

SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER BY USING ISOSULFAN BLUE

Lubna Mushtaque Vohra¹, Ayaz Ahmed Memon², Tanvir Khaliq³, Ahmer Adnan Lehri⁴

ABSTRACT

Objective: To determine the sensitivity of sentinel node involvement by breast cancer in case of clinically axillary lymph node negative breast cancer.

Methodology: The study was conducted at Pakistan Institute of Medical Sciences, Islamabad in department of general surgery ward 5 from March 2006 to July 2007. Thirty patients with tumor size of either T1 or T2 and clinically negative axillary lymph node were enrolled in this study. These patients were subjected to sentinel lymph node biopsy by blue dye injected in peri-tumor parenchyma then dissection was done to localize sentinel node followed by formal axillary dissection (level II). The histopathology of sentinel node was compared with axillary lymph node.

Results: Sentinel lymph node was successfully localized in all 30 patients (100%). The sensitivity, specificity, accuracy and false negative rate were 92.8%, 100%, 96.7%, 5.9% respectively. The axilla was metastatic in 14 cases (46.7%), one had negative sentinel lymph node but positive non sentinel lymph node (false negative), and four had sentinel lymph node metastasis alone.

Conclusion: Sentinel lymph node biopsy by using blue dye have a high diagnostic accuracy and prevent unnecessary dissection of axilla in majority of patients with early node negative breast carcinoma.

KEY WORDS: Breast Cancer, Sentinel lymph node, Sensitivity.

Pak J Med Sci October - Decmber 2009 (Part-I) Vol. 25 No. 5 786-790

How to cite this article:

Vohra LM, Memon AA, Khaliq T, Lehri AA. Sentinel lymph node biopsy in breast cancer by using isosulfan blue. Pak J Med Sci 2009;25(5):786-790.

1. Dr. Lubna Mushtaque Vohra, MCPS, FCPS
Medical Officer,
PIMS Islamabad
2. Dr. Ayaz Ahmed Memon, MCPS, FCPS
P.G Trainee, PIMS Islamabad
3. Dr. Tanvir Khaliq, FCPS, FRCS
Associate Professor,
PIMS Islamabad
4. Ahmer Adnan Lehri, MBBS
House Officer

Correspondence

Dr. Lubna Mushtaque Vohra,
R-167, Sector-10,
North Karachi,
Karachi - 758750, Pakistan.

Email: lubnamushtaque@hotmail.com

- * Received for Publication: October 28, 2008
- * Revision Received: July 4, 2009
- * Revision Accepted: July 21, 2009

INTRODUCTION

Breast tissue in females is under the influence of various hormones and subjected to constant physiological changes throughout reproductive life and beyond. These changes lead to number of pathological conditions both benign and malignant. Carcinoma breast is the most frequently encountered cancer among the women and a most frequently diagnosed carcinoma in Pakistani female, making second to lung cancer as a cause for cancer mortality.¹

In the year 2005, breast carcinoma caused 502,000 deaths (7% of cancer deaths, almost 1% of all deaths) world wide.² However in 2007, breast cancer is expected to cause 40,910 deaths

(7% of cancer deaths, 2% of all deaths) in United States.³ That shows number of cases have increased significantly since 1970s, a phenomenon partly blamed on modern life style in the western world. Lifetime risk of death from breast cancer is the 2nd highest following lung cancer; it is 1 in every 30 women or 3.3%.⁴

Because of high frequency of disease and the esthetic and symbolic value invested in the breast, breast carcinoma has always been a source of severe distress to patients and their families. So, for the same reasons, research in this field has been increased dramatically during the last two decades, resulting in extraordinary progress in understanding of the disease and in new, more effective and less toxic treatment.

Axillary nodal status is the significant prognostic pathologic variable in patients with early invasive breast carcinoma, a powerful predictor of recurrence and survival.⁵ Studies have showed that 30-40% of patients with breast cancer have axillary nodal involvement at the time of diagnosis.⁶

Over the past few decades breast cancer surgery has undergone significant changes, but the aim of surgical therapy of breast cancer is loco-regional tumor control. As such axillary dissection is currently an important part of breast surgery.⁷ However axillary lymph node dissection associated morbidity is well recognized i.e. wound infection, seroma, arm weakness, restriction in shoulder mobility, neurological complication and most important permanent lymphoedema which are seen in 7-37% women undergoing axillary lymph node dissection. These sequelae are a major cause of emotional distress, functional impairment and additional cost of treatment.^{8,9} This is particularly significant in 60-70% of patients who receive adjuvant therapy despite negative axillary lymph nodes, entirely on the basis of tumor characteristic. Therefore, newer methods that could replace axillary dissection are currently under investigation. Sentinel lymph node biopsy emerged as standard practice for assessing axillary lymph node status, with evident benefit of reduction of morbidity associated with complete axillary

lymph node dissection a minimally invasive procedure. Sentinel lymph node biopsy is now considered as the procedure of choice in the management of early breast carcinoma.^{10,11} Sentinel lymph node can be identified by either blue dye alone or radiocolloid alone or combination of both. The clear advantage of blue dye over radio colloid is that it is economical as it does not require sophisticated instruments. The studies found no difference in sentinel node localization with either blue dye or radioisotope, as localization can fail with radioisotope technique alone as sentinel node localization with blue dye only can be from 83-100%.¹²⁻²⁰

The aim of the study was to assess the sensitivity and specificity of sentinel lymph node in predicting the axillary lymph node status of patients with early invasive breast carcinoma by using blue dye only.

METHODOLOGY

Study was conducted at Pakistan Institute of Medical Sciences in department of general surgery ward 5. The duration of study was from March 2006 to July 2007. After taking informed consent only thirty patients with T1 and T2 size and clinically node negative breast carcinoma proven by triple assessment (combination of clinical assessment, radiological imaging and a tissue diagnosis) were included in the study with Non-probability convenience sampling as because of lack of awareness usually patients presents with T3 or T4 size in government setups like PIMS. Data were analyzed by SPSS version 10.

With histological proven diagnosis patients were prepared for sentinel lymph node biopsy and modified radical mastectomy. For localizing sentinel node only blue dye was used as the study was conducted in government hospital setup where cost of every procedure is dependent on our health budget which is 0.6% of total budget at the time. In these circumstances it is essential that diagnostic and therapeutic research be directed towards solving this problem in a cost effective way to avoid the morbidity of modified radical mastectomy without compromising the outcome. On the day of sur-

gery after giving anesthesia, 3-5ml of 1% Isosulfan blue dye was injected in peri-tumor area and after 10 minutes dissection was done in axilla for localization of sentinel lymph node by given incision under the axillary hair line that incorporates the incision of Modified Radical Mastectomy lymph node that turned blue was dissected out meanwhile modified radical mastectomy was done. The excised sentinel lymph node and level II axillary lymph node were processed for histology. The identification rate of sentinel lymph node by using blue dye only and the sensitivity, specificity and accuracy of sentinel lymph node to predict axillary status were calculated. (Table-I)

RESULTS

Age distribution showed that the age range of patients was 28-75 years with a mean age of \pm SD 46 ± 13 years. Most of the patients were in 31-40 years age group. The primary tumor was located in upper outer quadrant in 15 patients (50%) of cases while in upper inner, lower inner and lower outer quadrant distribution was 16.7% i.e. five in each quadrant. Right side of breast was involved in 60% i.e. Eighteen of 30 cases while left side in 40%, 7% had T1 tumor (<2-5cm in size) while 93% (28) of patients had T2 tumor (two-5cm in size). Histopathology of breast tissue showed infiltrating ductal carcinoma in 86% (26/30) of cases while lobular carcinoma, metaplastic carcinoma, papillary car-

cinoma, mixed infiltrating ductal and lobular carcinoma accounts for 3% each. Localization rate with blue dye was 100%.

The axilla was metastatic in 14 cases (46.7%), One had negative sentinel lymph node but positive non sentinel lymph node (false negative), and four had sentinel lymph node metastasis alone.

DISCUSSION

Sentinel node identification and accuracy increases with the surgeon's experience. The sensitivity, specificity, accuracy and false negative rate in different studies range from 83-100%, 100%, 92-100%, 0-16% respectively.¹²⁻¹⁵ Our results are comparable to these studies.

In the current study, sentinel lymph node mapping was done with blue dye alone showed high identification rate (100%). Previous papers have reported a sentinel lymph node identification rate between 83-100% by blue dye alone.¹²⁻¹⁸ The clear advantage of blue dye method in non affording presenting population in Pakistan was its economical cost^{19,20} and it did not require sophisticated equipment.

Considering that 50% of our population is female and carcinoma breast continues to be a heavy financial burden on our health infrastructure so it is essential that research should be directed to solve this serious health problem in cost effective way. Hasnain et al¹⁶ found no difference in sentinel node localization with either blue dye or radioisotope, as localization can be failed with radioisotope technique alone. Yong et al¹² reported localization rate 86%. He concluded that insufficient training was one of the cause as six surgeons were involved in their study and not all started doing sentinel lymph node biopsy at the same time, the medial location of the tumor was also the factor for failed localization.

While in ALAMNAC trial the factor identified to be the cause of failed localization with blue dye alone was high body mass index >30, as in obese person higher fat content in subcutaneous and axillary tissue

Table I: The values of test and disease positive (n=30)

	<i>Histopathology Positive</i>	<i>Histopathology Negative</i>	
Sentinel + lymph node	13	0	13
Sentinel - lymph node	1	16	17
	14	16	30
Sensitivity:	$13/14 \times 100 = 92.8\%$		
Specificity:	$16/16 \times 100 = 100\%$		
PPV:	$13/13 \times 100 = 100\%$		
NPV:	$16/17 \times 100 = 94.2\%$		
Accuracy:	$29/30 \times 100 = 96.7\%$		

made it difficult to localize blue node. He also concluded that the only surgeon's first case within the series had the high rate of failed localization.¹⁴

Chagpar et al²¹ in a recent large study concluded that tumor size more than 5cm, multifocality, grade III tumor, injection technique with blue dye and surgeon experience of fewer than 10 sentinel lymph node biopsies were a significant independent predictor of failed localization.

In this study, axilla was metastatic in (46%) i.e. 14/30 patients. Of these 14 patients with lymphatic metastasis four had sentinel lymph node metastasis alone (30.8%) while nine had both sentinel lymph node metastasis and one (false negative) had negative sentinel node but positive non sentinel lymph node. While the sentinel node and axilla, both were negative for metastasis in 53.3% (16/30). The metastasis in sentinel lymph node reported in literature is from 28-43% in T1-T2 tumor stage. Keludi et al¹ reported it 37.3% in T1 and T2 tumor. Curleyik et al¹³ reported 28.2% rate of metastasis in T1 stage.

Martin et al²² reported false negative rate of 7.9%. Independently associated risk factors of false negative rate were, tumor size <2.5cm, upper outer quadrant location, removal of single sentinel lymph node, previous excisional biopsy, presence of a single positive axillary lymph nodes, and use of immunohistochemistry. ALAMNAC validation phase showed that false negative rate can be reduced from 10%-1% by searching for >1 SLN as in multiple sentinel lymph node removal false negative rate was reduced to 1% in their trial.¹⁴ It is generally accepted that the false negative rate should be 5% or less when a surgeon experienced in technique performed. Soni et al¹⁰ concluded in his study that there is no single factor either related to patient or technique which can predict false negative rate. The only factor report definite correlation is experience of surgeon; accuracy is high in experienced hands. In current study the only patient which account for false negative rate was the first case in the

study and may be the technique in that case was the cause.

Gunay et al¹³ reported the rate of negative sentinel node and axilla in 70% of cases in T1 tumor, while Zaman et al¹⁵ also reported 70%, while in Kebudi et al¹ study it was 62%. However in our study it was 53.3% as 93% of patients had T2 tumor. It was reported that increasing tumor size increased the chances of node positivity for metastasis.

There are few areas in sentinel lymph node biopsy that still need to be addressed which include ideal number of sentinel lymph node removed, impact of missed involved axillary nodes and clinical effect of sentinel lymph nodes at extra axillary sites, of micrometastasis and isolated tumor cells in sentinel lymph nodes and survival.

CONCLUSION

Sentinel lymph node biopsy by using blue dye only is a new and cost effective technique with potential diagnostic value. Sentinel node biopsy has a valid role in staging of axilla and it offers minimal morbidity. Better results can be achieved after the initial learning curve of surgeon.

Limitations of study:

Sample Size: Only 30 Patients were included in the study .Due to lack of awareness most patient usually presents in T3 or T4 size, and only a small number of patients present with early breast cancer.

Localizing Technique: Only blue dye was used to localize the sentinel node as the study was conducted in a government hospital setup which are always faced with financial constraints. In these circumstances it is essential that diagnostic and therapeutic research be directed towards solving this problem in a cost effective way to avoid the morbidity of modified radical mastectomy without compromising the outcome. As such our study confirm that blue dye is an sensitive and specific for sentinel node biopsy and helps in general improvement of these patients .

REFERENCES

1. Kebudi A, Isgor A, Atay M, Yetkin G, Yazici D, Yildiz A. The safety and accuracy of sentinel-node biopsy in early-stage invasive breast cancer – Turkish experience. *J Invest Surg* 2005;18:129-34.
2. WHO Fact sheet No.297: Cancer [online] 2006 [cited 2007 Mar 13]. Available from: URL: <http://www.who.int/mediacentre/factsheets/fs297/en/index.html>
3. American cancer society. Cancer Facts and Figures 2007 [online] 2007 [cited 2007 Apr 26]. Available from: URL: http://www.cancer.org/docroot/stt/stt_0.asp
4. Schreer I, Frischbier HJ. Breast cancers screening projects: results. In: Friedrich M, Sickles AE (edi). *Radiological diagnosis of breast diseases*. Berlin-Heidelberg: Springer 2000;333-47.
5. Vijayakumar V, Boerner PS, Jani AB, Vijayakumar S. A critical review of variables affecting the accuracy and false-negative rate of sentinel node biopsy procedures in early breast cancer. *Nucl Med Commun* 2005;26:395-405.
6. O’Hea BJ, Hill AD, El-Shirbiny AM, Yeh SD, Rosen PP, Coit DG, et al. Sentinel lymph node biopsy in breast cancer: initial experience at Memorial Sloan-Kettering Cancer Center. *J Am Coll Surg* 1998;186:423-7.
7. Spillane AJ, Sacks NP. Role of axillary surgery in early breast cancer: review of the current evidence. *Aust N Z J Surg* 2000;70:515-24.
8. Taylor KO. Morbidity associated with axillary surgery for breast cancer. *ANZ J Surg* 2004;74:314-7.
9. Ververs JM, Roumen RM, Vingerhoets AJ, Vreugdenhil G, Coebergh JW, Crommelin MA, et al. Risk, severity and predictors of physical and psychological morbidity after axillary lymph node dissection for breast cancer. *Eur J Cancer* 2001;37:991-9.
10. Soni NK, Spillane AJ. Experience of sentinel node biopsy alone in early breast cancer without further axillary dissection in patients with negative sentinel node. *ANZ J Surg* 2005;75:292-9.
11. Aarsvold JN, Alazraki NP. Update on detection of sentinel lymph nodes in patients with breast cancer. *Semin Nucl Med* 2005;35:116-28.
12. Yong WS, Wong CY, Lee JS, Soo KC, Tan PH, Goh AS. Single institution’s initial experience with sentinel lymph node biopsy in breast cancer patients. *ANZ J Surg* 2003;73:416-21.
13. Gurleyik G, Aker F, Sekmen U, Saglam A. Accuracy of sentinel lymph node biopsy for the assessment of axillary status in patients with early (T1) breast carcinoma. *J Coll Physicians Surg Pak* 2005;15:697-700.
14. Goyal A, Newcombe RG, Chhabra A, Mansel RE. ALMANAC Trialists Group. Factors affecting failed localisation and false-negative rates of sentinel node biopsy in breast cancer – results of the ALMANAC validation phase. *Breast Cancer Res Treat* 2006;99:203-8.
15. Zaman MU, Khan S, Hussain R, Ahmed MN. Sentinel lymph node scintigraphy and radioguided dissection in breast carcinoma: an initial experience at Aga Khan University Hospital. *J Pak Med Assoc* 2006;56:153-6.
16. Haider MH, Khaliq T, Ahmed N, Shah SA, Rasheed R, Fatima S, et al. Sentinel node localization in breast carcinoma. *J Coll Physicians Surg Pak* 2005;15:215-7.
17. Hung WK, Chan CM, Ying M, Chong SF, Mak KL, Yip AW. Randomized clinical trial comparing blue dye with combined dye and isotope for sentinel lymph node biopsy in breast cancer. *Br J Surg* 2005;92:1494-7.
18. Kanwal S, Hussain R. Sentinel lymph node biopsy in early carcinoma breast with blue dye. *J Coll Physicians Surg Pak* 2005;15:515-6.
19. Khan SM, Khan AS, Khan KM, Khan M, Jan WA. Sentinel node biopsy in the management of axillary involvement in breast cancer. *J Postgrad Med Inst* 2005;19:204-7.
20. Hameed S, Hussain A, Riaz S. Sentinel lymph node: lymphatic mapping in patients with breast carcinoma. *Professional Med J* 2007;14:648-52.
21. Chagpar AB, Martin RC, Scoggins CR, Carlson DJ, Laidley AL, El-Eid SE. Factors predicting failure to identify a sentinel lymph node in breast cancer. *Surgery* 2005;138:56-63.
22. Martin RC, Chagpar A, Scoggins CR, Edwards MJ, Hagendoorn L, Stromberg AJ, et al. University of Louisville Breast Cancer Sentinel Lymph Node Study. Clinicopathologic factors associated with false-negative sentinel lymph-node biopsy in breast cancer. *Ann Surg* 2005;241:1005-12.