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Sentinel Lymph Node Biopsy in Breast Cancer

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Abstract. Sentinel lymph node biopsy in staging of early breast cancer is a feasible, accurate and reliable procedure. 90 patients with early breast cancer undergoing Sentinel lymph node biopsy in the Departments of Surgery at King Abdulaziz University and Bakhsh Hospitals between December 2000-2006. The objective of the study is to determine the feasibility, accuracy and technique of Sentinel lymph node biopsy in the management of early breast cancer and to predict axillary lymph node status. 57 patients had stage I breast cancer (63.3%). Different methods were used to localize Sentinel lymph node initially by using combination of lymphazurin blue and radioisotope in 12 patients (13.3%), lymphazurin in 25 patients (27.8%) and methylene blue in 53 patients (58.9%). Sentinel lymph node dentification rate was 98.9%. 60 (66.7%) had lumpectomy while 30 (33.3%) had mastectomy. Frozen section accuracy, sensitivity, specificity, positive and negative predictive values of Sentinel lymph node were (96.8%, 84.4%, 100.0%, 100.0%, 97.97%). Local breast recurrence rate was 3 (3.3%). Methylene blue is effective and safe in the detection of sentinel lymph node in patients with breast cancer; it is lower in cost and is readily available.

Keywords: Breast cancer, Sentinel lymph node biopsy, Blue dye.

Introduction

Sentinel lymph node biopsy (SLNB) is a technique used to identify the axillary lymph node status in patients with early breast cancer, which is important for staging, prognosis, adjuvant chemotherapy therapy and

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loco-regional disease control. SLNB has fewer complications than axillary lymph node dissection which include paraesthesia, hematoma, seroma, restricted shoulder motion and arm lymphoedema that occur in 14 to 28% of patients[1,2].

SLNB was introduced initially in 1977 by Cabanas for the staging of penile cancer[3,4]. The technique was adopted in the 1980s for the treatment of malignant melanoma. Krag *et al.* and Giuliano *et al.* first reported the usefulness of SLNB in the treatment of breast cancer in 1990[5,6]. The key factors of the success of SLNB include an identification rate of SNL ranges from 85-99% and a false-negative rate (FNR) of axilla of <5%. The FNR will be improved by the surgeon's experiences, cooperation and the experience of the team involved including the radiologist and pathologist[5]. Conversely a few reports highlight tumor related factors that are associated with an increased rate of SLN identification and patient related factors[6,7]. Techniques for performing SLNB vary from institution to institution. Some advocate blue dye only[8], others prefer radioisotope only[9]. However, some reports demonstrated improved identification and lower false-negative rates by using a combination of blue dye and radioisotope[10].

The aim of this study is to determine the feasibility, accuracy and technique of SNLB in the detection of early breast cancer.

Methods

A retrospective review of the medical records of patients presented to the Department of Surgery at King Abdulaziz University and Bakhsh Hospitals with breast cancer was evaluated from December 2000-2006. A total of 90 patients were enrolled in this study with ages ranges from 24-85 years. The hospitals' Ethical Committee permitting the review of the records of those patients approved this study. Enrollment criteria to this study are early breast cancer (AJCC 5th edition Stage T1 and T2, N0, M0). Exclusion criteria were (1) Multifocal multicentric cancer, (2) Axillary lymph node metastases on preoperative ultrasound, (3) Advanced breast cancer, (4) Previous breast biopsy and radiation, (5) Allergic reactions to vital dyes.

The clinical factors that were assessed in all of the patients include age at diagnosis, family history of breast cancer, tumor location,

operation performed and complication. Pathological factors evaluated were primary tumor size and histopathology.

All patients had preoperative radiological investigations including mammography and ultrasound scan of breast and axilla, which was performed by radiologists, specialized in breast cancer. SLN were identified by using either methylene blue in 53 cases (58.9%), lymphazurin dye in 25 cases (27.8%) and a combination of lymphazurin dye and radioisotope in 12 (13.3%). On the day of surgery, radioactive technetium Nano colloid 0.1 mCi was injected in the peritumoral area and 0.2 mCi was injected subdermally, 5 ml of 1% of isosulfan blue dye l, 5 mL of 1% methylene blue dye (Micromedex) was diluted with 5cc of saline and injected in peritumoral or subareolar area. The breast was then massaged for 5-20 min depending on the site of tumor. In cases of lumpectomy, a transverse incision was made just below hairline in axilla. When modified radical mastectomy was planned, incision lines were marked and incision for SLNB was made through the lateral part of these lines. Sentinel nodes were localized by careful dissection along blue-stained lymph vessels or guided by gamma detector (Navigator, USSC, Norwalk, CT). SLN was defined as any blue and/or 'hot' lymph node (specimen counts >10 Bq). All SLN were sent for frozen sections (FS) in which Hematoxylin and Eosin (Stain) (H&E) staining were used. If metastatic cancer was identified in the SLN, level 1 and 11 axillary lymph node dissection was performed. The initial 20 patients had both SLNB and Axillary Lymph Node Dissection (ALND) and were performed by one breast surgeon in order to establish the technique. The total number of SLN removed per patient was registered; it was between 1-8 lymph nodes.

Data were analyzed by using SPSS version 12, Chi square test, and p value.

Results

Table 1 shows demographic and clinical characteristics of all patients. There was one male (1.1%) in the study. Family history of breast cancer was positive in 9 patients (10%). SLN identification techniques were tested by different methods using methylene blue, Lymphazurin-dye, and radioisotope with Lymphazurin-dye performed in (58.9%, 27.8%, 13.3%) cases. Breast tumor locations were right, left, and bilateral respectively (58.9%, 40.0%, 1.1%). The site of tumor in the

breast is more in outer than inner quadrants (80% *vs.* 20%). Operation was mostly lumpectomy in 60 cases (66.7%), and no axillary lymph node dissection. The majority of patients 57 (63.3%) had tumor size of < 2cm.

Table 1. Demographic and clinical characteristics of patients.

Variables	Results (n = 90)
Age (years, means ± SD)	47.87 ± 12.930
(Range)	(24.00-85.00)
Sex (number, %)	
Male	1 (1.1%)
Female	89 (98.9%)
Family history (number, %)	
Positive	9 (10%)
Negative	81 (90%)
Sentinel lymph node technique (number, %)	
Methylene blue	53 (58.9%)
Lymphazurin-dye	25 (27.8%)
Lymphazurin-dye & radioisotope	12 (13.3%)
Tumor location (number, %)	
Right	53 (58.9%)
Left	36 (40.0 %)
Bilateral	1 (1.1%)
Operation type (number, %)	
Lumpectomy	60 (66.7%)
Mastectomy	30 (33.3%)
Site of tumor (number of patients, %)	
Outer quadrants	56 (80%)
Inner or central quadrant	14 (20%)
Axillary lymph node dissection (number, %)	
Yes	30 (33.3%)
No	60 (66.7%)
Breast tumor size (cm, means±SD)	2.11556 ± .834900 (0.6-4.0)
T1 (number of patients, %)	57 (63.3%)
T2	33 (36.7%)

SLN identification rates ranged from 95.6-98.9%. Total number of sentinel lymph node removed / patients is between 1-8 lymph nodes (1.54 ± 1.3).

Stages of breast cancer were I or II (63.3% *vs.* 36.7%). Histopathological types of breast cancer were as follows; invasive ductal carcinoma, invasive ductal carcinoma and ductal carcinoma in situ (DCIS), invasive lobular carcinoma, invasive tubular carcinoma respectively (91.1%, 5.6%, 2.2%, 1.1%). Recurrence rate in the breast was in 3 patients (3.3%) (Table 2).

Table 2. Results of breast cancer.

Variables	Number (%)
Cancer staging (number, %)	
1st stage	57 (63.3%)
2nd stage	33 (36.7%)
Breast cancer histopathology (number, %)	
Invasive ductal carcinoma	82 (91.1%)
Invasive ductal carcinoma and DCIS	5 (5.6%)
Invasive lobular carcinoma	2 (2.2%)
Invasive tubular pattern	1 (1.1%)
Hospital stay duration (days, means ± SD, range)	3.14 ± 1.045 (2-5)
Recurrence rate (number, %)	
Yes	3 (3.3%)
No	87 (96.7%)
Follow-up (months, means ± SD, range)	24.60 ± 14.313 (3-64)

Frozen section of SLNB accuracy, sensitivity, specificity, positive and negative predictive values were (96.8%, 84.4%, 100%, 100%, 97.97%, respectively) (Tables 3a, 3b).

Table 3a. Statistical formulas.

Outcome measure	Formula
Positive predictive value	TP/TP+FP
Negative predictive value	TN/TN+FN
Sensitivity	TP/TP+ FN
Specificity	TN/TN+FP
Accuracy	TP+TN/TP+TN+FP+FN

TP (true positive); TN (true negative); FP (false positive); FN (false negative)

Table 3b. Results of frozen section of sentinel lymph node in breast cancer patients.

Results	Frozen section (n=90)
True positive (number)	14 (15.6%)
True negative (number)	76 (84.4%)
False positive (number)	0
False negative (number)	3 (3.3%)
Sensitivity (%)	84.4%
Specificity (%)	100%
Positive predictive value (%)	100%
Negative predictive value (%)	97.97%
Accuracy (%)	96.8%

Discussion

A sentinel lymph node is defined as the first lymph node in a regional basin that receives lymphatic drainage from the site of the primary tumor. Axillary lymph node status is the best prognostic indicators in patients with breast cancer[1]. Regional control is important in patients with positive axillary lymph nodes. Axillary lymph node dissection can achieve both goals but it is recognized as the most morbid part of breast cancer surgery[13]. SLNB is an alternative to ALND for staging axilla in early breast cancer patients with minimal morbidity[2,12-14].

The concept of breast conserving therapy (BCT) as an alternative to mastectomy came in the 1990s. A number of studies showed that BCT resulted in overall survival rates that were similar to those of mastectomy[10]. It was also established that adjuvant radiation therapy to conserve the breast was necessary to achieve acceptable rates of local recurrence. Adjuvant radiation therapy reduces the recurrence rate from 19.6% after surgery alone to 6.7% with irradiation[3]. In this study, 66.7% of our patients had lumpectomy and most of them Stage 1 while 33.3% had mastectomy and most of them Stage 11 and those patients had either small size breast, multifocal lesions, extensive intraductal component and large tumor size.

Controversy remains regarding various technical identification aspects of SLNB. Some authors advocate a single technique[8] using either blue dye alone or isotope alone[11,16,17], while others maintain that a combination approach to identify SLN is preferable[15]. In this study, we use methylene blue dye alone, Lymphazurin-dye alone or a combination of Lymphazurin dye and radioisotope. Giuliano *et al.* [6] and Kern[19] used blue dye alone for detecting SLNs and reported identification rate to be 93.5% and 98%. Methods described in this study have proven valid in detecting SLN (detection rate of 95.6-98.9%), the false-negative rate of axilla 6.7% in the initial 20 patients. These results are fully acceptable when compared with international results[16-18].

In 2001, the first study of methylene blue injection for SLNB in breast cancer was published[24]. Mehylene blue has been utilized successfully in SLN mapping. A pilot study done at Cornell University Medical Center demonstrated the efficacy of methylene blue in accessing the lymphatic system in 27 (90%) of 30 of breast cancer patients[24]. Our

study revealed that initially combined techniques were used at our institution, however, in 2003, a nation wide shortage of Lymphazurin-dye and logistical factors with radioisotope, these promoted the clinical use of methylene blue. Our experience shows a success rate of 98.9% in identification of blue sentinel lymph nodes when methylene blue is used.

In this study, frozen section in detection of SLN was found to be highly accurate 96.8% with a low false negative rate of 3.3%. Sensitivity, specificity, positive and negative predictive values of frozen section was 84.4%, 100.0%, 100.0%, 97.97%, respectively.

Three patients (3.3%) showed negative SLN on frozen section and were readmitted for axillary lymph node dissection, where metastases were detected by immunehistochemical staining. Meanwhile, 66.7% of patients with negative SLNB did not have ALND and so were protected from ALND complications. Positive SLN at frozen section was 14 (15.6%) and all patients had axillary dissection at the same operation, those patients had T2 tumor size, high grade with lymphovascular invasion. In this respect, Krag *et al.*[5] reported sensitivity, accuracy, negative predictive value of SLNs to predict ALN status was 88.6%, 96.8%, 95.7%. Mikhitarian *et al.*[20,21] reported sensitivity, accuracy, negative predictive value, false negative rate, specificity and positive predictive values of pathological analysis of SLNB to predict ALNs pathological status were 84.1%, 94.7%, 92.6%, 15.9%, 100%, 100%[21.22].

The incidence of local-regional recurrence after breast conserving therapy for Stage 1 and 11 patients ranged between 5% and 22%[10]. Local recurrence rate in this study was 3 (3.3%) treated by mastectomy. Recurrence was within 1-3 years due to either failure to take radiotherapy or recurrence within the same quadrant but not directly at the site of initial carcinoma (multifocal ductal carcinoma in situ). No axillary recurrence is reported in our study. The reported axillary recurrence rate in literature is 0.25%[13].

There were 2 patients (2.2%) who had small areas of skin necrosis following methylene blue injection and were treated conservatively. No allergic reaction was reported in our patients. However, a review of the literature reveals that up to 2% of patients experience allergic reactions to

isosulfan blue. These reactions can vary from mild skin reactions to anaphylactic shock[23,24].

Conclusion

The sentinel lymph node biopsy has replaced routine axillary lymph node dissection as the new standard of care in early breast cancer. The technique represents a minimally invasive, highly accurate method for axillary staging, which could spare approximately 65-70% of patients to unnecessary axillary dissection and its related morbidity. Methylene blue is as effective as Lymphazurin-dye in the detection of SLN in patients with early breast cancer.

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الغدة الليفاوية الحارسة في سرطان الثدي المبكر

عدنان عبدالمعطي مرداد، و فاطمة خنيفس عوض الله الثبيتي

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جدة – المملكة العربية السعودية

المستخلص. بمراجعة ٩٠ مريضة بسرطان الثدي المبكر يخضعون لفحص عينة العقدة الليمفاوية الحارسة بقسم الجراحة بجامعة الملك عبدالعزيز ومستشفى بخش خلال شهر ديسمبر (٢٠٠٠– ٢٠٠٦). الهدف من الدراسة هو تحديد ملائمة ودقة وأسلوب فحص الغدة اللمفاوية الحارسة لعلاج مرضى سرطان الثدي المبكر. وتم تحديد الغدة الليفاوية الحارسة باستخدام الصبغة الزرقاء والمادة النووية في ١٢ (١٣,٣٪) والصبغة الزرقاء في ٢٥ (٢٧,٨٪) ومثيلين أزرق في ٥٣ (٥٨,٩٪). وتحديد معدلات العقدة الليمفاوية الحارسة يتراوح من ٩٥,٦–٩٨,٩٪. في الدراسة ٥٧ مريض بالمرحلة الأولى ٦٣,٣٪ من سرطان الثدي. ٦٠ (٦٦,٧٪) تلقوا استئصال الورم مع علاج إشعاعي بينما تم إزالة الثدي لـــ ٣٠ مريضة أي ٣٣,٣٪. وقسم التبريد لعينة الغدة الليفاوية الحارسة من حيث الدقة، والحساسية، والتحديد، وقيم افتراضية موجبة وسالبة كانت ٩٦,٨٪، و٨٤,٤٪، و١٠٠٪، و١٠٠٪، و٩٧,٩٧٪. ومعدل رجوع الورم موضعيًا كان ٣ (٣,٣٪). الغدة الليفاوية الحارسة دقيقة وعالية التقنية في التنبؤ بوضع الغدد الليمفاوية ونسبتها. والمثيلين الأزرق كالصبغة الزرقاء في تحري الغدة الليفاوية الحارسة في مرضى سرطان الثدي المبكر.