annals of Surgery* 2007; 246: 42-5.


The trial was funded by the Eastern Region R&D Directorate and supported by the National Cancer Research Network. Grant holders were Purushotham *et al*, the title was 'Sentinel lymphadenectomy in breast cancer: a randomised trial', the sponsor was Addenbrookes Hospital, Cambridge. The grant ran from 1999 to 2003 and totalled £175,000.

## 4. Details of the impact

The study findings led directly to a change in guidelines, a change in clinical practice and quantifiable improvements in patient morbidity.

**4a: Change to national and international recommendations**
Four examples of clinical guidelines around the world:

- **UK:** The SLNB technique is now recommended by the UK National Institute for Health and Clinical Excellence (NICE) [4]: *"Sentinel node biopsy ((SLNB) or axillary four node sampling) should be performed to stage the axilla for patients with early invasive breast cancer and no evidence of lymph node involvement on ultrasound or a negative ultrasound-guided needle biopsy. SLNB is the preferred technique."*
- **UK:** Surgical guidelines in the UK were updated to include the recommendation for sentinel node biopsy following the study publication in 2005 [5]. *"To minimise morbidity from axillary surgery to obtain staging information Sentinel node biopsy using the combined blue dye/radioisotope technique is a recommended axillary staging procedure for the majority of patients with early invasive breast cancer"*.
- **Europe:** The *European Society for Medical Oncology* recommend sentinel node biopsy as the standard of care in early breast cancer [6].
- **USA:** SLNB is endorsed as an alternative to ALND for the diagnosis of axillary metastases in patients with clinically node-negative early breast cancer in guidelines from the American Society of Clinical Oncology (ASCO), which cites this trial as evidence for the reduction in surgery-related morbidity [7], and by the US National Comprehensive Cancer Network Guidelines [8].
- **Australia:** The Australian guidelines on management of breast cancer recommend SLNB and explicitly cite this trial as evidence of the reduction in side effects [9].

**4b: Change to standard clinical practice**

SLNB has become routine in most breast centres. A survey published in 2010 reported that 69% of breast surgeons in the UK routinely use the practice now [10], compared with 10% before this trial was published [11]. Increasing trends in the use of SLNB have also been reported from Canada and Ireland [12,13].

**4c: Development of new surgical training**

Following the trial, successful training programmes have been established, aimed primarily at surgical technique, but also incorporating multidisciplinary training for nuclear medicine physicians, theatre nurses and pathologists [14].

**4d: Reduction in morbidity**

Around 38,000 women are diagnosed with invasive breast cancer in England per year. The Second All Breast Cancer Report reported 32% of patients receiving sentinel node biopsy in 2007 [15]. However, more than half the patients had missing data on axillary surgery in this audit. The audit of screen-detected cancers for 2010/11 reported that 76% of screen-detected cancers had sentinel node biopsy [16]. A local audit in Staffordshire reported 84% of patients with screen-detected cancers receiving sentinel node biopsy [17]. Taking the average of these three figures (probably conservative because the proportion is increasing with time), an estimated 64% of eligible UK patients currently have this procedure. This estimate is consistent with a survey of UK surgeons in 2008, which found that 69% routinely performed the operation [10].

The low incidence of lymphoedema observed in cohorts of patients treated with SLNB [18] compared with observations in the pre-SLNB era (see for example *British Journal of Surgery* 2000; 87: 1128) is consistent with the numbers reported in our study. This translates to 3,405 patients per year in UK (0.64 x (0.21-0.07) x 38,000) spared lymphoedema due to this procedure.

**4e Extension of the technique to other cancers**

The first cancer for which SLNB was introduced was melanoma. Following the success of this approach in breast cancer, researchers have begun to explore the use of the technique in other cancers, most notably of the head and neck [19].

## 5. Sources to corroborate the impact

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6. Association for cancer surgery (BASO): Surgical Guidelines for the Management of Breast Cancer. *European Journal of Surgical Oncology* 2009, S1-S22. doi:10.1016/j.ejso.2009.01.008 http://www.associationofbreastsurgery.org.uk/media/4565/surgical_guidelines_for_the_management_of_breast_cancer.pdf
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17. Apostolopoulos A, Basit A, Kirby RM *et al*. Conservation of the axilla: an audit of sentinel lymph node biopsy after a new start. *Clinical Breast Cancer* 2011; 11: 264-7.
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