

# *Lymphatic Mapping and Sentinel Node Biopsy in Breast Cancer : Current View*

**P. Purasiri, B.Sc, MD, ChM, FRCS(Ed), FRCS(Glasg)**

*Department of Surgery, Samitivej Srinakarin Hospital, Bangkok 10250, Thailand.*

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## **Abstract**

Axillary lymph node dissection for breast cancer generally is accepted for its staging and prognostic value, but the extent of dissection remains controversial. Blind lymph node sampling may miss some nodal metastases and axillary lymph node dissection may result in lymphedema. Sentinel lymph node biopsy is a recently developed, minimally invasive technique for staging the axilla in patients with early breast cancer. Lymphatic mapping techniques have the potential of changing the standard of surgical care of breast cancer patients and that the technique will avoid the morbidity associated with more extensive axillary dissection. A wide range of different methods and materials has been employed for lymphatic mapping. Sentinel lymph node biopsy is a valid technique in breast cancer management, which can yield valuable axillary staging information. The technique can enhance staging accuracy, and with further refinements and experience may replace the role of axillary lymph node dissection.

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The concept of the sentinel node is not new. Oliver Cope referred to the "delphian node" in 1963 as the lymph node that will foretell the nature of a disease process affecting a nearby organ. Subsequently, sentinel node biopsy was proposed as a method of disease staging that was not overly aggressive and did not compromise quality of life. Intraoperative lymphatic mapping and identification of the first ("sentinel") axillary lymph node draining the site of a primary tumour may allow some patients with breast cancer to avoid the formal extensive axillary clearance. Sentinel lymph node biopsy is a recently developed, minimally invasive technique for staging the axilla in breast cancer. In recent years, breast surgery has become progressively more conservative. Surgeons have moved away from mastectomy towards breast conserving operation. Axillary node status remains the most important prognostic factor in breast cancer. Formal

axillary clearance has remained the best method of breast cancer staging, yielding information for the planning of adjuvant therapy. However, there is controversy over the extent of axillary surgery required. Axillary dissection is associated with significant morbidity.<sup>1,2</sup> Nevertheless, not all women have axillary metastases, the overall incidence of metastatic disease in the axilla was 46 per cent.<sup>3</sup> Tumour of 1 cm in diameter or less, the incidence of axillary nodal metastases ranges from 3-22 per cent.<sup>4</sup> In the absence of local treatment to the axilla, the risk of axillary recurrence is as high as 21 per cent.<sup>5</sup> Following complete axillary dissection, the risk of recurrence is 1-3 per cent.<sup>6</sup> When axillary sampling is performed, there is the risk that inadequate surgery will under stage the axilla and patients who are node positive will go unrecognized and untreated, leading to increased axillary recurrence rates. There is potentially signi-

ficant morbidity attached to the procedure of axillary dissection. It is clearly an incentive to avoid axillary surgery in women who are lymph node negative. Recent techniques have been developed to allow the identification of positive nodes without clearing the whole lymphatic basin. The concept of the sentinel lymph node was originally introduced in 1977 in the management of penile carcinoma and stated that the first lymph node to receive lymphatic drainage from the site of the tumour should be the first site of lymphatic spread, therefore, a tumour-free sentinel node implies the absence of metastases in the entire lymphatic basin.<sup>7</sup> The concept of sentinel lymph node biopsy was then introduced to patients with cutaneous melanoma by Morton and colleagues by injecting the blue dye intradermally at the site of the melanoma.<sup>8</sup> This allowed intraoperative identification of blue-stained lymphatic vessels leading away from the primary tumour to the blue sentinel lymph node. Several vital blue dyes were studied and the conclusion was that isosulphan blue (monosodium salt of 2,5-disulphonated triphenyl methane) was the most useful for lymphatic mapping as it was weakly bound to albumin and was taken up selectively by the lymphatics. Methylene blue, a water-soluble dye, proved to have poor lymphatic uptake and caused background staining of the tissues. Cyalume, a fluorescent dye, was also examined and found to leak out into the interstitial tissue space, resulting in marked background fluorescence. For this reason isosulphan blue was chosen as the best agent for lymphatic mapping, as it rapidly enters the lymphatic vessels and is readily visualized in the vessels and sentinel lymph node with minimal diffusion into the soft tissues. However, the use of vital blue dyes in lymphatic mapping has some drawbacks. It may be difficult to visualize or to dissect out the blue-stained lymphatic vessels or nodes in the lymphatic basin. Furthermore, dye may pass rapidly to non-sentinel nodes, resulting in the staining of several nodes and preventing the true sentinel node from being found. In an attempt to avoid these pitfalls, some groups have advocated radionuclide techniques.<sup>9</sup> Veronesi and colleagues in Milan used radiolabelled particles, lymphoscintigraphy and a hand-held probe to locate the sentinel node and facilitate its removal during surgery, thereby avoiding the time-consuming process of dissecting along the blue lymphatic tract until the blue node is found.

### *The importance of axillary nodal staging*

The status of the lymph nodes in patients with early breast cancer remains the most powerful predictor of recurrence and survival. The presence of nodal metastases decreases 5 year survival by approximately 40 per cent, as compared with patients who are free of nodal metastases.<sup>3,10</sup> The number of positive lymph nodes also carries prognostic importance.<sup>3,10,11</sup> Furthermore, information obtained from pathological examination of axillary lymph nodes frequently changes the adjuvant therapy plan for women with non-palpable axillary lymph nodes.

### *Sentinel lymph node biopsy for nodal staging*

Sentinel lymph node biopsy offers the possible advantages of identifying patients who truly have nodal metastases, while sparing others the need for axillary dissection. Sentinel node biopsy is less invasive than a complete or level I-II axillary dissection. Early experience has demonstrated that the sentinel lymph node accurately reflects the status of the remaining axillary lymph nodes in most cases and suggests that sentinel node biopsy may eventually replace axillary dissection as the nodal staging of choice. Although sentinel lymph node biopsy for breast cancer may be considered a state of the art procedure, there are several reasons that sentinel node biopsy alone should not be accepted as standard practice for breast cancer staging until further studies validate this procedure. Before axillary dissection is abandoned as the standard staging procedure for breast cancer, sentinel lymph node biopsy must be proved to be as accurate as axillary dissection. It is currently accepted a false negative rate of 2-3 per cent for axillary node dissection.<sup>12,13</sup> Sentinel lymph node biopsy should be performed with a similarly low rate of false negative results. The sentinel lymph node biopsy seems to be more sensitive for detecting lymph node metastases due to more focused histological examination evaluation making it possible to detect occult nodal metastases more frequently than does routine axillary dissection.<sup>14</sup> It has been recognized for many years that several recent long term follow-up studies of large series of patients indicated that the presence of nodal micro-metastases correlated with decreased disease-free and overall survival.<sup>15,16,17,18</sup> In fact, if sentinel lymph node biopsy with diligent pathological examination identifies a



population of genuinely lymph node negative patients, these patients may not require adjuvant therapy at all. For internal mammary node metastases, even though in a multicenter prospective randomized trial demonstrated that routine dissection of the internal mammary nodes does not improve outcome,<sup>14</sup> their prognostic significance is as great as that of axillary lymph node. There are some debatable technical issues that require clarification as follow:

1. There is no clear indication for sentinel lymph node biopsy but it is appropriate for patients with stage T1-T2 breast cancer.

2. Contraindication should include palpable axillary node metastases, multifoci breast cancer and previous breast or axillary surgery.

3. The timing, dose, type of dye or radiocolloid injection and type of gamma counter may affect the result.

4. In some breast cancer the primary lymphatic drainage is to internal mammary node that can be identified by preoperative lymphoscintigraphy, however, it is also true that preoperative lymphoscintigraphy may fail to identify axillary drainage when it is present.

5. Conventional histology (haematoxylin & eosin) is less accurate than new techniques for detecting microscopic involvement, thus immunohistochemistry, polymerase chain reaction and cytokeratin are being used.

### ***Patient selection***

Any woman with invasive breast cancer is a potential candidate for lymphatic mapping and sentinel lymph node biopsy. In patients with ductal carcinoma in situ, the incidence of nodal metastasis on sentinel lymph node biopsy is 8.4 per cent; in patients with invasive tumours more than 5 cm in diameter, the incidence is 75 per cent. Surgeons must decide for themselves whether these patients should undergo nodal staging. However, if nodal metastases are found, subsequent treatment recommendations will be different. Contraindications to the sentinel lymph node biopsy are multifocal disease, inflammatory cancer, and extensive previous surgery or radiation therapy.

### ***Complications***

The complications of the procedure are similar to axillary nodes dissection. Surgical site infections

occur in fewer than 1 per cent, a seroma develops in about 10 per cent. Paresthesia or lymphedema after lymphatic mapping for breast cancer should never occur in contrast to axillary lymph nodes dissection.

### ***Clinical implication***

Giving the importance of regional node status, it makes sense to continue to perform an axillary staging procedure. The problem is that axillary nodal dissection is associated with significant complications that can lengthen hospital stay, increase cost, and cause the patient considerable discomfort. There are now numerous reports in the literature suggesting that lymphatic mapping techniques can be used in breast cancer patient to reduce this morbidity. Those patients who are sentinel lymph node negative can be spared having to undergo complete axillary lymph nodes dissection. Approaching the end of 1998, breast cancer centers across the world have studied more than 1,500 women with breast cancer who had undergone lymphatic mapping and sentinel lymph node harvesting. The mapping techniques vary slightly from center to center, however, most have obtained similarly high success rates. Nevertheless, some argued strongly for the viability of the procedure. Sensitivity and diagnostic accuracy rates for sentinel lymph node identification have consistently been higher than 95 per cent, and the false negative rate has ranged from 0-10 per cent, suggesting that lymphatic mapping has the potential for changing the standards of surgical management of breast cancer in the future.

Lymphatic mapping and sentinel node biopsy in breast cancer is a valid minimally invasive technique for staging the axilla in breast cancer management. The optimal technique utilizes a combination of vital blue dye and a radiolabelled colloid. Nevertheless, there remains controversial issues which require to be solved before sentinel node biopsy becomes a widely accepted part of breast cancer management.

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