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# Gamma probe sentinel node localization and biopsy in breast cancer patients treated with a neoadjuvant chemotherapy scheme

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## Summary

The aim of this study was to analyse the accuracy of scintigraphic and gamma probe sentinel node (SN) localization in breast cancer patients who have been submitted to neoadjuvant chemotherapy (NC). Seventy-six patients with single breast cancer were included in the study, and were classified into two groups. Group 1 consisted of 40 women who had received NC, and Group 2 consisted of 36 women who did not receive NC. All patients received 111 MBq (3 mCi) of $^{99}Tc^{m}$-nanocolloid in 3 ml, by peritumoural injection. Anterior and lateral thoracic scans were obtained 2 h post-injection. The following day (18–24 h post-injection) the patients underwent surgery and sentinel nodes were localized by using a gamma probe. Complete axillary lymph node dissection was performed in all patients. Histological analysis included haematoxylin–eosin in all cases and immunohistochemistry in 10 cases. In Group 1, SNs were localized in 36/40 patients, histological analysis was performed in 34 and there were four false negatives (22%). In Group 2, SNs were localized in 32/36 patients, histological analysis was performed in 29 and there were two false negatives (9%). Predictive negative values were 78% and 90% in Groups 1 and 2, respectively. In summary, sentinel node localization in breast cancer patients submitted to previous neoadjuvant chemotherapy is less accurate than in patients who do not receive this therapy. The procedure is not sufficiently accurate to localize the sentinel node, thus it cannot be recommended in these patients. (© 2001 Lippincott Williams & Wilkins)

**Keywords**: gamma probe, sentinel node localization, breast cancer, neoadjuvant chemotherapy.

## Introduction

### *Detection and analysis of sentinel nodes*

The histological status of axillary lymph nodes is one of the most important prognostic indicators in breast cancer patients [1]. Between 70% and 80% of these patients will have completely negative surgical axillary lymph node examination, and 3–12% will develop lymphoedema post-surgery.

Lymphoscintigraphy and radioguided biopsy of the sentinel node (SN) is a useful method for staging the regional drainage pathway in breast cancer. The sentinel lymph node is the first to receive drainage from the tumour. It can be detected by using different techniques. Once identified, the SN can be analysed and the involvement of other axillary lymph nodes can be inferred from its status. With this information it is possible to avoid a regional axillary lymph node dissection. If haematoxylin and eosin (H&E) staining and/or immunohistochemistry do not show an involvement of the SN, the probability of node involvement beyond the SN is less than 0.1% [2].

Some authors have reported the results of sentinel node mapping and surgical detection for breast using blue dye [3], or radioisotopes [4], or both [5]. In particular, in 1993 Alex and Krag described direct localization of sentinel nodes with radioactive tracers and a hand-held gamma probe [6].

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In conclusion, the sentinel lymph node status predicts distant basin status, especially in early stages of the disease. Basin involvement is less frequent in these patients and surgery can be targeted to the appropriate population [7].

*Neoadjuvant chemotherapy*

During the past 25 years, new concepts and discoveries have dramatically influenced the therapeutic management of breast cancer. The hypothesis formulated in the 1960s by Bernard Fisher contended that in most instances 'operable breast cancer is a systemic disease involving a complex spectrum of host–tumour interrelations and that variations in local–regional therapy are unlikely to affect survival' [8]. This 'paradigm' and the long-term results of clinical trials [9, 10] have been able to modify the traditional concepts of 'radical' surgery for the treatment of a 'local' disease as the breast cancer.

In patients with high-risk tumours, surgery should be considered an incorrect form of primary treatment and only appropriate variations in systemic drug therapy are likely to increase relapse free and total survival ratios through the eradication of distant micrometastasis [11]. This adjuvant treatment is called neoadjuvant (also primary, induction or perioperative) chemotherapy and has become a common approach for the treatment of a variety of neoplasms, including breast cancer [12–15].

It has been noted in animal models that the removal of a primary tumour may increase the growth rate of micrometastases. One possible explanation for this phenomenon, based on angiogenesis, is that some tumours have been shown to release factors that are angiostatic, and thus limit the growth of metastases by inhibiting new blood vessel formation [16, 17]. The removal of the primary tumour and loss of angiostatic factors, angiogenesis occurs in micrometastases which can then progress. As the number of tumour cells increases, the likelihood of chemoresistant clones being present increases. NC could minimize this phenomenon.

One of the first trials in the NC of breast cancer was initiated at the Milan Cancer Institute more than 20 years ago as part of the multidisciplinary studies that were designed for stage III disease [18]. Today, the long-term value of systemic adjuvant therapy in patients with advanced breast cancer is clearly established [19, 20].

There are several problems related to the use of NC in patients with early breast cancer [21]. For instance, accurate knowledge of pre-treatment pathological nodal status is unavailable, thus one of the most significant preoperative prognostic factor is unknown.

Neoadjuvant chemotherapy may be used if the tumour response to chemotherapy prior to surgery needs to be known or if breast conservation therapy is otherwise not possible [12]. In our hospital, the number of patients treated with NC has increased in recent years.

The aim of this study was to validate the SN radioguided detection in these patients in order to apply the technique in patients submitted to NC.

## Patients, materials and methods

Seventy-six consecutive female patients with single breast cancer who had not received surgery or radiotherapy were included in the study. Written informed consent was obtained from them all.

Patients were assigned to one of two groups, following the usual hospital protocol. Group 1 consisted of 40 patients (mean age 52 years, range 36–69 years) who had previously received NC (Table 1). Group 2 consisted of 36 patients (mean age 55 years; range 31–87 years) who have not received any chemotherapy (Table 2). An injection of tracer, 111 MBq (3 mCi) of $^{99}Tc^{m}$-nanocolloid, was administered peritumourally at four different points. Each injection volume was 0.75 ml.

*Scintigraphy*

Five-min anterior and lateral (hanging breast) thoracic projections including breast and axilla, were obtained at 2 h post-injection. A $^{57}Co$ flood phantom was positioned back to the patient to outline the anatomical contour and

**Table 1**. Group 1*: patients treated with neoadjuvant chemotherapy.

| *Parameter* | *n (%)* |
|---|---|
| Tumour localization | |
| External, upper left quadrant | 24 (60) |
| External, lower left quadrant | 7 (17) |
| Internal, lower right quadrant | 3 (7) |
| Internal, upper right quadrant | 6 (16) |
| Tumour size | |
| T1N0 | 4 (10) |
| T1N1 | 0 (0) |
| T2N0 | 10 (25) |
| T2N1 | 7 (17) |
| T3N0 | 12 (30) |
| T3N1 | 4 (10) |
| T4N0 | 2 (5) |
| T4N1 | 1 (3) |
| Histology | |
| Ductal grade 1 | 1 (3) |
| Ductal grade 2 | 12 (30) |
| Ductal grade 3 | 24 (60) |
| Others | 3 (7) |

*n = 40; mean age, 52 years, range, 36–69 years.

help localize the sentinel node. Once the SN had been detected its position was labelled on the skin using a permanent ink marker.

*Surgical localization*

Patients underwent surgery the following day (18–24 h post-injection). Intra-operative sentinel node localization was performed using a GAMMED 2 gamma probe. Once localized and removed from the patient, the SN was sent to the histology department. In order to select the true SN, the search of active ganglia continued until the activity in the axillary area was negligible. All patients underwent total axillary lymph node dissection.

*Histology*

The removed lymph nodes were paraffin-embedded intact and lamellated into pieces approximately 1 cm in size. Three HE stained sections were made per block. Sections were analysed by two expert pathologists.

Immunohistochemistry using the CAM 5.2 antibody was performed in 10 cases in order to detect micro-metastases.

**Table 2**. Group 2*: patients who did not receive neoadjuvant chemotherapy.

| *Parameter* | *n (%)* |
|---|---|
| Tumour localization | |
| External, upper left quadrant | 17 (47) |
| External, lower left quadrant | 8 (22) |
| Internal, lower right quadrant | 4 (11) |
| Internal, upper right quadrant | 7 (20) |
| Tumour size | |
| T1N0 | 15 (42) |
| T1N1 | 0 (0) |
| T2N0 | 17 (47) |
| T2N1 | 1 (3) |
| T3N0 | 3 (8) |
| T3N1 | 0 (0) |
| T4N0 | 0 (0) |
| T4N1 | 0 (0) |
| Histology | |
| Ductal grade 1 | 2 (5) |
| Ductal grade 2 | 20 (56) |
| Ductal grade 3 | 13 (36) |
| Others | 1 (3) |

*n=36; mean age, 55 years, range, 31–87 years.

## Results

*Group 1 (n = 40)*

*Lymphoscintigraphy* Axillary lymph nodes were seen in 29 patients. In 15 there was only one sentinel node. In the 14 remaining patients two or more lymph nodes were seen. In seven patients a double lymph drainage was observed: axillary and internal mammary chain (five patients), axillary and intramammary (one patient) and axillary and supraclavicular (one patient) (Fig. 1). Finally, in four patients no sentinel node could be identified; in one of them all the axillary lymph nodes were infiltrated. The mean number of lymph nodes seen by scintigraphy was 1.7.

*Surgery* In 34 of the 36 patients in whom scintigraphy showed the presence of at least one axillary SN, it could be localized and drawn out at surgery. In the two remaining patients no activity could be detected in the axilla, or in other lymph chains.

*Histology* Histological analysis was performed in the 34 patients in whom an SN could be identified and drawn out. Histopathology of the SN was compared to the histopathology of all the other lymph nodes drawn out by the surgeon.

In 14 patients the SN and all the other axillary lymph nodes were not metastasized (14 true negatives). In 16 patients, both the SN and other axillary lymph node were metastasized (16 true positives). In four of the 16 the SN was the only node involved. In four patients the SN was normal but metastases were found in other lymph nodes (four false negative results). The false negative rate was 22% and negative predictive value was 78% (Table 3). In two of the four false negatives cases tumour has decreased in size by more than 50% post-NC.

*Group 2 (n = 36)*

*Lymphoscintigraphy* Axillary lymph nodes were seen in 22 cases. In 12 there was only one sentinel node. In the 10 remaining cases, two or more lymph nodes were seen. In 10 patients a double lymph drainage was observed to axillary and internal mammary chain (nine cases) (Fig. 2) and axillary and intramammary chain (one case). In one case only the SN was localized in the internal mammary chain and in another case only intramammary nodes could be seen.

Finally, in two patients no sentinel node could be identified; in one of them all the axillary lymph nodes were infiltrated. The mean number of lymph nodes seen by scintigraphy was 1.6.

*Surgery* In 29 out of the 32 patients in whom the scintigraphy showed the presence of at least one axillary SN, it could be localized and drawn out at surgery. In two cases no activity could be detected in the axilla, or in

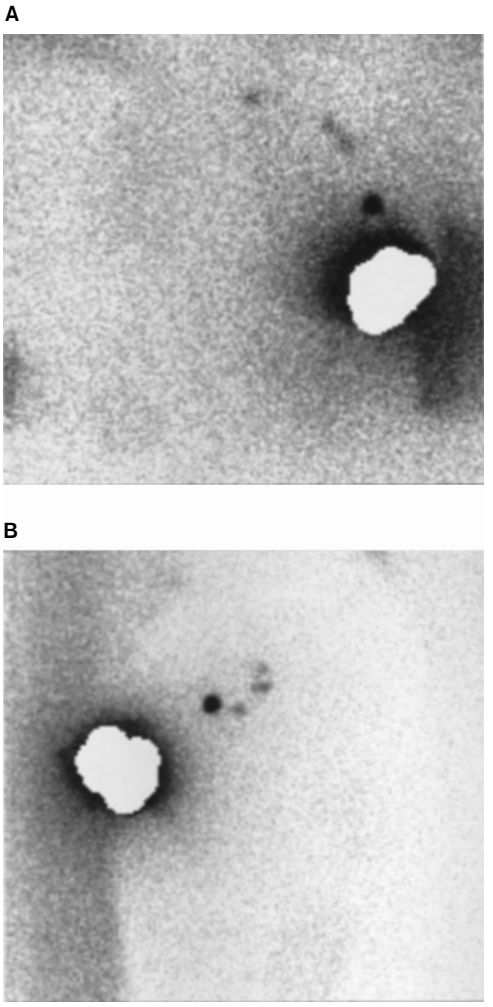


**Fig. 1.** Anterior (A) and lateral (B) views of a patient, showing drainage to the subclavicular area. Time post-injection, 2 h.

**Table 3**. Sentinel node and total axillary lymph node dissection histology in patients treated with neoadjuvant chemotherapy (Group 1).

| *Axillary lymph node dissection* | *Sentinel node dissection* | | *Total* |
|---|---|---|---|
| | *Positive SN* | *Negative SN* | |
| Positive total | 12 | 4 | 16 |
| Negative total | 4 | 14 | 18 |
| Total | 16 | 18 | 34 |

other lymph chains and in one patient the sample taken was found to be fatty tissue.

*Histology* Histological analysis was performed in the 29 patients in whom an SN could be identified and drawn out. Histopathology of the SN was compared to the histopathology of all the other lymph nodes drawn out by the surgeon.

In 19 cases the SN and all the other axillary lymph nodes were not metastasized (19 true negatives). In eight cases, both the SN and other axillary lymph nodes were metastasized (eight true positives). In four cases, the SN was the only node involved. In two cases the SN was normal but was found to metastasize in other lymph nodes (two false negative). The false negative rate was 9% and negative predictive value was 90% (Table 4).

## Discussion

Scintigraphic and gamma probe localization of sentinel node is a well-established method in patients with malign melanoma [22, 23]. However, the situation is different in

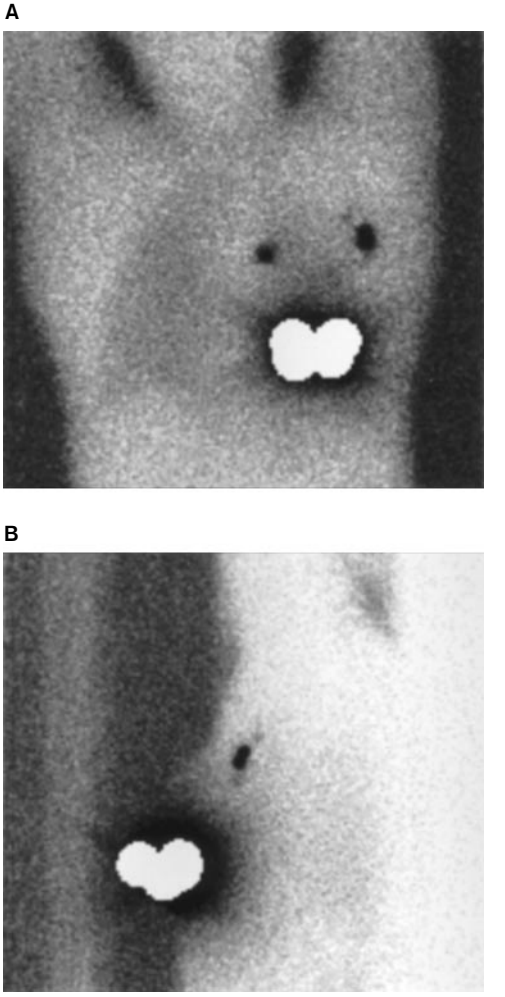


**Fig. 2.** Anterior (A) and lateral (B) views of a patient, showing drainage to the intramammary chain. Time post-injection, 2 h.

**Table 4**. Sentinel node and total axillary lymph node dissection histology in patients who were not treated with neoadjuvant chemotherapy (Group 2).

| *Axillary lymph node dissection* | *Sentinel node dissection* | | *Total* |
|---|---|---|---|
| | *Positive SN* | *Negative SN* | |
| Positive total | 4 | 2 | 16 |
| Negative total | 4 | 19 | 23 |
| Total | 8 | 21 | 29 |

SN, sentinel node.

other solid tumours, especially in breast cancer, where many factors, such as injection method, tracer and clinical indications, are still to be standardized [7].

Small single tumours (T1, T2), in untreated (surgery or radiotherapy) patients seem to be the more appropriate for the application of this methodology, identifying the SN and indicating selective lymphoscintigraphy, depending on the results of the histological study [24]. The method has been widely applied to untreated patients. Nevertheless, the influence of previous NC on SN localization has not been fully investigated.

In our hospital, NC is largely used prior to surgery and radiotherapy. In order to determine whether the large number of patients included in our protocol could benefit from this new methodology we decided to investigate this field [25].

There were no significant differences in tumour size or patients' ages between both groups. Our results show differences in the number and distribution of SN localization between the two groups studied. SNs were limited to the axilla in 72% of Group 1 patients, and 58% of Group 2 patients. The percentage of examinations in which no SN could be identified was 10% in Group 1 and 5% in Group 2. The mean number of SNs localized was quite similar: 1.7 and 1.6 in Groups 1 and 2, respectively.

These results indicate the greater difficulties in localizing SNs in patients submitted to NC, but the frequency of other lymph pathways is more frequent in untreated patients.

At surgery the efficacy was similar in both groups: the SN could be localized and extracted in 94% and 91% of Group 1 and Group 2 patients, respectively.

The more important point is the frequency of false negative results (negative SN and the finding of other lymph nodes that had metastasized). In Group 1, SNs were falsely negative in four patients, which means a false negative rate of 22% and a negative predictive value of 78%. In three of the four patients the size of the tumour had decreased significantly following chemotherapy.

In Group 2, the SN was falsely negative in only two patients, resulting in a false negative rate of 9% and a negative predictive value of 91%. These results agree with published results by other authors [5, 26] and support the use of this methodology in untreated patients.

This large difference between treated and untreated patients could be explained by changes in axillary lymph drainage due to chemotherapy. If the true SN (the first to receive drainage from the tumour) is metastasized, probably this node would respond to chemotherapy as does the primary tumour. In consequence, the lymph node tissue would be replaced by fibrotic tissue (which does not take up the colloid particles) and what the scintigraphy and probe identifies as a sentinel node could really be a second echelon. This false SN and other axillary lymph nodes could be metastasized or not depending on the evolution of the disease. The final results would be an increase of skip metastasis.

According to these results, the scintigraphic and probe localization of SNs cannot be recommended in breast cancer patients if they have undergone neoadjuvant chemotherapy.

One of the arguments against the use of NC is the increasing difficulty in staging the patients, which is essential for establishing a prognosis. One possible solution could be ambulatory localization of the SN, through a small axillary incision, prior to the commencement of chemotherapy. This study is being carried out in our department.

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