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*ORIGINAL ARTICLE*

# Sentinel node biopsy and neoadjuvant chemotherapy in the treatment of breast cancer

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## Summary

***Purpose:*** *Sentinel lymph node biopsy (SLNB) has become a safe and accurate alternative to axillary lymph node dissection (ALND) in the surgical management of early breast cancer. The aim of this study was to determine the false negative rate of SLNB in patients with advanced breast cancer after neoadjuvant chemotherapy.*

***Methods:*** *Forty-eight patients with 49 advanced breast cancers (one patient had bilateral disease) underwent neoadjuvant chemotherapy. All of them had SLNB, followed by standard level I/II ALND. SLNs were identified in 47 out of 49 tumors (detection rate 95.9%).*

***Results:*** *Axillary nodal metastases were detected in 28 patients; SLNs were positive only in 14 patients. Four sentinel internal mammary nodes were removed in 4 patients, while one of them was positive with micrometastasis but axillary nodes were negative. False-negative results occurred in 2 (7.14%) patients. The results of our study confirm that SLNB in patients with advanced breast cancer is not significantly altered by the preoperative chemotherapy. Biopsy results were very similar to those without any neoadjuvant chemotherapy.*

***Conclusion:*** *ALND, known for its serious complications, can be replaced in some cases by SLNB.*

**Key words:** breast cancer, chemotherapy, sentinel lymph node

## Introduction

Neoadjuvant chemotherapy was introduced in 1970 to enable removal of locally advanced breast cancer and to facilitate locoregional disease control. Several concerns include progression of the tumor in size, increased morbidity and loss of staging information. Clinical trials, however, proved the above worries were irrelevant [1]. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 has shown that surgery, which followed preoperative chemotherapy, had overall survival and disease-free survival equivalent to surgery followed by adjuvant chemotherapy. However, more patients were treated with breast-conserving surgery [2]. Preoperative chemotherapy is, therefore, increasingly indicated for women with early-stage disease [3-5].

ALND is a very important part of the management of breast cancer. The tumor can be reliably staged and controlled locoregionally. ALDN can even have some curative impact on the disease. ALND is, however associated with considerable morbidity. SLNB has therefore rapidly gained popularity as an accepted alternative to ALND in early stages of breast cancer. SLNB provides an accurate prediction of the status of the axillary lymph nodes and ALND can be avoided in selected groups of patients [6-11].

Neoadjuvant chemotherapy can not only decrease the tumors in size, but it can also change positive lymph nodes to negative ones [12]. So far, only a few retrospective studies with small series of patients referring to SLNB following preoperative chemotherapy have been published. The results are conflicting. The Consensus Conference in Philadelphia has, therefore, not

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recommended the routine use of SLNB following neoadjuvant therapy [6].

The aim of this study was to assess the false negative rate of SLNB after preoperative neoadjuvant chemotherapy and to define those groups of patients in which ALND could be avoided.

## Methods

A prospective study was launched at the Atlas Hospital Zlin in 1998, to confirm the accuracy, feasibility and reliability of SLNB in all breast cancer patients. In that study, after SLNB all patients underwent mastectomy with standard ALND. The false negative rate of SLNB was 4.6%.

Based on the results of that study the routine ALND in early breast cancer with negative SLN was terminated in 2002. The present study started in 2000 after approval by the Institutional Review Board and signed patient informed consent.

A total of 48 patients, one of them with bilateral carcinoma, underwent SLNB following neoadjuvant chemotherapy. Peritumoral and subdermal injection of patent blue was applied to map lymph nodes and to facilitate SLNB. As from 2000, radiocolloid 99mTc Nanocoll, Nycomed Amersham, has been used in combination with blue dye. C-Trak, Care Wise Medical Product, Morgan Hill device with gamma probe was used to identify SLNs. Different dosage of Nanocoll was tested, ranging from 50 to 200 MBq. The number of counts in the tumors and axillary nodes was monitored. The currently used dosage of Nanocoll is 100 MBq. Half of it is injected subdermally and the other half peritumorally. We used the following 2-day protocol [13]: at about noon, the day before surgery, radiocolloid is injected. All patients have lymphoscintigraphy. Surgery was performed the next morning. The time span between the radiocolloid application and operation was about 20 h. Internal mammary nodes detected by lymphoscintigraphy and subsequently certified by the gamma probe, were removed. The breast itself was massaged for 5-10 min after the patent blue application. Blue and radioactive nodes were removed and marked as SLN. ALND followed in all patients. The SLNs were evaluated into 2, 3 or more parts of equal thickness with 2 mm interval, fixed and embedded in paraffin. Out of each block of these 2 mm sections one 3 micron histological section was cut and stained by haematoxylin & eosin (H&E). Nodes with negative findings for metastasis and/or micrometastasis were examined by serial permanent sections and immunohistochemical (IHC) anticytokeratin staining, taking 1 IHC-stained section from 2 levels 50 microns apart. IHC staining with a monoclonal antibody cocktail (AE1/AE3, DAKO) was routinely used in negative nodes after H&E survey.

Before and after chemotherapy all of the patients were examined clinically, by mammography, breast ultrasound and some of them by MRI. FNA, core-cut, or excisional biopsy were done to confirm the diagnosis. Clinically suspicious axillary nodes were examined only by ultrasound. False negative SLNs were defined as negative sentinel node(s) in patients with one or more positive non-sentinel nodes obtained after ALND.

*Neoadjuvant therapy*

SLNB was performed in 48 patients with 49 tumors from September 2000 to March 2007. Patients with tumor size > 3 cm were indicated for neoadjuvant therapy. Some of those patients with borderline tumor size (< 3 cm) refused radical surgery and were, therefore, also included in the neoadjuvant therapy group. Five patients underwent a combination of neoadjuvant chemotherapy and radiotherapy. The majority of patients were treated with 2-4 cycles of FAC (5-fluorouracil, cyclophosphamide and doxorubicin) and AC (doxorubicin and cyclophosphamide). Two patients received FEC (5-fluorouracil, cyclophosphamide, epirubicin), one epirubicin and cyclophosphamide. Chemotherapy regimes differed as patients were medically treated in various oncological centers. The mean tumor size was 45.7 mm (range 20-60) in the group of 49 tumors, while it was 24.3 mm (range 0-60) after neoadjuvant therapy. Four patients did not respond to chemotherapy at all. Complete pathological response was observed in 5 patients (10.2%). The tumor was partially decreased in the remaining patients. All patients had postoperative adjuvant chemotherapy. Patients with breast-conserving surgery had additional radiotherapy with boost to the tumor bed.

*Patient and tumor characteristics*

Forty-eight patients with 49 breast cancers underwent neoadjuvant therapy followed by SLNB and mastectomy with ALND. The mean patient age was 57.14 years (range 34-75). The diagnosis was confirmed by FNA in 13 patients, by core-biopsy in 33 patients, and by excisional biopsy in 3 patients. The size of the tumor at the time of diagnosis was T2 in 16 cases, T3 in 20 cases, T4a in 5 cases, T4b in 3 cases, and T4c in 5 cases. Twenty-three patients had clinically positive axillary nodes before any therapy but FNA biopsy was not performed. There were 41 ductal, 5 lobular, 0 medullary and 3 other types of cancer (Table 1). Thirty-three patients underwent modified radical mastectomy and 16 breast-conserving surgery. Modified radical mastectomy was performed in all patients treated by radiotherapy and preoperative chemotherapy. When a decreased size of the tumor mass following neoadjuvant therapy enabled a safe and cosmetically acceptable result, breast-conserving surgery was indicated.

## Results

The lymphatic mapping and SLNB were successfully performed in 47 tumors (95.9%) and in 48 patients. The blue dye alone was initially used in 4 patients.

A combination of blue dye and radiocolloid was used in all of the remaining patients. In 47 tumors axillary SLNs were removed and in 4 patients (8.3%) internal mammary SLNs were simultaneously dissected. Lymphatic mapping and SLNB failed in 2 patients. The combination of the blue dye and radiocolloid technique was used in both unsuccessful mappings. There were no hot spots at lymphoscintigraphy and no radiocolloid was detected in the nodes. There were no visible blue lymphatic vessels and no blue nodes. Twenty eight of the successfully mapped patients had axillary metastases. SLNs were positive in only 12 patients (42.8%). Altogether, we identified 126 axillary SLNs with a mean number of 2.6 (range 1-7) per patient. A total of 453 nodes were classified as non-SLNs, 39 axillary SLNs were positive. The mean number of axillary nodes was 12.4 (range 2-17). Micrometastasis in axillary SLNs was identified in 4 patients (out of 7 axillary SLNs). Lympho-

**Table 1.** Tumor characteristics

| *Characteristics* | *N (%)* |
|---|---|
| T stage | |
| 2 | 16 (33) |
| 3 | 20 (41) |
| 4a | 5 (10) |
| 4b | 3 (6) |
| 4c | 5 (10) |
| N stage | |
| 0 | 15 (31) |
| 1 | 18 (37) |
| 2 | 5 (10) |
| x | 11 (22) |
| Resid. tumor size (mm) | |
| 0 | 5 (10) |
| 0-20 | 7 (13) |
| 20-50 | 35 (67) |
| >50 | 5 (10) |
| pT stage | |
| 0 | 5 (10) |
| 1c | 8 (16) |
| 2 | 31 (64) |
| 3 | 5 (10) |
| pN stage | |
| 0 | 21 (43) |
| 1 | 24 (49) |
| 2 | 3 (6) |
| 3 | 1 (2) |
| pM stage | |
| 0 | 46 (100) |
| TNM stage | |
| I | 6 (12) |
| IIA | 20 (41) |
| IIB | 18 (37) |
| IIIA | 4 (8) |
| IIIC | 1 (2) |

**Table 2.** Characteristics of disease with false negative sentinel lymph nodes

| *Characteristics* | *1st patient* | *2nd patient* |
|---|---|---|
| Histology | IDCA | IDCA |
| Localization | UIQ | LOQ |
| Tumor size before NAC (mm) | 55 | 60 |
| Tumor size after NAC (mm) | 20 | 0 |
| T before NAC | 4a | 4b |
| N before NAC | 1 | 1 |
| TNM stage after NAC | IIB | IIA |
| Surgery performed | M | M |
| Axillary SLNB | 3 | 2 |
| Positive SLNB | 0 | 0 |
| Number of non SLN | 10 | 9 |
| Positive non SLN | 1 | 1 |

IDCA: intraductal invasive carcinoma, UIQ: upper inner quadrant, LOQ: lower outer quadrant, M: modified radical mastectomy, NAC: neoadjuvant chemotherapy, SLNB: sentinel lymph node biopsy, SLN: sentinel lymph node

scintigraphy confirmed internal mammary hot spot in 4 patients. They were harvested in all 4, but only 1 node was found in each of them. One patient had positive internal mammary node with micrometastasis, while her axilla was negative. Where combination of blue dye and radiocolloid method was used, the SLNs were both blue and radioactive in 87 cases (69.0%); radioactive only in 33 cases (26.2%); and blue only in 6 (4.8%) cases. Lymph nodes with metastasis were blue and radioactive in 28 cases (71.8%); radioactive only in 9 cases (23.1%); and blue only in 2 cases (5.1%). Two patients had negative SLNs and positive non-SLNs, for a false negative rate of 7.14% (Table 2). Each patient with false negative SLN had one non-SLN positive only.

## Discussion

For many decades ALND represented the gold standard of surgical treatment for patients with early-stage breast cancer; it determined the status of the regional lymph nodes and the prognosis. SLNB has rapidly become an accurate and reliable alternative to ALND in patients with clinically negative axilla [6,14]. Being a minimally invasive procedure, it replaced the more radical ALND, similarly to breast-conserving surgery replacing mastectomy in patients with early breast cancer. It is known that preoperative chemotherapy does not improve survival compared to postoperative chemotherapy. Breast-conserving surgery greatly improves the patients' quality of life. Many of them have negative axillary nodes and are still undergoing routine ALND. The number of studies and patients relating neoadjuvant therapy with consequent SLNB is small, however the results are encouraging showing that between 40-60% of patients had negative axillary lymph nodes [15-27]. In our study, 43% of the patients had negative axillary nodes and we believe that all these patients can avoid ALND.

There is limited knowledge about the impact of chemotherapy on the lymphatic draining system and whether the shrinkage and scarification of the tumor can modify the process of SLNs identification [27,28]. Many believe that the lymphatic flow can be significantly altered and damaged. If it is so, the number of SLNs, the counts and their localization should differ when compared to lymphatic mapping without preoperative chemotherapy [15]. Contrary to our expectations the number of counts was higher in SLNs with chemotherapy. We do not have any convincing explanation for the higher uptake of the radiocolloid. We performed a retrospective SLN examination and found no explanation for this higher uptake.

The rate of failed lymphatic mapping in our study was small and was not significantly changed by preop-

erative chemotherapy. Subdermal injection of radiocolloid and blue dye might play an important role in our high success rate. The changes in the tumor and surrounding tissues caused by chemotherapy are probably not expressed so much in the subdermal lymphatic vessels [26]. We had 2 failed lymphatic mappings only. One of them was with 16 positive axillary nodes. A massive engorgement of the axillary nodes by the tumor could explain the failure. Patients with such a massive tumor involvement of the axilla will surely not be suitable for SLNB.

Not only the tumor size but also lymph nodes can be downstaged by neoadjuvant therapy [11]. The most important question is: does preoperative chemotherapy have the same impact on all lymph nodes? [27-30]. One fourth of our patients had only SLNs involved, reflecting a strong feasibility of this method. All other studies presented similar results [16,22,24,29]. Micrometastasis in SLNs occurred in 5 patients, and in the internal mammary nodes in only 1 patient. Internal mammary nodes are the second regional basin of the lymph drainage from the breast. Routine dissection of internal mammary nodes has only prognostic value and does not improve survival [31,32]. The feasibility of SLNB could be validated in all our patients in all aspects. Internal mammary hot spots were seen on lymphoscintigraphy in 4 patients and each of them had one SLN removed. One node harbored micrometastasis. Despite the small number of patients with sentinel internal mammary nodes (4 patients), one was positive (25%); these SLNs were not blue and the number of the counts was the same as in internal mammary nodes without chemotherapy. Therefore, this also supports the feasibility of the method.

The usual mean number of harvested SLNs in the literature is about two [7,24]. This corresponds with our figure of 2.7. In our study, the mean number of SLNs did not differ from that without chemotherapy and confirmed that chemotherapy does not significantly alter the identification of SLNs. The localization of nodes was very similar to that of early breast cancer.

The radiocolloid technique showed to be a more sensitive method of identification than the blue dye, not only in the detection of SLNs but also in the metastatic SLNs [7]. The number of counts was not lower in tumors with chemotherapy compared with tumors without chemotherapy.

A very important attribute to lymphatic mapping is the rate of false-negative nodes. Current single-institution studies have shown variability from 0 to 33% [15-27]. Unfortunately, the reported series contained very small numbers of patients. The majority of them are retrospective and come from the learning period of the method. The highest number of false-negative figures (33%) comes from the Nason et al. study. The mapping was successful in 13 out of 15 patients. Nine of them had positive lymph nodes and 3 were false-negative [17]. Piato et al. examined 41 patients; 15 patients were axillary SLN-positive and 3 false-negative (17%), a percent that is too high. The authors therefore do not recommend SLNB after neoadjuvant chemotherapy [23]. Fernandez and colleagues compared two similar groups of patients after neoadjuvant chemotherapy and without such chemotherapy (n=40 and 36, respectively). Similarly to Piato et al., they showed a great difference in false-negative SLN identification rate between the two groups of patients. The rate SLNB performed after neoadjuvant chemotherapy and without chemotherapy was 22% and 9%, respectively. They also do not recommend the use of the procedure [19]. Contrary to Nason, Piato and Fernandez results, 5 studies, reported zero false-negative SLNs identification [15,18,21,29,30]. Conclusions and recommendations from these studies vary due to small numbers of patients. However, the majority of them identify the method as reasonably feasible and reliable. The largest retrospective study is a multicentre one by Mammounas et al, which was part of a randomized trial NSBAP B-27 and evaluated the effect of neoadjuvant chemotherapy. Because SLN was not mandated in the study, there was no predefined protocol dictating the method of lymphatic mapping or approach to SLN. The false-negative rate was 11% [27,28]. These results are comparable to those evaluating lymphatic mapping before chemotherapy [15,24,26]. The false-negative rate in our study was 7.14% and did not fundamentally differ from the SLNB trials before neoadjuvant therapy [33,34].

Numerous studies have proved that the precise evaluation of the sentinel axillary nodes before surgery is very difficult and not reliable enough. The gold standard of assessment of the status of lymph nodes remains only the histopathologic examination. Currently, SLNB following neoadjuvant chemotherapy should not be done outside of approved clinical trials. SLNB done before neoadjuvant chemotherapy is, therefore, momentarily the only way helping to spare a selective group of patients with negative axillary nodes from ALND [5,35-37]. SLNB prior to neoadjuvant chemotherapy allows staging of clinically node-negative group of patients and also avoids lymphatic scarring or uneven tumor response in the axillary nodes caused by chemotherapy. There is definitely a percentage of patients after chemotherapy with positive nodes that are downstaged to node-negative at the time of surgery. SLNB after chemotherapy would not be able to differentiate between patients who were node-negative prior to chemotherapy and those who were downstaged [35,38]. SLN identification done before neoadjuvant chemotherapy accu-

rately determines the stage of the axilla but has a number of disadvantages. The neoadjuvant chemotherapy decision is mostly based on tumor characteristics and the status of lymph nodes is minimally considered. About 30-40% of positive nodes are sterilized by preoperative chemotherapy. In this group of patients the ALND may be avoided by performing SLNB after neoadjuvant chemotherapy. According to the present protocol, all patients after neoadjuvant chemotherapy are directly indicated for ALND [5,28,29,39].

In summary, our study confirmed that the SLNB in patients with advanced breast cancer is not significantly modified by neoadjuvant chemotherapy. The results are very similar to those without preoperative chemotherapy. The method is therefore feasible, accurate and reliable and can identify a selected group of patients where ALND and its complications can be avoided.

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