Sentinel Node Localization in Breast Cancer Using Intradermal Dye Injection: Results, Influencing Factors and Learning Curve

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To evaluate the identification rate, false negative rate, concordance, negative predictive value of sentinel node localization in breast cancer using intradermal isosulfan blue injection whether this is accurate enough for surgical approach in breast cancer surgery and whether there is a significant learning curve for this technique. Factors affecting the outcomes of the procedure are also determined.
From August 2002 to September 2003, 66 cases of stage 0-IIIB operable breast cancer patients underwent sentinel lymph node biopsy before standard breast cancer operation. Overall, identification rate was 80.3%, false negative rate was 10.6%, concordance was 86.8%, negative predictive value was 83.3%, sentinel node was the only node that was positive in 45.5%, and mean operative time was55.1minutes. Factors found to lower sentinel node identification rate are neoadjuvant chemotherapy and large tumor (T3-4) while previous excision was not found to affect the identification rate. There is significant learning curve in this technique and this should be performed at least 40-45 cases in the learning phase to accomplish a high identification rate and lower false negative rate before implicating into clinical practice.

Keywords: *Sentinel node, Breast cancer, Intradermal dye, Results, Influencing factors, Learning curve*

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The sentinel lymph node (SLN) is the first lymph node in a nodal basin to drain the primary tumor. In theory, a malignancy from a primary breast cancer spreads to axillary lymph nodes (AXLNs) and progresses in an orderly fashion from primary tumor to the sentinel lymph node and subsequently to the other AXLNs; therefore, SLN is the node most likely to contain metastatic tumor cells. If the SLN is not involved, then other AXLNs should have a very low likelihood to be affected by metastasis. However, sentinel lymph node biopsy requires validation by a backup axillary lymph node dissection (AXLD) in a defined series of cases before becoming standard practice, to establish individual and institutional success rates and the frequency of false negative results.

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Objective

The primary objective was to find out if the SLN can be detected in sufficient numbers of breast cancer patients to be useful as a prognostic sign, whether it reflects the state of the entire axilla, in terms of identification rate, concordance, false negative rate, negative predictive value of the procedure and to find out if there is factors influence the detection rate of the procedure (previous surgical scar, neoadjuvant chemotherapy, large tumor). The secondary objective was to determine if there is a definite learning curve for sentinel lymph node biopsy (SLNB).

Material and Method

From August 2002 to September 2003, a total of 66 operable breast cancer patients (stage 0, I, II, IIIA and IIIB) who were planned to have AXLD as well as resection of primary tumors were enrolled at the Surgical Oncology Unit. The operation was performed by single surgeon (T.R.). The age of the patients ranged from 17 to 83 years (mean 47.8, median 46.0 years). Tumors were in Tis, T1, T2, T3 and T4 in 5, 21, 31, 5, 4 cases (7.6, 31.8, 47.0, 7.6, 6.1%), respectively. There were stage 0, I, IIA, IIB, IIIA, IIIB in 5, 13, 27, 13, 4, 4 (7.6, 19.7, 40.9, 19.7, 6.1, 6.1%) cases, respectively. 11 patients (16.7%) had neoadjuvant chemotherapy, 32 patients (48.5%) had previous surgical primary tumor biopsies. 56 patients (84.8%) underwent Modified radical mastectomy (MRM), and 10 patients (15.2%) underwent breast conservative surgery (BCS).

After induction of general anesthesia, Isosulfan blue dye (manufactured by Pharmaceutical department, Siriraj Hospital, Bangkok) was injected at the diseased breast, intradermal, 4 quadrants periareolar with total volume of 2 ml. A 10-minute interval was allowed before incision was made for the dye particle to traverse to the SLN. The dye injection site was locally massaged simultaneously at this period to potentiate disperse of the dye particle. In the case of MRM, the incision at the breast was made. Mastectomy was performed in conventional fashion. SLNB was done by following blue dye tracts visualize intraoperatively into the stained nodes, which were identified as SLNs. SLNs were separately sent for pathological examination (H&E technique). Following SLNB, AXLD level I-II was performed. Other non-staining lymph nodes, which were identified as non-SLN, were separately examined pathologically with the same technique. In case of BCS, after 10 minutes interval, an axillary incision was made. SLNB was performed in the same pattern as previously described, followed by AXLD level I-II. Then, a wide excision of primary tumor was subsequently performed.

Factors postulated to affect the identification rate of SLN; so called, previous surgery, neoadjuvant chemotherapy, and large tumor, were recorded and analyzed.

To determine the learning curve of this investigational procedure, data was also divided into 3 sequential groups containing 22 patients in each group and separately analyzed and compared. A p-value less than 0.05 was shown statistical significance.

Results

Overall, the identification rate of SLNB was 80.3%. False negative rate was 10.6%. There was concordance in 86.8%. There were positive SLN in 11/53 (20.8%); in these positive SLN, the SLN was only node that positive in 5/11 (45.5%). Negative predictive value was 83.3%. Mean and median numbers of SLN was 4.2, 3.0 (range1-13), non-SLN was 15.3, 13.0 (range 3-35), total LN was 18.6, 17.0 (range4-35). Mean operative time was 55.1min (range 37-80 min). Results of the total 66 cases were presented is Table 1.

Neoadjuvant chemotherapy was found to lower the SLN identification rate significantly (p = 0.001). Previous excision or surgical scar was not found to affect SLN identification rate (p = 0.85). Large tumor size (T3-4) was found to significantly reduce SLN identification rate compared to T1-2 ($p < 0.001$). On the contrary, T2 tumor had SLN identification rate comparable to T1 tumor (p = 0.33).

Concerning the results of each group, identification rate was significantly improve after the first 22cases (86.4% vs 68.2%) and was constant after that. False negative rate was doubly decreased in the later group compared to the former group (13.3% vs 36.4% and 6.3% vs 13.3%) Negative predictive value and concordance were gradually increased from the first group to the last group while operative time was gradually decreased. More early stage patients in the later group as shown in Table 2 may explain why node positive rate decreased in the later group compared to the former group. Results of each group in different periods are shown in Table 1.

Table 1. Results of each group in different periods

Parameter	First 22 cases (No.1-22)	Later 22 cases (No.23-44)	Last 22 cases (No.45-66)	Total 66 cases (No.1-66)
Identification rate	15/22 (68.2%)	19/22 (86.4%)	19/22 (86.4%)	53/66 (80.3%)
False negative rate	4/11 (36.4%)	2/15 (13.3%)	1/16 (6.3%)	7/42 (10.6%)
Negative predictive value	7/11 (63.6%)	13/15 (86.7%)	15/16 (93.7%)	35/42 (83.3%)
Concordance	11/15 (73.3%)	17/19 (89.5%)	18/19 (94.7%)	46/53 (86.8%)
Node positive	4/15 (26.6%)	4/19 (21.1%)	3/19 (15.8%)	11/53 (20.8%)
SN only node positive	3/4 (75%)	2/4 (50%)	0/3 (0%)	5/11 (45.5%)
Mean operative time (min)	62.3 (50-80)	57.1 (38-78)	46.0 (37-65)	55.1 (37-80)

Table 2. Stage distribution in each group

Staging	First 22 cases	Later 22 cases	Last 22 cases
0	1 (4.5%)	2 (9.1%)	2 (9.1%)
I	3 (13.6%)	4 (18.2%)	6 (27.3%)
IIA	6 (27.3%)	9 (40.9%)	12 (54.6%)
IIB	6 (27.3%)	6 (27.3%)	1 (4.5%)
IIIA	4 (18.2%)	0 (0%)	0 (0%)
IIIB	2 (9.1%)	1 (4.5%)	1 (4.5%)
Total	22 (100.0%)	22 (100.0%)	22 (100.0%)

Discussion

Sentinel lymph node is the first lymph node to receive lymphatic drainage from primary cancer and therefore, the node most likely to contain metastatic tumor cells. The concept of the sentinel node was proposed n the 1950s when it was recognized that one or two nodes trapped the majority of radiolabelled tracer during lymphoscintigrams. Some years later, Morton et al[1] clarified many of the technical aspects of intra-operative lymph node mapping in melanoma using patent blue dye. SLNB has now become a standard part of melanoma management.

In breast cancer, the concept has been validated in the study by Turner et al[2], which indicated that the sentinel lymph node is the first port for metastatic disease in the axilla. SLNB is a new component of the surgical treatment of breast cancer for predicting histological finding in the remaining axillary lymph nodes.

In melanoma, SLNB with blue dye and radiolabelled trace should have an accuracy rate approaching 100%, false negative rate of 1-3% and be successful at detecting SNs almost 98% of the time[3]. In breast cancer, the results are not as good. This is partly due to the relative novelty of the procedure in breast cancer patients, the different lymphatic drainage patterns and lymphatic flow rate within the breast.

There are two commonly used tracers to identify SLN, which are blue dye and radiolabelled tracer. In general, studies using both dye and radiocolloid or radiolabelled tracer alone had a higher detection rate of the SN and the lower false negative rate compared with dye alone[4]. The identification rate for blue dye, radiocolloid, and both are 66-94%, 69-98%, and 90-100%, respectively. False negative rate for blue dye, radiocolloid, and both are 8%, 4%, and 4%, respectively. Accuracy of blue dye, radiocolloid, and both are 95-100%, 97-100%, and 93-100%, respectively[5-19]. Most authors have noted cases where a SN that was missed by the blue dye technique was picked up by the radiocolloid method and vice versa, indicating that the two methods are complimentary. In the present study, blue dye (Isosulfan blue) alone was used as it is a simple technique, a cheaper agent and fewer instruments required than radiocolloid. Different routes of dye injection also have variable results. In this study, intradermal injection technique was used to see the efficacy of this route.

Several factors have been identified that may influence the detection rate and false negative rate of SLNB. Timing of tracer or dye injection before SLNB play role in detection rate. In the present study, a 10 minute interval was used before making the incision according to the study of Bergkvist L[20], which showed that dye injected less than 5 minutes or more than 30 minutes before the start of the operation lowered the detection rate.

Neoadjuvant chemotherapy has been claimed to contribute to affect detection rate and false negative rate of SLNB. Data is still controversial. Nason et al[21] found that preoperative chemotherapy was associated with the high false negative rate (33% compared to the overall false negative 16%), while other studies[22-25] found that this did not adversely impact the false negative rate or identification rate. In the present study, neoadjuvant chemotherapy was found to associate with higher false negative rate ($p = 0.001$)

Previous excision was another factor associated with a slightly higher failure rate, possibly as a result of disruption of breast lymphatics. Nason et al[21] found that the false negative rate for previous excision was not different from the overall false negative rate (11% vs 16%) Haigh et al[26] also found the success rate of SLN localization to be unaffected by a previous biopsy. In the present study, previous excision was not found to be associated with a higher false negative rate ($p = 0.85$)

Large tumors, which are likely to harbor nodes replaced by tumor or lymphatic blocked with cancer are associated with a higher false negative rate of SLN detection. Nason et al[21] found that T3 tumor size was associated significantly with increased false negative rate. In the present study, the result showed, (same as Nason's) that there was significantly lower identification rate comparing T1-2 and T3-4 ($p < 0.001$). However, there was no difference in identification rate comparing T1 (< 2cm) and T2 tumor ($p = 0.33$). This can explain the lower identification rate in first 22 cases compare to other later periods as there were more larger tumor or advanced disease in the first period.

Learning curve is a major component for this investigational procedure to be successful both the high detection and low false negative rate. There are marked differences in performance of individual surgeons and identification rates varied from 25-100%[27]. Success rates improved with later series within the same institution. Tafra L[28] reported in a single institution series that the second series success rate improved compared with their initial series. Data has shown a decrease in the false negative rate to < 5% after 20-30 procedures are performed. There are data to support at least 20 cases done in conjunction with axillary dissection or under direct supervision. There was a rapid decrease of the false negative rate after 20 cases[29]. The present data, despite performing by single surgeon, also confirmed this regime as shown that identification and false negative rate were markedly improved for the later subsequent group of patients. The identification rate was improved dramatically in the second subsequent group or after 22 cases (86% compared to 68%) and remained static afterward. Meanwhile, the false negative rate was doubly decreased in the subsequent group (36% in the first 22 cases, 13% in second 22 cases and 6% in last 22 cases). The authors suggest from the present data that the learning curve for this innovative procedure should be not less than 40-45 cases before the surgeon can accomplish the acceptably high identification rate and low false negative rate.

In conclusion, sentinel node localization has an acceptable high accuracy to determine axillary lymph node status and stage of disease. This minimally invasive surgery will spare non-disease axilla to avoid conventional axillary dissection. However, some factors which appeared in each patient (neoadjuvant chemotherapy, large tumor) may influence the outcome of this technique which the surgeon should keep in mind. Moreover, the learning curve plays an important role in this technique and should be done by experienced surgeons.

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การตรวจหา Sentinel node ในมะเร็งเต้านมโดยวิธีฉีดสีเข้าใต้ผิวหนัง: ผลลัพธ์, ปัจจัยที่มีผล, ช่วงการเรียนรู้

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เพื่อประเมินผลการตรวจใช้ sentinel lymph node ในการผ่าตัดผู้ป่วยมะเร็งเต้านมโดยวิธีฉีดสี isosulfan blue เข้าใต้ผิวหนังว่าจะมีความแม่นยำเพียงพอในการนำไปใช้เป็นวิธีผ่าตัดกับผู้ป่วยได้หรือไม่ และช่วงการเรียนรู้วิธีดังกล่าวมีความสำคัญก่อนการนำไปใช้จริงหรือไม่ นอกจากนี้ยังศึกษาปัจจัยที่อาจกระทบต่อผลการตรวจด้วยวิธีนี้

ได้ศึกษาผู้ป่วยมะเร็งเต้านมระยะที่สามารถผ่าตัดได้ตั้งแต่เดือนสิงหาคม พ.ศ.2545 ถึงเดือนกันยายน พ.ศ.2546 จำนวน 66 รายซึ่งอยู่ในระยะตั้งแต่ 0-IIIB โดยทำผ่าตัด sentinel lymph node biopsy ก่อนแล้วจึงทำการผ่าตัดรักษามะเร็งเต้านม โดยวิธีมาตรฐานต่อไป ผลการศึกษา โดยรวมวิธีดังกล่าวมี identification rate 80.3%, false negative rate 10.6%, concordance 86.8%, negative predictive value 83.3%, sentinel node เป็นเฉพาะ node ที่ให้ผลบวก 45.5%, ค่าเฉลี่ยเวลาในการผ่าตัด 55.1นาที ปัจจัยที่พบว่ามีผลทำให้ identification rate ลดลงอย่างมีนัยสำคัญคือ การได้รับเคมีบำบัดก่อนการผ่าตัดและการที่ก้อนมะเร็งมีขนาดใหญ่ (T3-4) ในขณะที่การได้รับการผ่าตัดก้อนเนื้อออกมาก่อนไม่มีผลต่อ identification rate ช่วงการเรียนรู้มีความสำคัญสำหรับวิธีนี้ และควรจะต้องผ่าน 40-45 ราย ไปก่อนเพื่อให้ได้ identification rate สูงและ false negative rate ต่ำก่อนที่จะนำวิธีนี้ไปใช้ในทางคลินิกต่อไป
