Croat Med J 2005;46(3):377-381

Axillary Recurrence Rate in Breast Cancer Patients with Negative Sentinel Lymph Node

Marko Snoj, Matej Bračko[1], Ivana Žagar[2]

Departments of Surgery, [1]Pathology, and [2]Nuclear Medicine, Institute of Oncology, Ljubljana, Slovenia

Aim To assess the axillary recurrence rate in operable breast cancer patients with clinically negative axilla after negative sentinel lymph node in whom axillary lymph node dissection had not been performed.

Methods Fifty consecutive female operable breast cancer patients with negative sentinel lymph node biopsy in whom axillary lymph node dissection had not been performed were included in the study and prospectively followed, with median follow-up time of 32 months (range 10-50 months). Sentinel lymph node biopsy was performed by the triple method.

Results The sentinel node identification rate was 100%. In only one of 50 patients with negative sentinel lymph node, axillary recurrence developed 26 months after surgery. This was the sole patient with sentinel lymph node biopsy after previous surgical biopsy. After treatment, all patients were alive and with no evidence of disease.

Conclusions Omitting axillary node dissection after negative sentinel node biopsy in operable breast cancer patients proved to be safe. Patients with previous open surgical biopsy should be given special attention in the follow-up.

Sentinel lymph node biopsy in breast cancer is a relatively new, minimally invasive procedure which allows precise axillary staging by surgical removal of the sentinel node, avoiding unnecessary axillary lymph node dissection when the sentinel lymph node is histologically proven not to be invaded by metastasis. In 40-60% of patients with clinically negative axillary lymph nodes, this procedure can prevent axillary lymph node dissection and avoid all related morbidity (1,2).

Axillary lymph node dissection in breast cancer has been a standard of surgical treatment from the very beginning, and axillary lymph node status, after primary tumor status (3), has been considered to be the most important independent prognostic factor for recurrence and survival (4). If sentinel lymph node biopsy is to replace the axillary lymph node dissection in breast cancer treatment, it must be as accurate in the staging of the axilla as axillary lymph node dissection.

Recent studies reported low clinical recurrence rate in the patients in whom the axillary lymph node dissection was omitted after a negative sentinel lymph node biopsy (5-9). It is well known that the majority of axillary recurrences develop in the first three years after the operation. We therefore report on a series of 50 consecutive breast cancer patients in whom the axillary node dissection was not carried out because sentinel lymph node biopsy revealed no metastatic involvement. The patients were operated on by the same surgeon. The median follow-up was 32 months (range 10-50 months). The aim of our study was to evaluate the recurrence rate, especially the axillary recurrence rate, thereby adding some new data to the future guidelines for follow-up.

Patient and Methods

Patients

From February 2000 until October 2003, a triple method sentinel lymph node biopsy was performed by a single surgeon (M.S.) in 90 consecutive female patients with invasive breast carcinoma of 0.5-3 cm in diameter and with clinically negative axilla on palpation, after a 0% false negative rate had been proven by the axillary lymph node dissection in our initial 36 patients (10). In 50 of these patients, the axillary dissection was omitted because of negative sentinel lymph node biopsy. The demographic and tumor characteristics of the patients are shown in Table 1. Before starting sentinel lymph node biopsy, all patients signed the informed consent. The study was approved by the Medical Ethics Committee at the Ljubljana Institute of Oncology.

Table 1. Demographic and tumor related factors in sentinel lymph node negative patients in whom axillary lymph node dissection was omitted

Parameter	Data
No. of patients	50
Median age (years, range)	56.5 (40-82)
Type of surgery (No. of patients):	
ablation	5
breast conservation	45
Mean (±SD)* tumor size (cm)	1.27±0.54
Median (range) tumor size (cm)	1.25 (0.5-2.5)
Histological type (No. of patients):	
ductal	45
lobular	3
other	2
Histological grade (No. of patients):†	
I	13
II	11
III	26
Previous surgical biopsy	1

*SD – standard deviation.
†Elston's modification of Scarff-Bloom-Richardson's method (11).

Lymphoscintigraphy

All patients received 0.2 mL ^{99m}Tc nanocolloid of human serum albumin (Nanocoll, Amersham-Health, Milan, Italy) with the activity of 60 MBq injected peritumorally and divided into two injections. In the cases of previous surgical biopsy, the injections were given intraparenchymally, as close to the cavity as possible.

Immediately after the injections, scintigraphic examinations were carried out: the acquisition of the first 20 frames (60 seconds/image) was followed by early 5-minute anterior and lateral view static images, using a single-head gamma camera (General Electric 400T, Horsholm, Denmark). Delayed static images (anterior, lateral, and sometimes anterior-oblique views) were obtained 2 hours post injection and were repeated after another 2-4 hours with simultaneous emission-transmission scanning using a double-head gamma camera (Elscint, Haifa, Israel) with ^{57}Co flood source. The area of maximal sentinel lymph node activity was located with a point ^{57}Co source and marked with indelible ink on the patient's skin. The patient was referred to the operating room within 24 hours after the radiotracer injection, with a hard copy of the scan and a report of the referring nuclear medicine specialist.

Surgical Technique

In the operating theatre, the patients were again injected peritumorally with 1 mL of isosulfan blue dye (Patent Blue V, Laboratoire Guerbet, Roissy, France). In the cases of previous surgical biopsy, the injection was given intraparenchymally as close to the cavity as possible.

The injection place was massaged for 5 minutes. We used an intraoperative gamma probe (Navigator GPS, Radiation Monitorig Devices Inc., Watertown, MA, USA) for the identification of a sentinel lymph node. Surgical incision was made and the sentinel lymph node was excised. The sentinel lymph node was defined as the only hot or blue node, the hot or blue node receiving afferent lymphatic from the tumor, and the hot or blue node which was the first one in sequential pattern. The *ex-vivo* 10-second count was recorded on every removed sentinel lymph node.

Pathology

Sentinel lymph nodes larger than 0.5 cm were halved, and those smaller than 0.5 cm were processed and paraffin-embedded intact. As there was no consensus among different studies as to how many step sections were needed (12) and as we participated in several clinical studies with different demands, we changed our protocol for sectioning lymph nodes twice during the period of this study. At first, only 3 levels from each block were cut. In the following period, we continued with multiple levels at 50 μm and, finally, with multiple levels at 250 μm interval through the entire block, producing a pair of sections from each level. At the first step, one section of each pair was stained by hematoxylin-eosin. If metastases were not detected at this point, the remaining sections were stained with CKMNF 116 antibody against

cytokeratin (DAKO 1:100) using TechMate stainer (DAKO, Carpinteria, CA, USA).

If the sentinel lymph node was positive, a complete axillary node dissection or irradiation of the axilla was performed. In this study, all lymph nodes containing metastatic cells were considered positive.

All patients were followed-up by clinical examination regularly at 3-month intervals in the first two years after operation and, after that, twice a year. Mammography was performed at least once a year.

Results

The identification rate in the entire series of patients was 100%, ie all 90 patients had a sentinel lymph node.

Median observation time was 32 months (range 10-50 months) in 50 sentinel lymph node negative patients. Median tumor size was 1.27 cm and, on average, 1.46 sentinel lymph nodes per patient were removed; 50 sentinel lymph nodes were hot and blue, 17 hot only, and 3 blue only. In only one patient, axillary recurrence was revealed 26 months after sentinel lymph node biopsy. This was a 47-year-old patient with a 1.7 cm large invasive ductal carcinoma revealed on open surgical biopsy. Later on, re-excision and sentinel lymph node biopsy were performed (Fig. 1A-C). After the removal of a single active and blue sentinel node, the axilla was examined for radioactivity and hard nodes. In the re-excised tissue, there was no residual tumor, and in the sentinel lymph node, no metastatic involvement was detected by hematoxylin and eosin, and immunohistochemical staining performed on the pairs of sections taken from 20 levels at 50 μm intervals. The tumor was hormonal and c-erb-2 negative. The patient received adjuvant systemic CMF therapy and radiotherapy of the breast.

Twenty-six months later, a palpable lesion of 2 cm in diameter was found in the ipsilateral axilla. The fine needle biopsy confirmed a metastasis of adenocarcinoma. The mammography was normal. There were no signs of distant recurrence. The axillary lymph node dissection was carried out and 1 out of 11 lymph nodes was positive, showing extracapsular extension. The patient received Adriamycin-based systemic therapy. Sixteen months following the therapy, the patient was asymptomatic and without clinical evidence of recurrence.

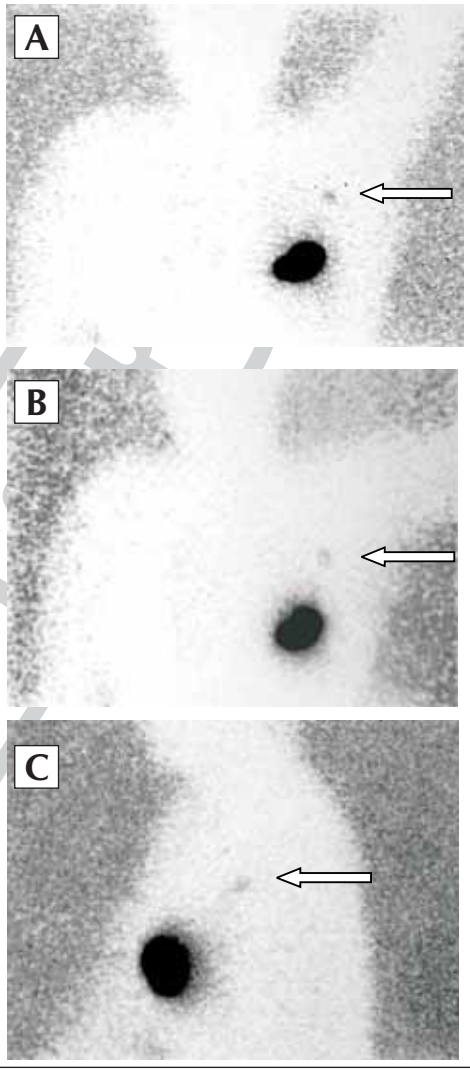

Figure 1. Breast lymphoscintigraphy in a patient in whom sentinel lymph node was negative and who later developed axillary reccurence: (**A**) anterior view, with the left arm elevated, (**B**) anterior view with the left arm abducted, and (**C**) left lateral view. Focal tracer uptake corresponding to the sentinel lymph node is visible in the left axilla (arrow).

All the other patients with sentinel lymph node negative are alive with no clinical evidence of disease.

Discussion

In our series, axillary lymph node dissection was omitted in 50 consecutive breast cancer patients with clinically negative axilla after negative sentinel lymph node biopsy. During the me-

dian follow-up of 32 months, we registered only a single axillary recurrence in the only patient with the sentinel node biopsy carried out after previous surgical biopsy. This finding suggests that such patients should be given special attention in the follow-up.

In operable breast cancer sentinel lymph node biopsy is expected to reduce the axillary lymph node dissection-related morbidity after the removal of the negative sentinel lymph node. Numerous validation studies have shown that the false negative rate is below 2% (13). In these initial studies, false negative rate was calculated on the basis of the concordance of the sentinel lymph node negativity with the subsequently performed axillary lymph node dissection results. The validation study of our own carried out at the beginning of 2000 showed a 0% false negative rate and a 100% identification rate (10). The same trend of low clinical axillary recurrence rate was expected in the results of the follow-up studies of the patients in whom the axillary lymph node dissection was omitted due to a negative sentinel lymph node. In our patient group, we found only one axillary recurrence in a patient with negative sentinel lymph node. The causes of it might be numerous.

It is well known that metastatic lymph nodes may not entrap nanocolloid because macrophages might have already been saturated by malignant cells (14). Therefore, the lymphatic drainage is transferred to another lymph node which then becomes hot and is considered as a sentinel lymph node. Hence, the palpatory exploration of the axilla attempting to find eventual hard nodes after the removal of sentinel lymph nodes is of great importance. Although it was done in our patient with initially negative sentinel lymph node, no suspicious lymph nodes were found. Another possible explanation of a false negative finding is that metastatic involvement was present in the sentinel lymph node, but was not revealed in histopathologic processing due to the large distance between two cuts, resulting in too thick slices. It has to be noted that our patient with a false negative sentinel lymph node was the only patient in our series who had undergone a previous open surgical biopsy; it is therefore possible that macrophages in the true sentinel lymph node might have been saturated by the wound healing debris.

Some studies (15,16) comparing fine needle biopsy, core biopsy, and open surgical biopsy performed prior to the sentinel lymph node biopsy did not show any difference regarding the identification rate and false negativity rate, although other studies did show reduced identification rate (17,18) and increased false negative rate (19) in the patients with previous surgical biopsy. All these studies validated the false negative rate by the concordance of the results of sentinel lymph node biopsy and subsequent axillary node dissection, and not by the axillary recurrence rate which could be presented only in the follow-up. In our validation study of 36 patients, we included two cases of sentinel lymph node biopsy performed after previous surgical biopsy and we did not find any false negative cases (10). Therefore, the patients with sentinel lymph node biopsy performed after open surgical biopsy should be given special attention in the follow-up, because so far no study data have been gathered on axillary recurrence in such patients.

It is important that the axillary recurrence rate in our patient series is comparable to historical series of axillary dissection in node-negative breast cancer patients. Recht et al (20) retrospectively analyzed the incidence of axillary recurrence rate as the first site of failure in node-negative patients after breast conservative surgery and found it to be 2.1%. The results of our study are comparable to that, showing that the sentinel lymph node biopsy procedure is as safe as the axillary node dissection.

A few recent studies have shown low axillary recurrence rate in the patients with negative sentinel lymph node in whom the axillary dissection was omitted. Guilliano et al (5) showed no axillary recurrence in 67 patients after negative sentinel lymph node, and Reitsamer et al (6) pointed out the same in 200 patients. On the contrary, Roumen et al (7), Guenther et al (8), and Chung et al (9) detected axillary recurrence in 1 patient out of 100 sentinel lymph node negative patients, in 1 out of 205 patients, and in 3 out of 206 patients, respectively. Considering the results of all the studies, the axillary recurrence rate in the sentinel lymph node negative patients is low, regardless of a wide variety of techniques used for sentinel lymph node biopsy.

The reasons for axillary lymph node dissection in operable breast cancer patients are threefold: to prevent axillary recurrence, to prognosticate, and to benefit from the improved survival rate.

At the moment, it is too early to compare the survival of the patients in whom the axillary lymph node dissection was omitted with that of the patients in whom it was performed. There is one study claiming that there is no difference (21), but the observation time was too short. The other two reasons for axillary lymph node dissection may be easily compared with the sentinel node biopsy only. Moreover, the sentinel node biopsy is associated with significantly less shoulder pain, with faster restitution of shoulder mobility, and a shorter hospitalization period (22,23).

We regard omitting the axillary lymph node dissection in the sentinel node biopsy negative breast cancer patients as safe enough to be accepted as a standard. Patients with sentinel node biopsy performed after surgical biopsy should be given special attention in the follow-up.

Acknowledgements

We acknowledge the financial support of this study by the Ministry of Education, Science, and Sport of the Republic of Slovenia, grant number L3-4278.

References

1 Lin PP, Allison DC, Wainstock J, Miller KD, Dooley WC, Friedman N, et al. Impact of axillary lymph node dissection on the therapy of breast cancer patients. J Clin Oncol. 1993;11:1536-44.

2 Ivens D, Hoe AL, Podd TJ, Hamilton CR, Taylor I, Royle GT. Assessment of morbidity from complete axillary dissection. Br J Cancer. 1992;66:136-8.

3 Goldhirsch A, Glick JH, Gelber RD, Coates AS, Senn HJ. Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. Seventh International Conference on Adjuvant Therapy of Primary Breast Cancer. J Clin Oncol. 2001;19:3817-27.

4 Mustafa IA, Cole B, Wanebo HJ, Bland KI, Chang HR. Prognostic analysis of survival in small breast cancers. J Am Coll Surg. 1998;186:562-9.

5 Giuliano AE, Haigh PI, Brennan MB, Hansen NM, Kelley MC, Ye W, et al. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. J Clin Oncol. 2000;18:2553-9.

6 Reitsamer R, Peintinger F, Prokop E, Rettenbacher L, Menzel C. 200 Sentinel lymph node biopsies without axillary lymph node dissection – no axillary recurrences after a 3-year follow-up. Br J Cancer. 2004;90:1551-4.

7 Roumen RM, Kuijt GP, Liem IH, van Beek MW. Treatment of 100 patients with sentinel node-negative breast cancer without further axillary dissection. Br J Surg. 2001;88:1639-43.

8 Guenther JM. Dye-directed sentinel node biopsy for breast cancer. Ann Surg Oncol. 2002;9:S54.

9 Chung MA, Steinhoff MM, Cady B. Clinical axillary recurrence in breast cancer patients after a negative sentinel node biopsy. Am J Surg. 2002;184:310-4.

10 Snoj M, Golouh R, Movrin-Stanovnik T, Vidergar-Kralj B. Added value of blue dye in sentinel node biopsy for breast cancer. J Exp Clin Cancer Res. 2003;22:551-5.

11 Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991;19:403-10.

12 van Diest PJ. Histopathological workup of sentinel lymph nodes: how much is enough? J Clin Pathol. 1999;52:871-3.

13 Cody HS III. Sentinel lymph node biopsy for breast cancer: does anybody not need one? Ann Surg Oncol. 2003;10:1131-2.

14 Guenther JM. Axillary dissection after unsuccessful sentinel lymphadenectomy for breast cancer. Am Surg. 1999;65:991-4.

15 Haigh PI, Hansen NM, Qi K, Giuliano AE. Biopsy method and excision volume do not affect success rate of subsequent sentinel lymph node dissection in breast cancer. Ann Surg Oncol. 2000;7:21-7.

16 Wong SL, Edwards MJ, Chao C, Tuttle TM, Noyes RD, Carlson DJ, et al. The effect of prior breast biopsy method and concurrent definitive breast procedure on success and accuracy of sentinel lymph node biopsy. Ann Surg Oncol. 2002;9:272-7.

17 Borgstein PJ, Pijpers R, Comans EF, van Diest PJ, Boom RP, Meijer S. Sentinel lymph node biopsy in breast cancer: guidelines and pitfalls of lymphoscintigraphy and gamma probe detection. J Am Coll Surg. 1998;186:275-83.

18 Layeeque R, Kepple J, Henry-Tillman RS, Adkins L, Kass R, Colvert M, et al. Intraoperative subareolar radioisotope injection for immediate sentinel lymph node biopsy. Ann Surg. 2004;239:841-5.

19 Feldman SM, Krag DN, McNally RK, Moor BB, Weaver DL, Klein P. Limitation in gamma probe localization of the sentinel node in breast cancer patients with large excisional biopsy. J Am Coll Surg. 1999;188:248-54.

20 Recht A, Pierce SM, Abner A, Vicini F, Osteen RT, Love SM, et al. Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. J Clin Oncol. 1991;9:988-96.

21 Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med. 2003;349:546-53.

22 Peintinger F, Reitsamer R, Stranzl H, Ralph G. Comparison of quality of life and arm complaints after axillary lymph node dissection vs sentinel lymph node biopsy in breast cancer patients. Br J Cancer. 2003;89:648-52.

23 Burak WE, Hollenbeck ST, Zervos EE, Hock KL, Kemp LC, Young DC. Sentinel lymph node biopsy results in less postoperative morbidity compared with axillary lymph node dissection for breast cancer. Am J Surg. 2002;183:23-7.

Received: December 23, 2004
Accepted: March 31, 2005

Correspondence to:
Ivana Žagar
Department of Nuclear Medicine
Institute of Oncology
Zaloška 2
1000 Ljubljana, Slovenia
izagar@onko-i.si