Evaluation of the gamma probe guided sentinel lymph node biopsy and the blue dye technique in the management of breast cancer

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Keywords:
– Breast carcinoma
– Sentinel lymph node
– Lymphoscintigraphy
– ^{99m}Tc-nanocolloid
– The dye technique

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Received:
16 December 2009
Accepted revised:
8 March 2009

Abstract

The aim of this study was to evaluate the efficacy of lymphoscintigraphy, gamma probe guided sentinel lymph node biopsy (GP-SLNB) in the management of breast cancer and study the follow-up results. *Fifty two patients* (mean age 47.28±9.7; range 23-69yr) with operable breast carcinoma and clinically negative axilla were studied. Scintigraphy for the detection of SLN was performed 2-4h before surgery by injecting technetium-99m labeled nanocolloid intradermally in the peritumoral region. First lymph node (LN) to appear on the scan was labeled as SLN and by using the GP was marked on the skin. Blue dye was also injected in all patients intraoperatively and hot and/or blue LN were studied in the axilla using the GP. *The SLN was identified* in 50 patients (96% success rate) while in 2 patients SLN was not visualized on imaging. The blue dye successfully localized SLN in 45/52 (87%) of the cases. Of the 52 patients, 16 had axillary lymph node dissection (ALND), including 14 SLNB positive for lymph node metastases cases and the two cases in which no SLN was imaged. In the remaining 36/52 cases SLN were negative for metastases and patients on the follow-up remained disease free (NPV 100% for a follow-up period of 12-36 months). The success rate, sensitivity, negative predictive value, and accuracy were 96%, 93%, 100%, and 98% using the GP-SLNB, 87%, 80%, 100%, and 93% using blue dye, and 98%, 100%, 100%, and 98% using combined methods, respectively. *In conclusion,* lymphoscintigraphy, GP-SLNB has a higher success rate and sensitivity versus the dye technique and when combined with the blue dye technique its sensitivity increases to 100%. We found a high negative predictive value for SLNB and the recurrence rate in these negative SLNB was comparable to the ALND.

Hell J Nucl Med 2010; 13(1): 30-34 • Published on line: 10 April 2010

Introduction

Sentinel lymph node biopsy (SLNB) is often used for diagnostic purposes in breast cancer patients and has been accepted by a consensus conference in 2001 as a routine test before axillary lymph node dissection (ALND) in clinically negative lymph node breast cancer patients [1-3]. The development and refinement of SLNB has decreased the morbidity of surgical treatment since fewer nodes are removed, especially of axillary nodes. Axillary dissection could then be reserved for patients with positive findings of malignancy in the SLN or in whom the SLN could not be localized. Multisectioning instead of limited sectioning of nodes and the use of immunohistochemical staining have also increased the sensitivity of diagnosing micrometastases [2].

The possibility of having axillary nodal metastases in early breast cancers (T1a-b, tumor size less than or equal to 1cm) is about 20%-30% and rises to 30%-40% for T1c lesions (size 1-2cm) [2]. By SLNB, up to 70% of patients with clinically N0 disease were found to be free from metastatic disease [4].

The SLNB is highly reproducible, accurate and associates with less morbidity as compared to ALND [5-9]. Sentinel node can be identified in 80% to 100% of the patients. Reported false-negative rates vary considerably and range from 1% to 10% [9, 10]. The aim of this study was to evaluate the suitability and efficacy of SLNB using imaging and gamma probe and the blue dye technique for surgical planning of breast cancer and to report the outcome data on short term follow-up.

Patients and methods

Fifty two consecutive patients with early invasive breast cancer (mean age, 47.28yr; median age 47yr; age range, 23-69yr) and clinical staging T1-T3, N0, M0 were studied between Sep-

tember 2005 and December 2007. Patients with clinical evidence of axillary metastases, previous axillary lymphadenectomy, locally advanced disease, treatment with chemotherapy or radiotherapy prior to breast surgery and pregnant or lactating women were excluded. Routine informed consent was obtained for all patients after the procedure was explained to them. The study protocol was approved by our hospital research and ethical committee.

Lymphoscintigraphy (LS)

Thirty seven MBq of technetium-99m nanocolloid (^{99m}Tc-NC) was divided in 4 aliquots of 0.3-0.5mL, that were intra-dermally injected, either in the peritumoral region of each palpable tumor, or above and below the scar in case the patient had an excision biopsy. Patients were imaged using a dual-head gamma camera with a low-energy, high-resolution, parallel-hole collimator. Dynamic images (128x128 matrix) of 1min per frame for 30min were obtained in the anterior projection followed by static anterior and lateral images of 3min each. The patient's ipsilateral arm was raised above the head. Transmission images using a cobalt-67 flood source was used to outline the body contour. The dynamic images were reframed to 3min per frame, for review.

Gamma probe (GP)

The gamma rays detecting probe (GP) was a Scinti-Probe MR 100, from Pol.hi.tech. Carsoli; Italy (Fig. 1). Radioactivity detected by this probe was transduced into digital readout and acoustic signals. The intensity and frequency of the acoustic signal was directly proportional to the level of radioactivity. This probe was used both in the imaging room and preoperatively in the operating theater to confirm the skin projection of SLN seen on scintigraphy.

Lymphatic mapping with isosulfan blue

The isosulfan blue vital dye in a dose of 2-5mL was injected in the subareolar region, outside the areolar border using a 25-gauge needle, 10-15min before surgery. A gentle massage followed for 5min at the site of the injection.

Lymph node biopsy

During surgery, the GP with an audible guidance system was used to confirm the location of the SLN. The skin was incised directly over this point, and the node emitting the highest activity was excised. Sometimes two or more nodes where picked up by the GP. In such cases, those nodes with counts 10 times more than the background were removed, irrespective of the status of the blue dye. Once removed however, each node was rechecked by the probe and the node with the highest radioactivity was labeled as the SLN. For each serially numbered SLN and non SLN, a notation indicated whether it was blue dye positive, radiocolloid positive, or both.

Histopathology examination

All nodes removed from the axilla were histologically examined using a standard technique. Briefly, the nodes were freed from fat tissue and those with greatest diameter >0.5cm were bisected longitudinally, whereas those with a diameter of <0.5cm were embedded as such in the fixing fluid. Three different sections were obtained, 0.3-1mm apart and stained with hematoxylin and eosin. All SLN, along with other axillary lymph nodes, obtained on ALND underwent frozen sectioning, hematoxylin and eosin staining for gross metastases, and if negative, immunohistology (cytokeratin) staining, for the detection of micrometastases (Fig. 2A, B and 3A, B).

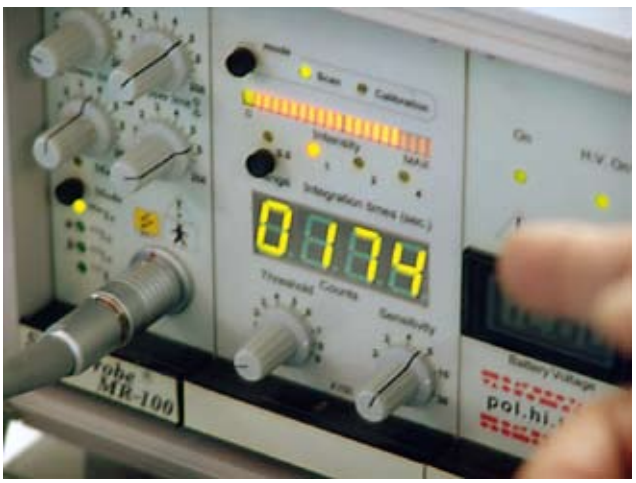

Figure 1. Gamma ray detecting probe showing the digital output and acoustic signal.

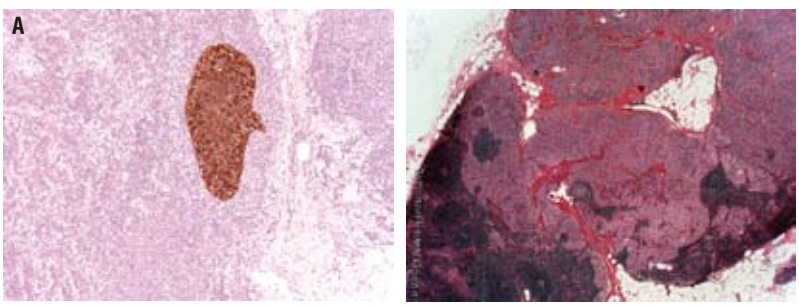

Figure 2. (A) Slides showing macro-metastases H&E stain. (B) Histopathology slides showing micro-metastases with pan cytokeratin (CK) positive immunostain.

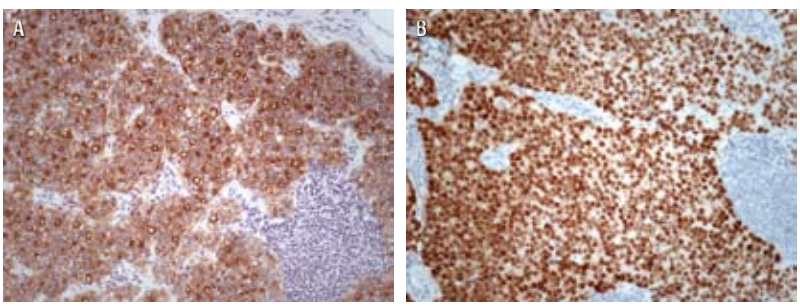

Figure 3. Histopathology slides (a) lymph nodes metastases with cytokeratin positive (b) lymph nodes metastases with ER positive immunostain.

Results

One or more SLN were identified on imaging in 50/52 patients (96.2% success rate) while in 2 patient SLN were not visualized. In 36/50 cases only 1 SLN was visualized, in 8 cases 2 and in the remaining 6 cases, 3 SLN were seen on imaging. All SLN were in the ipsilateral axilla. When lymphoscintigraphy (LS) revealed more than one node, the first node to become active always showed the highest uptake in the early and delayed images and was regarded, on the basis of imaging, as the SLN (Fig. 4). Of the 50 gamma probe localized SLN 14 were found by biopsy positive for metastases. One out of two failure cases of GP localization was also positive for lymph node metastases (sensitivity 93% (14/15) (Table 1). In 8/14 the SLN was the only metastatic node. In one case micrometastases were only detected by immunohistochemistry. In the remaining 36/50 cases, SLN biopsy was negative for metastases. All these 36 cases remained free of disease in the follow-up period of 12-36 months (negative predictive value of 100%). Standard follow-up procedure included clinical examination plus mammography and breast ultrasound.

Blue dye successfully localized the SLN in 45/52 cases and was positive in one out of two cases which were negative with GP localization. Out of 45/52 cases 12 were positive for metastases and the remaining 33 were negative on SLN biopsy (Table 2). Three of the 7 blue dye failure cases had positive lymph node metastases (sensitivity 80%) (12/15).

Axillary lymph node dissection with quadrantectomy or modified radical mastectomy was performed as a secondary procedure in all positive SLN biopsy cases and in the case in which both techniques failed to identify any SLN. In the remaining 36/52 patients with negative SLNB, ALND was not done and the patients were followed for a period of 12-36 months. Invasive ductal carcinoma was the commonest pathology and was found in 39 patients. The type of carcinoma, tumor size and tumor location are presented in Table 3.

Table 1. *Comparison of success rate, sensitivity, negative predictive value (NPV) and accuracy*

Method	Success rate	Sensitivity	NPV	Accuracy
Lymphoscintigraphy (LS) and GP	96% (50/52)	93% 14/15)	100% (36/36)	98% (50/51)
Blue dye	87% (45/52)	80% (12/15)	100% (33/33)	93% (45/48)
LS + blue dye	98% (51/52)	100% (15/15)	100% (37/37)	98% (51/52)

Gold standard: Histopathological examination and follow-up

Table 2. *Lymphoscintigraphy, blue dye and histopathology findings*

Characteristics	No of patients (%)
SLN detected on lymphoscintigraphy	50/52
SLN positive for metastases	14
SLN negative for metastases	36
SLN detected on blue dye	45/52
SLN positive for metastases	12
SLN negative for metastases	33

Table 3. *Patients characteristics and histopathology findings*

Characteristics	
Median age (range)	47.28±9.7; range 23-69yr
Tumor size in cm	Number of Patients %
<1.0	8
1.1-1.5	14
1.6-2.0	18
>2.0	12
Histological types	
Ductal infiltrating	39 (75)
Lobular infiltrating	6
Medullary carcinoma	4
Invasive mucinous carcinoma	3
Site	
Right breast	24
Left breast	28
UOQ	34
UIQ	12
LOQ	3
LIQ	1
central	2
Grade	
I	16
II	28
III	8

Discussion

In our study, SLN was successfully localized by LS and GP in 50 patients. The technique failed in 2 cases, in 1 of which, blue dye revealed a node which showed metastases on histological examination. According to the literature, false negative results are found when SLN are heavily embedded with metastases or when there is a technique failure due to the relatively large size of nanocolloid particles, clumping, and failure to enter into the lymphatic channels. We have used the multiple subdermal peritumoral injections of the radioactive tracer advocated by Veronesi et al. (2006) [4], who reported a SLN identification rate of 98.2% and a false negative rate of 4.7%.

The number of patients in whom gamma probe successfully identified SLN in our

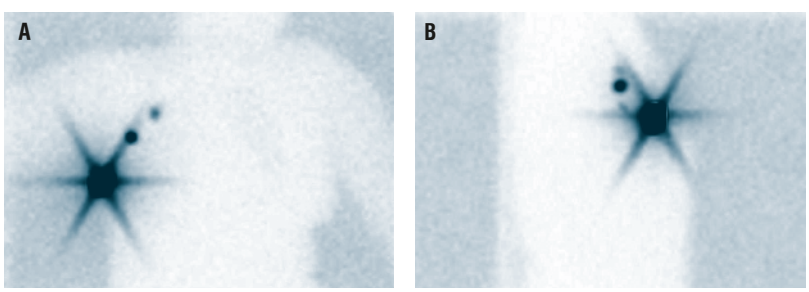

Figure 4. Technetium-99m-nanocolloid scintigraphy. (A) Anterior view (B) Right lateral view.

study, was comparable with that of most published studies [5, 11]. There is evidence to suggest that patients who previously had an excisional biopsy, those who have clinically palpable lymph nodes, and those who have received neoadjuvant chemotherapy are all more likely to have false negative results on SLNB [12, 13]. All these factors appear to disrupt the normal function of the lymphatic system and the uptake of the dye or of the radiopharmaceutical. Therefore we excluded from this study patients who had excisional biopsy with neoadjuvant chemotherapy. It is also unlikely that SLNB is appropriate for patients who have large tumors. All the above should be considered by clinicians before recommending SLNB.

In our patients, blue dye successfully localized SLN in 45 cases (87%) as compared to 50 (96%) cases with LS. Others reported a mean success rate with the blue dye of only 81% and a false negative rate of 9% for identifying SLN [14]. The greatest proportion of successful mapping and the lowest false negative rates were associated with studies in which both blue dye and radiolabeled colloid were used [15]. Our results with this combined technique show that while the success rate for the blue dye and the radiopharmaceutical was 87% and 96% respectively, the overall success rate was 98%, suggesting that the use of the combined technique results in a much higher rate. In addition, research has shown that for less experienced surgeons, a combination of radiolabeled colloid, LS, and blue dye afford the highest accuracy rate with the lowest false-negative results [16, 17].

It has been reported that the incidence of recurrent axillary lymph node metastases after negative findings on SLNB is comparable to that following ALND [18, 19]. Current practice at major cancer centers in the United States and Europe is to perform SLNB initially and to reserve completion ALND only for patients in whom the findings of SLNB indicate axillary metastases [20]. Recent studies showed that, among patients with a positive SLN, 48% had additional nodal disease on ALND [2]. We followed the standard practice of performing an axillary clearance when a SLN could not be located by either technique or in all cases with positive SLNB [20]. In our study, ALND was not done in 36/52 patients with no evidence of metastatic disease in the SLNB. All these 36 patients remained disease free for the follow-up period (NPV of 100%, taking follow up period as a gold standard). Although this follow-up period appears to be relatively short (12-36 months), it is pertinent to note that according to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 study the majority of axillary relapses in patients treated without axillary dissection occurred within the first 2 years [21]. Various studies reported axillary recurrence rates after a negative SLNB in breast cancer patients ranging from 0% to 1% (median 0.6) [22-24]. The very low rate of axillary recurrence in all these studies, in conjunction with our own results, supports the idea that GP-SLNB without ALND can be safely offered to SLN-negative breast cancer patients.

The GP-SLNB procedure is very much a skilled team effort of surgeons, pathologists, radiologists, nuclear medicine physicians, clinicians, nursing and the pharmacy personnel in order to produce fewer false negative and more true positive findings of SLN identification.

In conclusion, according to our findings, GP-SLNB was characterized by a high success rate and accuracy and recurrence rates of SLNB were comparable to those of ALND but with relatively fewer complications. The GP-SLN in conjunction with the blue dye technique had the highest sensitivity and very low false negative results. Further studies with longer follow-up periods will assess the recurrence rate after the GP SLNB.

Bibliography

1. Schwartz GF, Veronesi U, Clough KB et al. Consensus Conference Committee. Consensus conference on breast conservation, Milan, Italy, April 28-May 1, 2005. *Breast J* 2006; 12: 398-407.
2. Lyman GH, Giuliano AE, Somerfield MR et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol* 2005; 23: 7703-7720.
3. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer* 2006, 106: 4-16.
4. Veronesi U, Paganelli G, Viale G et al. Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. *Lancet Oncol* 2006; 7: 983-990.
5. Veronesi U, Paganelli G, Viale G et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 2003; 349: 546-553.
6. Rodier JF, Velten M, Wilt M et al. Prospective multicentric randomized study comparing periareolar and peritumoral injection of radiotracer and blue dye for the detection of sentinel lymph node in breast sparing procedures: FRANSENODE trial. *J Clin Oncol* 2007; 25(24): 3664-3669.
7. Canavese G, Catturich A, Vecchio C et al. Sentinel node biopsy compared with complete axillary dissection for staging early breast cancer with clinically negative lymph nodes: results of randomized trial. *Ann Oncol* 2009; 20: 1001-1007.
8. Veronesi U, Galimberti V, Mariani L et al. Sentinel node biopsy in breast cancer: early results in 953 patients with negative sentinel node biopsy and no axillary dissection. *Eur J Cancer* 2005; 41: 231-237.
9. Zavagno G, De Salvo GL, Scalco G et al. A randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. *Ann Surg* 2008; 247: 207-213.
10. Vijayakumar V, Boerner PS, Jani AB. 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.
11. Aarsvold JN, Alazraki NP. Update on detection of sentinel lymph nodes in patients with breast cancer. *Semin Nucl Med* 2005; 35: 116-128.
12. Ozmen V, Unal ES, Muslumanoglu ME et al. Axillary sentinel node biopsy after neoadjuvant chemotherapy. *Eur J Surg Oncol* 2010; 36: 23-29.
13. Chakera AH, Friis E, Hesse U et al. Factors of importance for scintigraphaphic non-visualization of sentinel nodes in breast cancer. *Eur J Nucl Med Mol Imaging* 2005; 32: 286-293.
14. Cody HS. Clinical aspects of sentinel lymph node biopsy. *Breast Cancer Res* 2001; 3: 104-108.
15. Albertini JJ, Lyman GH, Cox C et al. Lymphatic mapping and sentinel biopsy in the patient with breast cancer. *JAMA* 1996; 276: 1818-1822.
16. Takei H, Kurosumi M, Yoshida T et al. Current trends of sentinel

lymph node biopsy for breast cancer-a surgeon's perspective. *Breast Cancer* 2007; 14: 362-370.
17. Derossis AM, Fey J, Yeung H et al. A trend analysis of the relative value of blue dye and isotope localization in 2,000 consecutive cases of sentinel node biopsy for breast cancer. *J Am Coll Surg* 2001; 193: 473-478.
18. Sanli I, Lemaire BM, Muller AJ et al. Axillary recurrence after negative sentinel lymph node biopsy: frequency and factors influencing recurrence on the long term. *Breast* 2009; 15: 236-241.
19. Swenson KK, Mahipal A, Nissen MJ et al. Axillary disease recurrence after sentinel lymph node dissection for breast carcinoma. *Cancer* 2005; 104: 1834-1839.
20. Edge SB, Niland JC, Bookman MA et al. Emergence of sentinel node biopsy in breast cancer as standard-of-care in academic comprehensive cancer centers. *J Natl Cancer Inst* 2003; 95: 1514-1521.
21. Fisher B, Jong-Hyeon J, Anderson S et al. Twenty-five year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. *N Engl J Med* 2002; 347: 567-575.
22. Heuts EM, van der Ent FW, Hulsewé KW et al. Incidence of axillary recurrence in 344 sentinel node negative breast cancer patients after intermediate follow-up. A prospective study into the accuracy of sentinel node biopsy in breast cancer patients. *Acta Chir Belg* 2007; 107: 279-283.
23. Poletti P, Fenaroli P, Milesi A et al. Axillary recurrence in sentinel lymph node-negative breast cancer patients. *Ann Oncol* 2008; 19: 1842-1846.
24. Langer I, Marti WR, Guller U et al. A. Axillary recurrence rate in breast cancer patients with negative sentinel lymph node (SLN) or SLN micrometastases. *Ann Surg* 2005; 241: 152-158.