

History, Present Status and Future of Sentinel Node Biopsy in Breast Cancer

The Mary Béves Lecture

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The word 'Sentinel' is defined in The Oxford English Dictionary as 'a guard, one who keeps watch or a sentry'. When translated to the concept of a tumour and its lymph node drainage, the sentinel node could be interpreted to mean the lymph node that guards or keeps watch over a tumour. The sentinel lymph node can thus be defined as the first lymph node that drains a primary tumour within the regional lymphatic basin of that tumour. We know that tumour progression in breast cancer often occurs in an orderly, progressive fashion (1, 2). So in theory, if the sentinel node is tumour free then the rest of the nodes in the lymphatic basin should also be uninvolved by the tumour.

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HISTORY

The concept of the sentinel node being predictive of the status of the regional lymphatic basin is commonly attributed to Ramon Cabanas, a South American surgeon, following his pioneering work on the lymphatic drainage in carcinoma of the penis (3). However, the first reported clinical study on sentinel node biopsy was published nearly 20 years prior to Cabanas's publication. Ernest Gould and his colleagues from the Washington Hospital Centre published their work on the sentinel node in tumours of the parotid (4). In 1951, quite by chance, while performing a total parotidectomy for a recurrent, benign, mixed tumour, they noticed a normal-looking node at the junction of the anterior and posterior facial vein. This node was sent for frozen section analysis and was found to be positive for tumour. Based on this histology, the patient went on to have a radical neck dissection. They called this node the 'sentinel node' and as a consequence of this observation, in the next 6 years, 28 patients who had parotid tumours had a sentinel node removed prior to the parotid surgery. Twenty of these patients had benign parotid tumours and hence negative sentinel nodes on frozen section. Of the 8 patients who had malignant parotid tumours, 3 patients had positive sentinel node biopsies and went on to have radical neck dissection, while 5 patients who had negative sentinel node biopsies had no further surgery to the

lymphatic basin. All patients with malignant tumours were followed-up for between 2 and 6 years and none of the patients who had the regional lymphatic basin untreated developed any nodal recurrence. Although this follow-up period could be criticized for not being long enough, the concept of the sentinel node had now been established and the concept of treating the regional lymphatic basin on the basis of the sentinel node status had been introduced.

In 1976 Ramon Cabanas presented his work on sentinel node biopsy in carcinoma of the penis at the annual meeting of the Society of Surgical Oncology, New York. In a study including 100 patients, Cabanas used lymphangiograms to locate the sentinel lymph node. Of these 100 patients, 80 had carcinoma, 10 had benign lesions of the penis and 10 patients were normal controls. Of the 80 patients with carcinoma of the penis who had lymphangiograms, 46 had sentinel node biopsies. Fifteen of the 46 patients who had positive sentinel node biopsies went on to have inguinal block dissection based on the results of the sentinel node biopsy. In 12 of the 15 patients in whom the sentinel node was positive, this was the only node in the entire lymphatic basin to be involved. Cabanas drew the following conclusions from his work: 1) that the lymphangiograms he performed had identified the anatomical site of the sentinel node in carcinoma of the penis, 2) the sentinel lymph node was the first site of metastases and may be the only lymph node involved, 3) in carcinoma of

the penis, initial bilateral sentinel lymph node biopsy should be followed by inguinal block dissection if the sentinel node is positive for metastases. If the sentinel node is negative for metastases, then no further surgical therapy to the regional nodes is indicated (3).

Around the same time as Cabanas's work, Donald Morton and his co-workers were then applying the sentinel node concept in the management of malignant melanoma. Much of the work on sentinel lymph node biopsy in the management of malignant melanoma was done in the 1980s and early 90s after Morton *et al.* had published their results on sentinel node biopsy in malignant melanomas. This work was initially conducted on cats, followed by a large series on patients with malignant melanoma where Morton *et al.* successfully identified the sentinel node in 194 of 237 patients using patent blue V or isosulphan blue dyes, injected peroperatively at the site of the melanoma. While Gould *et al.* stumbled across the sentinel node quite by chance in tumours of the parotid and Cabanas described the sentinel node in carcinoma of the penis as an anatomically fixed node in the groin following experimental work on the lymphatic drainage of the penis, Morton *et al.* were the first to describe the intraoperative mapping and intraoperative localization of the sentinel node using a blue dye. They were also the first to point out the fact that there was a learning curve involved in this new operative technique. In their publication in 1992 they give a detailed account of the operative technique of localizing the sentinel node using patent blue V or isosulphan blue in patients with malignant melanoma (5). Recently, the concept of the sentinel node has been examined in connection with breast cancer and early results from around the world are promising.

SENTINEL NODE BIOPSY IN BREAST CANCER

One of the early studies on sentinel node biopsy in breast cancer was published by Giuliano *et al.* from Santa Monica, California in 1994 (6). In this study 1% isosulphan blue vital dye was used to localize the sentinel lymph node: 3-5 ml dye was injected into the breast tumour and surrounding parenchyma and through an axillary incision the blue-stained lymphatic tract was followed to a blue-stained lymph node or nodes. In their series of 174 patients, Giuliano *et al.* were able to localize a sentinel lymph node in 114 patients (66%). In 109 of the 114 patients who had sentinel nodes localized, there was a positive correlation between the sentinel node and the axillary node status. The concept that the sentinel node could be localized in breast cancer and that the sentinel node was predictive of the axillary lymph node status was thus established. Giuliano in his publication also graphically points out the importance of the surgical learning curve in this new surgical technique.

Over the next few years there was a move towards refining the technique of localizing the sentinel node in breast cancer and this led to the introduction of using a radiopharmaceutical, which was injected around the tumour and traced to the sentinel node using lymphoscintiscans preoperatively and a gamma detector probe peroperatively (7). The last 5 years have seen an explosion in the interest shown by surgeons throughout the world in the introduction of sentinel node biopsy in breast cancer. A large number of individual series of experiences in localizing the sentinel node in breast cancer have been published. Some studies have used blue dye alone (6), some radioisotope alone (8) and some have used a combination of radioisotope and blue dye (9) in the localization of the sentinel node in breast cancer. In the published literature it is suggested that a combination of blue dye and radioisotope gives better results than either technique used on its own in the localization of the sentinel node in breast cancer (10).

PRESENT STATUS AND THE NEED FOR STANDARDIZATION

It is quite obvious from the review of the literature that there are a number of variables in the localization of the sentinel lymph node in breast cancer. Some centres have used only radioactive colloid, while others have used only blue dye and a few centres have used both the radioactive colloid and blue dye. The other variables have been the site of injection of the dye, the dose of radioactivity used, the use of preoperative lymphoscintiscans, the timing of lymphoscintiscans and the use of a hand-held probe to locate the sentinel node. The pathological assessment of the sentinel node is another area that needs to be investigated. The gold standard for the assessment of lymph node status in breast cancer in the United Kingdom is haematoxylin and eosin staining of a routine paraffin section of the lymph node, following the guidelines of the National Health Service Breast Screening Programme (NHSBSP). However, with the introduction of sentinel node biopsy, there is the possibility of more detailed evaluation of the sentinel node, as fewer nodes will be processed. Serial sectioning, immunohistochemistry and polymerase chain reaction (PCR) are assessments that are already being carried out in many centres on the sentinel node, and judging from early results there seems to be a trend towards making immunohistochemistry the gold standard in the assessment of the sentinel node in breast cancer. With so many different variables present in previous published studies, it would be logical to standardize the procedure of localization and assessment of the sentinel node in breast cancer.

Some American centres have started using the results of sentinel node biopsy in breast cancer to make definitive treatment decisions on the management of the axilla (11).

The Dutch and Danish groups are about to start doing likewise (personal communication). We in the United Kingdom, like most of the authors writing on this subject, feel that this new technique should be validated by a randomized trial in comparison with conventional therapy before it is accepted into the routine management of breast cancer.

THE FUTURE

A recent leading article in the *British Journal of Surgery* ends with a note of caution, to the effect that, before sentinel node biopsy is adopted routinely in breast cancer management, the outcome of several prospective clinical trials that are presently comparing safety and survival in patients staged by this new approach with that of patients receiving traditional axillary management should be awaited (12). A commentary in the *Lancet* expresses regret that sentinel node biopsy is now commonly used outside clinical trials and calls for surgeons to resist commercial pressure and media-driven patient requests to perform sentinel node biopsies until proof of its value is available (13). After discussing the need for randomized clinical trials, an editorial in the *British Medical Journal* states that the introduction of sentinel node biopsy in breast cancer into clinical practice before results from randomized trials are available should not be supported (14). A review article in the *British Journal of Surgery* on sentinel node biopsy in breast cancer ends by saying that, for sentinel node biopsy to become a worthwhile and accepted part of breast cancer management, it will be necessary to demonstrate in randomized controlled trials that patients with a negative sentinel node biopsy do not require further treatment to the axilla, and that such management does not adversely affect either their disease-free or overall survival (10). The foreword to a recently published textbook on the sentinel node in surgical oncology states that sentinel node biopsy in breast cancer is unlikely to prove its worth until it has been subjected to a large, pragmatic, randomized, controlled trial, comparing unselected axillary node clearance with management dependent on the outcome of the sentinel node biopsy (15). So the need, and the call for randomized trials to validate sentinel node biopsy in breast cancer is clear.

The Medical Research Council has funded a randomized multicentre trial—the ALMANAC trial (Axillary Lymphatic Mapping Against Nodal Axillary Clearance)—which commenced in June 1999. It is hoped that this large multicentre trial across the UK, involving around 17 centres including teaching and district general hospitals, in addition to validating the procedure of sentinel node biopsy in breast cancer, will also take into consideration the morbidity, health economics and psy-

chosocial effects of an axillary procedure. The trial will comprise two phases. Phase 1 will be an audit phase, where the trial centres will perform a sentinel node biopsy in 40 patients prior to the definitive axillary procedure and if these results are satisfactory, they will proceed to Phase 2, which is the randomized phase. In Phase 2, patients will be randomised to one of two treatment arms. The first arm will receive conventional treatment to the breast cancer and an axillary staging or treatment procedure. The other arm will receive conventional treatment to the breast cancer along with a sentinel node biopsy. Patients with a positive sentinel node biopsy on routine paraffin histology will then go on to have the axilla treated by either further surgery or radiotherapy while patients with a negative sentinel node biopsy will have no further treatment.

The European School of Oncology in Milan, Italy, is also conducting a randomized, controlled trial similar to Phase 2 of the ALMANAC trial in Milan, where patients are randomized to receive either conventional treatment to the axilla or sentinel node biopsy-directed treatment of the axilla. Several trials are also ongoing in the USA and a trial is proposed by the EORTC breast group.

It is suggested that if the results of these randomized trials are successful, this new surgical technique will be introduced as part of the routine management of the axilla in breast cancer.

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