

Lymphatic Mapping with Isosulfan Blue and Sentinel Lymph Node Biopsy for Breast Cancer Patients

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Abstract

Background: Lymphatic mapping and sentinel lymph node biopsy has been studied worldwide to establish its role in staging for breast cancer patients. Theoretically, axillary dissection could be omitted if the first tumor draining node (sentinel node) contained no cancer. We studied the technical feasibility of lymphatic mapping with isosulfan blue and sentinel lymph node biopsy in breast cancer patients.

Patients and Methods: After informed consent, patients who had axillary dissection as a part of their treatment during December 1998-May 1999 were included. Isosulfan blue dye, amount of 3-5 ml, was injected into breast tissue around the palpable breast mass or around the biopsied cavity. The axilla was explored to identify a blue staining lymph node (sentinel node). Then the sentinel lymph node was biopsied and complete axillary dissection was performed for pathological comparison.

Results: Of 15 patients, 12 patients had modified radical mastectomy and 3 patients had partial mastectomy + axillary dissection as their treatment. The sentinel lymph node was able to identify in 13 patients (87%). Sentinel lymph node can accurately diagnose axillary metastasis when compared to the axillary dissection in 12 out of 13 patients (92%), with 7 true negative, 5 true positive and 1 false negative.

Conclusion: The technique of lymphatic mapping using isosulfan blue dye and sentinel lymph node biopsy is feasible and reproducible for breast cancer patients in Thailand. Further studies should be carried out to ensure the usefulness of sentinel lymph node biopsy technique, which depend on the proportion of sentinel node identified and the accuracy comparing to axillary dissection.

The rationale for Sentinel Lymph Node (SLN) biopsy is based on the hypothesis that there is an orderly progression of breast cancer metastasis in a lymphatic basin, with the sentinel node being the first node to receive lymphatic drainage from the tumor site. Currently axillary lymph node metastases are the

most reliable prognostic factor which determines treatment planning. The majority of breast cancer patients are not found to have axillary node metastases and therefore do not benefit from axillary lymph node dissection (ALND). Theoretically, axillary dissection could be omitted if the first tumor draining node

(sentinel node) contained no cancer. The lymphatic mapping and SLN biopsy method to identify axillary node negative patients will not be clinically useful if (1) the sentinel node cannot be reliably identified, and if (2) the sentinel node does not accurately predict the status of the remaining axillary nodes.

Several techniques for axillary lymphatic mapping are being studied, which include using Isosulfan blue dye¹ or radiolabeled (Technetium-99) sulfur colloid² or a combination of both.³ Lymphatic mapping using blue dye has been found to be useful in breast cancer patients in several reported series^{1,4} but this technique does not allow for localization of the node before dissection and can be difficult to master. The Technetium-99 technique either alone or in combination with blue dye is reported to have better results compared to blue dye alone, however, requires more time and personnel.⁵ Therefore, SLN mapping using the isosulfan blue dye technique alone should be evaluated thoroughly to determine its feasibility and accuracy for lymphatic mapping in breast cancer.

Since studies of blue dye SLN mapping without Tech-99m have been reported from a few institutions and the sentinel lymph node technique has never been reported in Thailand, this pilot study was undertaken to determine the reproducibility of this technique. Our aims were: (1) to determine the ease and frequency of blue node identification in our patient population, and (2) to assess the pathologic status of the blue node(s) with respect to the remaining axillary lymph nodes.

MATERIALS AND METHODS

Patients

Breast cancer patients scheduled to have axillary lymph node dissection as a part of their treatment were illegible for this study. Intraductal, invasive ductal or invasive lobular breast cancer patients were included regardless of T and N staging, but excluded if they had previous ipsilateral axillary surgery or breast irradiation, preoperative chemotherapy for breast cancer, or inflammatory breast cancer.

From December 1988 through May 1999, fifteen patients, after informed consent (approved by Siriraj's Ethics Committee), were included in the study. All

patients were women with a median age of 44 years (range, 31 to 74 years). The surgical procedures for these 15 patients included modified radical mastectomy for 13 patients (80%), and lymphectomy or partial mastectomy plus axillary lymph node dissection for 3 patients (20%). Among these patients the mean primary tumor size was 2.3 ± 0.9 cm (range, 1.0 to 4.0 cm). The locations of the tumors were as follows: 3 cases in the upper outer quadrant, 3 in the upper inner quadrant, 3 in the lower outer quadrant, 2 in the lower inner quadrant, and 3 in the subareolar region.

Lymphatic Mapping Technique

Isosulfan blue dye lymphatic mapping was based on the technique described by Giuliano, et al¹ and Ratanawichitrasin, et al.⁶ All patients in our study received general anesthesia, underwent the blue dye lymphatic mapping procedure followed by, SLN biopsy, and a standard axillary lymph node dissection. The blue dye lymphatic mapping procedure involved the injection of, a total of 3 to 5 ml of 1 per cent isosulfan blue (Siriraj Hospital Pharmacy, Bangkok) vital dye in approximately 0.5 ml quantities into the breast parenchyma surrounding the breast mass, or around the prior breast biopsy site, using a 25-gauge needle. The injection site was then gently compressed for a few minutes to enhance the uptake of the dye by lymphatic system, but with effort to avoid potential dissemination of tumor cells. Within about 15 minutes of dye injection, but prior to mastectomy or ALND, an effort was made to identify a blue-staining node(s), by visual inspection. This identification process was done through a separate axillary incision for patients who were having an axillary dissection with a partial mastectomy, or through the lateral aspect of the mastectomy incision for mastectomy cases. During this process an attempt was made to identify a blue-staining lymphatic tract and trace it to a blue-staining node which was considered the SLN group. Once identified, the blue nodes were removed and submitted as separate specimens. The nodes were then divided, fixed, sectioned, stained with hematoxylin-eosin, and analyzed. All remaining axillary lymph nodes were removed following identification and excision of the blue staining node.

The patient was advised that urine and feces may be blue for 24 hours following isosulfan blue administration.

Statistical Analysis

A comparison of the sentinel lymph node status with that of the remaining axillary nodes is reported as true positive + true negative cases/total cases (accuracy) to evaluate clinical usefulness of the SLN procedure. Sensitivity and specificity are the methods to report the efficacy of a new technique when compare to gold standard. However, in this case, total axillary lymph nodes include the SLN, the specificity, which is always 100 per cent, would not be reported. In addition number of cases in which a SLN was identified was compared with the number of cases in which SLN mapping was attempted to determine the feasibility of using Isosulfan blue dye alone for SLN mapping.

RESULTS

Surgical Dissection

Isosulfan blue dye was injected around the tumor in 2 cases, and around the biopsy cavity in 13 cases. The average amount of dye injected was 4.0 ± 0.8 ml (range, 3 to 5 ml). The average number of injection sites per patient was 8.6 ± 1.8 (range, 4 to 11). The time between blue dye injection and starting SLN dissection average 12.5 ± 2.1 minutes (range, 10 to 16).

As the sentinel node dissection was begun, care was taken to not divide any of the blue-staining lymphatic tracts. It was possible to identify blue lymphatic tracts in 67 per cent (10/15) of our patients. Blue lymphatic tracts were useful in helping to identify blue-staining nodes, but nodes were not identified as SLN without some blue staining of the node itself. Blue-staining lymph nodes were identified in 87 per cent (13/15) of our patients. Overall, the mean number of blue-staining lymph nodes was 2.5 ± 1.9 per case. Only one blue-staining node was found in 38 per cent (5/13) of cases. The intensity with which lymph nodes stained blue varied. In 6 (46%) cases the nodes were stained intensely; in 5 (38%) cases, staining was moderately; and in 1 (8%) only faint staining was evident.

Lymph Node Evaluation

The relationship between the histopathology of the SLN and that of the other axillary lymph nodes from axillary dissection are shown in Table 1. From the 13 patients in whom a sentinel node was identified, the mean number of nodes removed from axillary dissec-

Table 1 Relationship between lymph node status and sentinel lymph node status.

Sentinel Lymph Node Status	Axillary Lymph Node Status	
	Negative	Positive
Negative	7	1
Positive	0	5

tion was 19.8 ± 8.3 nodes. Seven cases (54%) did not have metastases in either the sentinel or the remaining nodes. Six cases (46%) were found to have node metastases. Five of the six node-positive cases had a positive SLN, and in three of these five the SLN was the only positive node. Overall, there was a 92 per cent accuracy (ture positive + true negative) in predicting axillary lymph node status by using the SLN as an indicator.

Side Effects

Most patients excreted blue dye in the urine and feces for times ranging from several hours to a few days after the procedure. However, these did not result in any clinical complication.

DISCUSSION

There is considerable interest in axillary lymphatic mapping and sentinel lymph node dissection in breast cancer so that potential complication of full axillary dissection can be avoided. Initial reports from several investigators are very encouraging. Whether the identified sentinel node actually a true sentinel node can only be answered when a complete node dissection is undertaken and when there are a sufficient number of node positive cases among those in which a node was identified to make a reliable determination of the false negative incidence.

In several large series the SLN identification rate has been very high (98-100%) depending upon the experience of the surgeons and the techniques used. Most investigators report that learning these techniques requires time and experience. Usually the SLN identification rate is lower in the learning period. Our initial experience utilizing blue dye in patients with breast cancer was encouraging. Blue stained nodes were identified in 87 per cent our cases, an improvement over the initial experience of Giuliano et

al¹ in which only 65 per cent of cases had a blue node identified. Our results are also comparable to the initial result of blue dye used in combination with Technetium-99, as reported by Albertini et al,³ with a 92 per cent identification rate.

Once the sentinel node is able to be identified the technique will only be useful clinically if its pathology status reflects that of the remaining nodes. In this study we had a 92 per cent accuracy result, with one false negative case (false negative rate = 16% [1/6]). Giuliano et al reported a 95.6 per cent predictive result in his first report of mapping 114 cases with 5 false negative cases (false negative rate = 22% [5/23]). Veronesi et al reported similar results (97.5%) using lymphoscintigraphy alone,² with 4 false negative cases (false negative rate = 5% [4/85]). Our result of SLN biopsy has a comparable of accuracy and false negative rate as other initial reports. However, most of the other investigators used cytokeratin immuno-histochemical staining techniques and prepared multiple lymph node sections for their SLN analysis to reduce the number of false negative. Giuliano reduced the false negative cases by more than half, while Veronesi detected micrometastasis in 18 of 85 cases (21%).

Whether identification of patients with micrometastatic disease by using immunohistochemical staining could influence treatment and ultimate survival is a different question. There are no long term data to support treating patients with micrometastasis differently from standard node-negative patients.^{7,8} We used only routine standard pathological examination, involving one section per node and did not apply any immuno staining to increase the chance of detecting metastases, which considered to be appropriate for the economic status of our country.

Our experience with the blue dye lymphatic technique certainly suggests that it is an excellent initial step, which is likely to be quite beneficial and cannot be appreciated with the use of Technetium-99 scanning alone, to visualize lymphatic pathways and trace them to lymph nodes. Whether this technique will be able to stand alone without the use of Technetium-99 scanning requires further investigation.

CONCLUSIONS

The technique of lymphatic mapping using

isosulfan blue dye and sentinel lymph node biopsy is feasible and reproducible for breast cancer patients in Thailand. The high diagnostic accuracy of this technique, the lack of complications and the short time needed to perform the technique are attractive features. Further studies should be carried out to ensure the usefulness of sentinel lymph node biopsy technique, which depend on the proportion of sentinel node identified and the accuracy comparing to axillary dissection.

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