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

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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.

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 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 Monitoring 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 CKMN 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%, i.e., 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.

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-
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 three-fold: 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.

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References


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