Institution: Cardiff University

Unit of Assessment:1

Title of case study: Cardiff research yields evidence for benefits of sentinel node biopsy and spearheads training in the technique as a standard of care in breast cancer surgery

1. Summary of the impact

Research at Cardiff University is underpinning the abandonment of the 100-year-old surgical practice of removing all axillary lymph nodes in cases of breast cancer. Such surgery frequently caused arm lymphoedema, loss of arm mobility and lymphatic system damage. Cardiff led the seminal ALMANAC trial which showed that full node clearance was unnecessary if a biopsy of the first draining 'sentinel' node was cancer-free. Cardiff then spearheaded the impact on practice through a training and awareness programme for surgeons, primarily in the UK, but also in China, India, Brazil and Turkey. By 2010 these efforts had established the Sentinel Lymph Node Biopsy (SLNB) procedure as standard in the UK, while the study was also cited in USA guidelines. The main beneficiaries of the impact are the 50-75% of breast cancer patients who now enjoy lower levels of pain, shoulder disability and arm lymphoedema. Healthcare providers also benefit financially from a reduced need for extensive surgery.

2. Underpinning research

Demonstrating the benefits of sentinel node biopsy

Each year, breast cancer affects more than 1.38 million women worldwide, more than 37,000 of them in the UK. For more than a century, surgeons advocated radical surgery to remove all the axillary lymph nodes that drained the cancer-affected breast, as a way to diagnose and treat lymph node involvement. Until recently 90% of patients worldwide underwent this extensive surgery risking arm lymphoedema and damage to the lymphatic system. The sentinel lymph node biopsy (SLNB) procedure, which removes only one or two of the closest nodes to the cancer, was first explored in the USA in the 1990s. Some breast surgeons used it to help identify 'sentinel' lymph nodes in the axilla, these being the first lymph nodes to which breast cancer cells may have spread from a primary site. Critically, the procedure had not undergone any formal evaluation or been compared to the previous 'gold standard' of axillary node clearance. By the late 1990's practice in some US academic comprehensive cancer centres was changing in favour of the technique, although the question of whether SLNB accurately defined node status remained unanswered [source:JNCI J Natl Cancer Inst (2008)100(7):449-450]. Accordingly the value and potential impact of the SLNB technique remained speculative.

In 1999 Robert Mansel (Professor of Surgery, Cardiff University; 1992-present) initiated and led the UK randomised trial of the SLNB technique. Preparatory work, funded by a peer-assessed MRC grant, involved initial training of the new technique to surgeons who had not practised it in order to standardise the surgical technique. This preparation also incorporated research studies to assess the 'learning curve' for surgeons becoming competent in the technique. [3.1,3.2,3.3]

On the basis of this work, Cardiff launched the MRC multicentre UK ALMANAC (Axillary Lymph node Mapping Against Normal Axillary Clearance) randomised clinical trial to compare sentinel node biopsy with standard axillary surgery. The trial (supported by grants from R&D Wales and Amersham Health), was, at the time of its report, the largest randomised trial of the preferred dual technique of using radioactive isotope and blue dye in combination as markers. The trial comprised 1031 patients from 14 UK surgical centres, with Mansel as the Principal Investigator, Newcombe as the statistician (Cardiff University 1992-present), and Cardiff as the co-ordination centre. Patient quality of life assessments for the trial were provided by Sussex University (Prof Lesley Fallowfield).

Initially, Cardiff research evaluated the factors that could determine the likelihood of additional positive nodes in the axilla in the presence of sentinel node metastasis. Overall, in patients with a positive SLN, the difference in the number of positive and negative sentinel lymph nodes removed and size of the metastasis in the sentinel lymph node, all predicted the frequency of additional positive nodes[3.1] . Research also established: the frequency of internal mammary drainage in patients undergoing sentinel lymph node lymphoscintigraphy[3.2]; the value of preoperative lymphoscintiscans in sentinel node visualisation[3.3]; and the relevance of multiple sentinel nodes[3.4].
The final analysis of the ALMANAC study[3.5] showed that SLNB was a safe and effective alternative

to routine axillary dissection for nodal staging in early-stage breast cancer. Compared with standard axillary treatment, SLNB was associated with reduced arm morbidity and better quality of life with no increase in anxiety. The collective research also established that the majority of women with breast cancer could benefit from this intervention, particularly those with small cancers detected by the NHS Breast Screening Programme, 75% of whom have a negative axilla.

Technique refinement – validating intra-operative assessment

Continued clinical research was undertaken by Goyal (Lecturer, Cardiff University; 2004-8), Douglas-Jones (Senior Lecturer, Cardiff University; 1995-2011) and Mansel – establishing the first clinical trial of an intra-operative method of assessing cancer invasion of the sentinel node, using PCR quantification of 2 breast markers[3.6]. The research demonstrated that the presence of cancer in the sentinel node could be ascertained at the time of surgery, enabling surgeons to immediately treat the axilla in patients with a sentinel node invaded by cancer, rather than having patients return for a second surgical procedure. The research was published in Breast Cancer Research and Treatment and was the first publication on this methodology in the UK and the first to suggest the practicality of intra-operative assessment[3.6]. The quality of the research and its potential benefit to patient care was recognised by a Medical Futures Innovation Award from the Dept of Health in 2007.

3. References to the research

3.1 **Goyal A, Douglas-Jones A, Newcombe R G, Mansel R E**, on behalf of the ALMANAC Trialists Group. Predictors of non-sentinel lymph node metastasis in breast cancer patients. *European Journal of Cancer* 2004, 40: 1731-1737 DOI: 10.1016/j.ejca.2004.04.006. ISSN: 0959-8049.

3.2 **Mansel RE, Goyal A, Newcombe RG**; ALMANAC Trialists Group. Internal mammary node drainage and its role in sentinel lymph node biopsy: the initial ALMANAC experience. *Clin Breast Cancer*. 2004 Oct;5(4):279-84; discussion 285-6. DOI 10.3816/CBC.2004.n.031(available on request from HEI)

3.3 **Goyal A, Newcombe RG, Mansel RE** on behalf of the ALMANAC Trialists Group. Role of routine preoperative lymphoscintigraphy in sentinel node biopsy for breast cancer. *European Journal of Cancer* 2005 41: 283-243. DOI:10.1016/j.ejca.2004.05.008

3.4 **Goyal A, Newcombe RG, Mansel RE**; Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) Trialists Group. Clinical relevance of multiple sentinel nodes in patients with breast cancer. *Br J Surg*. 2005 Apr;92(4):438-42. DOI: 10.1002/bjs.4906

3.5 **Mansel RE**, Fallowfield L, Kissin M et al. Randomised multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer. The ALMANAC trial. *JNCI* 2006 , 98: 599-609 DOI: 10.1093/jnci/djj158

3.6 **Mansel RE, Goyal A, Douglas-Jones A** et al. Detection of breast cancer metastasis in sentinel lymph nodes using intra-operative real time GeneSearch BLN assay in the operating room: results of the Cardiff study. *Breast Cancer Res Treat*. 2009 Jun;115(3):595-600 DOI:10.1007/s10549-008-0155-6

3.7 **Mansel RE**, MacNeill F, Horgan K, Goyal A, Britten A, **Townson J,** Clarke D, **Newcombe RG** and Keshtgar M.Results of a national training programme in sentinel lymph node biopsy for breast cancer. *British Jnl Surgery*, 2013,100:654-661 DOI: 10.1002/bjs.9058

The Validation phase of the ALMANAC study was supported by a grant from the UK Medical Research Council. MRC grant No G9720984 Grant ID 53983. The ALMANAC multicentre trial of sentinel node biopsy (Jan 1999 to Nov 2000), total value £570K, PI Mansel

4. Details of the impact

Cardiff's demonstration of the effectiveness of SLNB has helped establish the technique as the global standard of care. As a result, beneficiaries include:

- Breast cancer patients enjoying improved quality of life
- Healthcare providers making time and cost savings on surgery
- Surgical practitioners, who have been quickly and safely trained in a new technique

Impact on surgical training

As a result of the conclusive results of the ALMANAC trial, Mansel, designed, secured funding for, and led a collaboration between Cardiff University and the Royal College of Surgeons[5.6] to set up and participate in a national training programme called "NEW START" (funded by the Department of Health). NEW START was directly informed by the ALMANAC findings, both on the

effectiveness of the dual technique and the surgeons' 'learning curve'. The programme, designed to introduce the benefits of the research rapidly to the UK population, was introduced in 2004 and closed to new enrolments in December 2008. On completion, more than 200 breast surgeons, operating on over 6,500 patients in 103 centres, had been trained. The programme held centrally audited data on the surgeons, and issued certificates of completion of training when they met a pre-defined standard of performance. The programme results published in 2013 showed that surgeons, who had never done the procedure before, were subsequently skilled to carry out this technique, with a less than 10% risk of missing cancer in lymph nodes [3.7].
The programme involved close collaboration with the Administration of Radioactive Substances Advisory Committee (ARSAC) which licences the use of all medical isotopes[5.7]. This helped to exercise control over unregulated and untrained enthusiasts who wished to perform the procedure without suitable training. NEW START also ran training workshops internationally (China/India/Brazil/Turkey), funded by the International Union Against Cancer (UICC), to spread the benefits in the international population.

Impact on clinical guidelines
Following the conclusive results of the ALMANAC and other trials, sentinel node biopsy has become the standard of care for breast cancer surgery patients. It was adopted as the preferred method of axillary staging and the recommended procedure for suitable patients in national clinical guidelines in the USA (2010)[5.5] and the UK (2009)[5.3], and in the surgical guidelines of the Association of Breast Surgeons (2009)[5.4]. The ALMANAC trial is cited in all three guidelines as having demonstrated the benefits to patients. Further NICE guidance, drafted and undergoing consultation as of July 2013 and published the following month, recommended the intra-operative node assessment trialled by Mansel and cites NEW START and the ALMANAC findings on the effectiveness of SLNB.

Impact on patients
Annual audits of breast screening in the UK show that no patients were reported to have SLNB in 1997/8 (the year that the MRC ALMANAC trial started). By 2009/10 the audit showed that 67% of 13,226 patients with invasive cancer were undergoing SLNB. The latest figures, for 2011/12, show that of the 14,449 patients with invasive cancer undergoing axillary surgery, 84% had sentinel node biopsy[5.1].
The ALMANAC trial and other studies demonstrated the significant improvement in quality of life that sentinel node biopsy has for the 50-75% of women with early breast cancer where no lymph node invasion has occurred. The adoption of this method as the preferred axillary staging technique for breast surgeons means that most patients now avoid the major morbidity associated with having all the lymph nodes removed. These women experience lower levels of pain, decreased arm and shoulder stiffness, and a decreased risk of lymphoedema compared to those who received axillary node clearance. A recent decision model analysis of SLNB's effectiveness against axillary node dissection concluded that SLNB was more effective with an average of 8 quality of life years gained per 1000 patients over a 20 year period.[5.8]
The research to refine methods for testing the molecular pathology of the removed sentinel node within the operating theatre[3.6] using PCR quantification of two breast markers, also benefits patients. The speed of the new test means that full axillary node clearance is possible, when necessary, immediately following the biopsy. Patients avoid undergoing a second surgical procedure and hospitalisation. They also avoid the anxiety patients may experience of awaiting biopsy results (and possible additional surgery).
The impact of sentinel node biopsy was summarised in a 2011 Clinical Breast Cancer paper by staff at the University Hospital of North Staffordshire, who had undergone New Start training. :
They found the technique allowed conservation in 80% of the patients with negative sentinel lymph nodes and stated: "Overall, sentinel node biopsy has revolutionized the management of the axilla for the majority of patients". [5.2]

Impact on professional practice
The section of the 2009/10 breast screening audit dealing with SLNB (section 7.2) confirms the vital influence of the NEW START programme in driving the adoption of the new technique among surgeons. It states: "The overall use of SLNB has increased by 9% since 2008/09 as the roll out of

the NEW START Programme has continued." The same section of the 2011/12 audit restates that the recommended technique should be the combined isotope/ blue dye technique, which is that advocated by ALMANAC and specified in the NEW START programme.
In its 2009 guidelines, the Association of Breast Surgeons recommends that practitioners take part in "NEW START or equivalent training programmes."[5.4] The NICE Guidelines state that SLNB should only be performed by teams "validated in the use of the technique, as identified in the NEW START training programme."[5.3]
The close collaboration with ARSAC allowed the safe introduction of the isotope/dye technique in nearly all hospitals across the UK over the 2007-2010 period as shown by the national breast screening data[5.1] The figures for 2011-12 show the dual isotope/dye technique was used in 79% of SLNB procedures.
The NEW START educational workshops held abroad speeded up the introduction of sentinel node biopsy in many parts of the world where no facilities existed for training. As a result, a cohort of highly trained surgeons can now train the next generation around the globe in the technique For example, In 2009, Mansel conducted a workshop for 50 consulting surgeons and surgical trainees in the principles of SLNB at Kolkata, India. In 2011, he signed an agreement to establish a standardised approach to SLNB at Chongqing, the most advanced cancer hospital in western China.

Impact on healthcare costs
The recent decision model analysis of SLNB compared with axillary node dissection[5.8] noted that SLNB was less costly over 20 years with $883 saved per patient. Cardiff's role in the development of intra-operative sentinel node pathology testing has also helped reduce healthcare costs. A recent paper from Spain shows that the testing makes a per patient saving of 439 Euros compared to conventional post-operative histology (Guillen-Paredes MP et al Cir esp 2011;89:456-62 available as .pdf from HEI). The 2013 NICE guidelines conclude the techniques would represent "a cost-effective use of NHS resources".

5. Sources to corroborate the impact

5.1 Annual audits of screen detected breast cancers are at http://www.cancerscreening.nhs.uk/breastscreen/publications. The 09/10 audit confirms the influence of NEW START on surgical training, the 11/12 audit gives latest available figures for the increase in patients having sentinel node biopsy.

5.2 Apostolopoulos A., Basit A., Kirby RM., Adjogatse JK., Lambert G, Chan KY, Hancock A, Hackney L, Wall M. Conservation of the Axilla: an audit of sentinel lymph node biopsy after a NEW START. *Clinical Breast Cancer* 2011; 11:264-7. DOI: 10.1016/j.clbc.2011.04.007 Corroborates the revolutionary effect of sentinel node biopsy on patient management.

5.3 The 2009 guidelines for breast cancer published by NICE recommend sentinel node biopsy as the preferred method of axillary staging, and also endorse the NEW START training programme (http://www.nice.org.uk/nicemedia/pdf/CG80NICEGuideline.pdf)

5.4 SLNB is included in the surgical guidelines produced by the Association of Breast Surgeons at BASO in 2009, which also endorses NEW START DOI:10.1016/j.ejso.2009.01.008 (http://www.cancerscreening.nhs.uk/breastscreen/publications/ABS-BASO-guidelines.pdf)

5.5 US NCCN Guidelines. The benefits to patients shown by the ALAMANAC study are quoted in the 2010 edition. (username morgande@cardiff.ac.uk password REF2014) http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

5.6 Testimony from Royal College of Surgeons breast tutor corroborate the collaboration between Cardiff University and the Royal College of Surgeons in delivering NEW START the resulting improvement in professional practice

5.7 Testimony from Chair, Administration of Radioactive Substances Advisory Committee (ARSAC) confirms the research was central to setting up NEW START, leading to safe implementation of the isotope/dye procedure

5.8 Verry et al. Effectiveness and cost-effectiveness of sentinel lymph node biopsy compared with axillary node dissection in patients with early-stage breast cancer: a decision model analysis. *Br J Cancer*. 2012 March 13: 106(6): 1045-1052. DOI:10.1038/bjc.2012.62 Corroborates the quality of life and healthcare costs benefits of SLNB.

(All web pages, testimonies and documents saved as pdfs and available on request from the HEI.)