

The value of sentinel node biopsy in breast cancer

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Introduction

Breast cancer is the fifth most common cause of cancer deaths in the world. Approximately 4.7 deaths per 100,000 Sri Lankan women were due to breast cancer in 2001 [1]. The national cancer registry reports that cases of breast cancer in the country have increased from 4.6 per 100,000 women in 1985 to 9.8 in 2005 [1]. Sri Lanka has a lower risk of breast cancer compared to many developed countries.

In breast cancer, lymph node status is an important factor to stage the disease and to determine the most appropriate therapy. The first node that the tumour fluid passes through in a group of lymph nodes is called the sentinel lymph node. Thus it is the protective node that acts as the first filter against harmful material. The term sentinel comes from the French word *sentinelle* which means "to guard over" or "vigilance."

Many studies have shown that a metastatic tumour has a higher probability of being present in the region of the inflow junction of the afferent lymphatic vessels [1, 2]. Since breast cancer spreads from the tumour bed to the sentinel lymph nodes before it spreads to other axillary nodes, sentinel nodes, after identification, can be surgically excised for histopathological analysis.

In patients with clinically node-negative invasive breast cancer sentinel lymph node biopsy (SLNB) is reasonably reliable and a minimally invasive method for determining the status of regional lymph nodes [3].

The traditional procedure for staging breast cancer has been axillary lymph node dissection (ALND) which involves removing level I and level II lymph nodes. Since all of the lymph nodes are examined for the presence of cancer cells it is the most accurate method to assess the nodal status and it is the universal standard.

The drawback of ALND is that the procedure is associated with postsurgical complications such as lymphoedema, disruption of nerves in the axilla, chronic shoulder pain, weakness in the upper limb and joint dysfunction. Additionally, the survival advantage of ALND has been challenged.

Sentinel node biopsy is associated with fewer complications that may develop after the procedure. Compared to ALND, sentinel node biopsy usually takes less time to be performed. It is less painful. Unlike ALND it requires a much smaller incision and it is associated with a shorter recovery period. The identification rate of sentinel lymph node biopsy has an accuracy of more than 95%, and the axillary recurrence rate after SLNB is less than 1% [4]. In addition the accuracy involved with a sentinel node biopsy is better than that of ALND with a false-negative rate of 8% [5]. Furthermore, there is no difference in local recurrence or survival at follow up [5].

The way pathologists process and evaluate sentinel lymph nodes is different from how they would evaluate the nodes retrieved in an axillary dissection. Specifically, the pathologist looks at many more portions of the sentinel node and performs special studies to enhance the ability to identify cancer cells in

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those nodes. This provides a greater in-depth look at each sentinel node. Although long-term results are forthcoming, the clinical advantages of SLNB are apparent, and the procedure is becoming the preferred option by patients and breast cancer surgeons as the standard method.

To identify and locate the sentinel node among other lymph nodes, the surgeon may use one of the following methods:

Radioisotope alone

This involves an injection of a small dose of technetium-99, a low-level radioactive tracer. The surgeon injects this tracer into the breast near the tumour or underneath the nipple. The tracer then mixes with the fluids that travel to the lymph nodes. Later during surgery the surgeon uses a Geiger counter to determine which lymph node contains the radiation. This method pinpoints the sentinel lymph node. Depending on the preference of the surgeon, the isotope may be injected 20 minutes to eight hours before the surgery. This can be injected either around the tumour or underneath the nipple and areola. Both techniques are used and both are very successful. The sentinel node identification rate is 98% with a false negative rate of 11% [5].

Blue dye injection

For visual confirmation of the sentinel lymph node, the surgeon usually injects a blue dye called isosulfan blue (Lymphazurin 1%) near the tumour. When the surgeon makes the incision after injecting the dye, the sentinel lymph is coloured blue. The surgeon may inject this a few minutes before the actual surgery or during the surgery. This dye turns the urine green for about 24 hours and occasionally creates a temporary bluish stain on the breast tissue. The success rate of locating the sentinel lymph node with an injection of blue dye alone is 98% without false negative results [5]. The reported allergic reaction rate for Isosulfan blue dye ranges from 1% to 3%. Although rare, life threatening anaphylaxis and hypotension also have been reported. Overall, isosulfan blue dye has excellent results for lymphatic mapping in breast cancer.

Combination of blue dye and radioisotope

The combination of radioisotope and blue dye for lymphatic mapping improves sentinel node identification with a 98% success rate [5].

The sites for injecting mapping agents

There are two sites to inject mapping agents; subareolar or dermal injection and peri-tumoural injection. Mammary lymphatics develop as radial extensions from the nipple breast bud. Nearly all breast tissue lymphatic drainage passes through the subareolar plexus of Sappey and then the axillary nodal basin; hence dermal and subareolar injections are potential approaches for injection of mapping agents. Peritumoural injections of mapping agents are used to replicate the intramammary lymphatic pathways that may have been traversed by metastases. In patients with non palpable or multicentric tumours, the dermal and subareolar injection sites are particularly advantageous. They also eliminate the shine through effect.

On the other hand peri-tumoural injection has been proved difficult and time consuming for these patients because it requires the use of additional imaging modalities to guide the peri-tumoural injection of the radioisotopes. Peri-tumoural injections also have a higher potential shine through, where residual radioactivity from the peri-tumoural injection site creates misleading background activity detected by gamma probe of the axilla. A potential disadvantage to subareolar and dermal injections is that up to 10% of breast cancers may demonstrate non-axillary lymphatic drainage with sentinel nodes found in the internal mammary or supraclavicular nodal basins. Additionally, subareolar and dermal injection of blue dye may cause considerable postoperative discoloration of the breast (blue breast), which may last for several months.

Preoperative lymphoscintigraphy (PL)

Patients undergoing lymphatic mapping with radioisotopes most often receive a preoperative lymphoscintigraphy (PL) to aid in SLN identification. PL typically consists of anterior and lateral views and specific patient positioning to optimize transit time

and radioisotope drainage. Routine scanning is initiated 20 minutes after radioisotope injection and images are repeated until the primary SLN basin is identified and with an adequate uptake of the radioisotope. The patient then is taken to the operating room for SLNB. PL will identify the primary drainage pattern and the internal mammary (IM) sentinel nodes as well.

The need to perform lymphoscintigraphy prior to SLNB has been proved beneficial in showing that at least one radioactive SLN will be identified intraoperatively but it does not accurately predict the number of SLN in 40-50% of the patients [6, 7]. The number of hot spots in preoperative mapping should serve as a rough indicator of the smallest number of nodes the surgeon should attempt to resect but not the exact number of nodes expected to be found.

Since we do not perform internal mammary chain sentinel node biopsy, we find lymphoscintigraphy unhelpful from a surgical point of view.

Timing of radioisotope injection

Lymphatic mapping with radioisotope is performed either as a one or two day procedure. The single day procedure requires breast injection on the morning of the surgery, followed by serial imaging at one to several hours after injection until the SLN is identified. The two day mapping procedure involves injection of radioisotope one day before the operation. Based on the current literature, a two day lymphatic mapping procedure is safe and more reliable for SLNB in breast cancer.

Sentinel node biopsy after neoadjuvant chemotherapy

The use of neoadjuvant chemotherapy has increased in patients with operable breast cancer during the past several years. It increases the incidence of breast conserving surgical procedures [8, 9] as well as improvement in disease free and overall survival.

In a considerable proportion of patients (30% - 40%) axillary lymph nodes are downstaged by neoadjuvant chemotherapy [8, 10, 11]. Thus, a proportion of patients who are initially node-positive, and in whom sentinel nodes become

uninvolved after the administration of neoadjuvant chemotherapy, could be spared from an axillary dissection.

So far SLNB is not acceptable for patients with positive nodes in the axilla at the initial diagnosis even if their axillary metastases are downstaged to negative by neoadjuvant chemotherapy. In theory excessive fibrosis of the tumour lymphatics and the potential obstruction of lymphatic channels with cellular material or tumour emboli will occur after preoperative chemotherapy [12, 13, 14].

Thus SLNB after neoadjuvant chemotherapy results in a lower identification rate and a higher false negative rate than SLNB before treatment.

Non sentinel node involvement

When breast cancer spreads via lymphatics to the axillary basin additional axillary nodes can be involved which are not sentinel nodes. The strongest predictor of no sentinel node involvement are multiple probe detected hot nodes and positivity of more than one hot node.

Other predictors of non sentinel node involvement are more than one sentinel node involvement, the ratio of positive sentinel nodes to total sentinel node of greater than 0.5 and the presence of extracapsular invasion of the sentinel metastasis [5].

In the event of non sentinel node involvement with positive sentinel node, it is advisable to proceed with ALND.

Axillary recurrence after SLNB

In a meta-analysis published in 2008 forty eight selected studies had 14959 sentinel node negative breast cancer patients. They were followed up for a median of 34 months. Axillary recurrence was observed in 67 patients after sentinel node biopsy with a recurrence rate of 0.3%. The sensitivity was 100%. Therefore axillary recurrence rate in patients after SLNB was acceptably low [5].

Conclusion

The value of SLNB in staging and prognosis of breast

cancer with early stage disease is defined clearly. Its role in locally advanced disease and in those receiving neoadjuvant chemotherapy is not yet well established. Thus, patients who have negative sentinel lymph nodes may be spared an ALND. Until data from clinical trials are available, completion of ALND still remains the standard treatment for patients with positive SLNs.

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