

Detection of metastases in the sentinel lymph nodes of primary breast cancer patients by lymphatic mapping and intraoperative gamma probe: initial experience

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This study documents our initial experience for visualisation of sentinel lymph nodes (SLNs) with lymphoscintigraphy and intraoperative detection of SLN with the handheld gamma probe in patients with primary breast cancer. Fourteen women with palpable breast cancer had peritumoral injection of ^{99m}Tc labeled nanocolloid in four different regions. 1mCi of ^{99m}Tc labeled nanocolloid in 0.8 ml saline were divided into four equal portions. Thirty minutes' dynamic images and static images, every 30 minutes for 3 hours, were obtained. After intraoperative identification and resection of the SLN(s), all the patients underwent full axillary dissection. We were able to visualize and localize the SLN(s) in all patients. An average of 30.1 lymph nodes (range 19-44) were harvested. Metastatic involvement of the axillary nodes was found in only 4 of the 14 patients in this series (28.6%). In one of these 4 patients with axillary involvement, the sentinel lymph node was the only involved node. In the other three patients, metastases were also found in lymph nodes other than the SLN. Our initial experience is promising that SLNs can be accurately localised with our technique of combination lymphoscintigraphy and intraoperative gamma probe. The SLN was predictive of the presence or absence of LN metastasis in all patients. If our future results accumulate to give the same success rate with no or very infrequent false evaluations, we might then proceed to targeting only the SLN as a reliable predictor of the axillary LN status. [Turk J Cancer 2001;31(1):27-34]

Key words: ^{99m}Tc labeled nanocolloid, breast carcinoma, sentinel node

Since 1867, when a theoretical basis for the surgical treatment of the axillary lymph nodes in breast cancer was stated by Moore in his article, axillary lymph node dissection has been carried out as an indispensable phase of the breast cancer treatment (1). For accurate staging and prevention of local recurrence, complete removal of at least level I and II lymph node groups is recommended (2,3). Nodal metastases from invasive breast cancer have clinical significance for three major reasons. First, the pathologic identification of nodal metastasis is an important prognostic indicator of systemic disease (4,5). The correlation is very strong, and the presence or absence of nodal metastases remains the single most important predictor of the eventual appearance of systemic metastases. Second, axillary node status has a particular value in the staging and choice of adjuvant therapy of the breast cancer patients (6,7). Unfortunately, physical examination, radiologic imaging of the axilla, or prognostic models based on primary tumor characteristics cannot accurately predict the occurrence of axillary metastases (6,8-10). Therefore, the National Institutes of Health Consensus Conference has recommended a level I and II axillary lymph node dissection for staging and regional control of breast cancer (11). It has been shown that for qualitative (metastases present or not) and quantitative evaluation of axillary status, sampling of at least 3-5 or 10 lymph nodes is required (12-13). And third, progressive growth of nodal metastasis, if left untreated, can cause local recurrences (14,15). On the other hand, axillary dissection has many short and long term morbidities. Loss of sensation, swelling, seroma, infection, nerve injuries, restriction of arm movements, and lymphedema are the most frequently encountered complications (16-21). In order to avoid these complications, some investigators have advocated a limited axillary sampling (22). Nevertheless, such an approach has the potential risk of missing some of the axillary metastases (23).

The philosophy of axillary dissection for breast cancer has changed in the last few decades from therapeutic resection to selective diagnostic sampling. Only 50-60% of the primary breast cancer patients has nodal metastases (24). The sampling serves as a guide to adjunctive therapy and the reduced dissection should decrease the incidence of arm complications. The preponderance of breast lesions is now detected early, and such cases are candidates for breast conservation surgery which most women choose (24-26). This usually entails lumpectomy with clear margins, axillary sampling and radiotherapy to decrease the risk of local recurrence and makes the results equivalent to modified radical mastectomy alone. Lymphatic mapping techniques using vital dyes or radionuclides with sentinel node biopsy is now thought to solve this problem and emerging as a technique to replace routine axillary node dissection. The concept of sentinel lymph node biopsy was first described by Cabanas in 1977 for the treatment of penile carcinomas (27). It has been suggested that the first lymph node draining the tumour area must be the first lymph node involved by the tumour. According to this hypothesis, if sentinel lymph node (SLN) is negative, then the whole lymphatic bed beyond this point will be negative. The initial experience in intra-operative lymphatic mapping has been gained from patients with melanoma. The first successful trial with this technique in breast cancer using vital dye was reported in 1994 by Giuliano et al (28). The authors identified sentinel nodes in 114 of 174 (65.5%) procedures and accurately predicted axillary nodal status in 109 of 114 (95.6%)

cases. Since then, many studies, including pre-operative lymphoscintigraphy followed by intra-operative gamma-probe scanning technique, have been carried out to assess axillary status more accurately.

We report our initial results of an ongoing prospective study, using pre-operative lymphoscintigraphy and intra-operative gamma probe to investigate the efficacy of SLN biopsy for determining axillary status.

Patients and Methods

We have completed an initial study of 14 female patients with carcinoma of the breast, in whom gamma-probe-guided detection of the radiolabeled primary lymph node(s) was performed.

All 14 patients had primary breast carcinomas, which were confirmed by incisional or excisional biopsies performed within the previous two weeks. In two patients, stereotactic biopsies had revealed carcinoma. None had received prior breast surgery, chemotherapy or radiotherapy. Patients with advanced tumors necessitating neoadjuvant chemotherapy were excluded.

After total mastectomy or quadrantectomy (one patient) was completed, the axillary space was entered and gamma-probe biopsy of the hot radiolabeled primary lymph node(s) was performed (details below). Then all node bearing tissue in levels I, II and III of the axilla were harvested in the conventional fashion. After complete lymphadenectomy, the axillary space was checked with the gamma detector to ensure that all radioactive lymph nodes were removed. The SLN(s), and levels I, II, and III were then submitted separately for histologic evaluation.

Lymphoscintigraphy was performed the day before surgery with double head rectangular gamma camera equipped with low energy, general purpose collimator (General Electric, Maxxus, Wisconsin, USA). Images were obtained with a symmetrical 20% window over the ^{99m}Tc energy peak (140 keV). 1mCi ^{99m}Tc labeled nanocolloid (Amersham Sorin Sr1, Sallugia, Italy) in 0.8 ml saline was divided into four equal portions and circumferentially injected into breast tissue around the primary tumor or into the biopsy cavity if prior excisional biopsy had been performed. Immediately after injection of ^{99m}Tc -nanocolloid, dynamic images were acquired in a fashion of 30 frame of 30 sec, 64x64 matrix. Then, anterior, oblique and lateral static images were obtained every 30 min for 4 h, acquisition time per images being 5 min. After obtaining the last images, the SLN lymph node(s) was marked with a suitable pen.

The gamma probe, which contained a cesium-iodine crystal for measurement of gamma rays and consisted of stainless steel sleeve with 30 and 60 degree collimators, was used intraoperatively to locate the SLN(s) (Neoprobe 1500–Neoprobe Corp, Ohio, USA). After excision of primary lesions, the skin was incised directly over marked area. After mastectomy or quadrantectomy was completed and the axillary space was entered, the nuclear medicine staff used gamma probe to detect the node(s) emitting the highest activity within the axillary region. Sometimes, more than one node were picked up by the gamma probe. The SLN(s) was excised and the lymphatic basin was checked again for any remaining spike radioactivity. The radioactivity of excised SLN(s) was also confirmed. All nodes from the axilla, three classical levels, were examined for extra sentinel lymph node which was not visualised. Then

complete axillary dissection was performed. All nodes and sentinel lymph node(s) were examined by the pathologist using a standard technique.

Results

Patient/disease characteristics and the pathologic results obtained for the sentinel and other lymph nodes are summarized in table 1. Lymphoscintigraphy with ^{99m}Tc -nanocolloid revealed sufficient uptake of radioactivity in SLNs. Although SLN could not be visualised on dynamic images, all the SLNs were identified on static images mostly obtained 3 hours after tracer injection. Oblique images provided the best perspective to separate the SLN from the primary injection site while anterior images were useful to evaluate the internal mammarian region.

Table 1

Patient/disease characteristics and the pathologic results obtained for the sentinel and other axillary lymph nodes

n	TNM	Palpable LN	Total no of LNs harvested	No and level of metastatic LNs	SLN detected at operation	Metastasis in SLN	Metastasis in LNs other than SLN
1	T ₁ N ₀ M ₀	-	21	0	yes	no	no
2	T ₁ N ₀ M ₀	+	32	0	yes	no	no
3	T ₂ N ₁ M ₀	+	20	1 (level I)	yes	yes	no
4	T ₂ N ₀ M ₀	-	24	0	yes	no	no
5	T ₁ N ₀ M ₀	-	44	0	yes	no	no
6	T ₁ N ₀ M ₀	+	35	0	yes	no	no
7	T ₂ N ₁ M ₀	-	19	4 (levels I+II)	yes	yes	yes
8	T ₂ N ₁ M ₀	+	36	13 (levels I+II+III)	yes	yes	yes
9	T ₂ N ₀ M ₀	-	25	0	yes	no	no
10	T ₁ N ₀ M ₀	-	25	0	yes	no	no
11	T ₂ N ₀ M ₀	-	28	0	yes	no	no
12	T ₂ N ₁ M ₀	+	34	7 (levels I+II)	yes	yes	yes
13	T ₁ N ₀ M ₀	-	44	0	yes	no	no
14	T ₂ N ₀ M ₀	-	34	0	yes	no	No

Intraoperative use of gamma probe was easy to detect SLN which denoted the highest activity in the axillary region. An average of 30.1 lymph nodes (range 19-44) were harvested. Metastatic involvement of the axillary nodes was found in only 4 of the 14 patients in this series (28.6%). In one of these 4 patients with axillary involvement, the SLN was the only involved node. In the other three patients, metastases were also found in lymph nodes other than the SLN. In other words no skip metastases were observed. Thus, the positive (and negative) predictive value of our initial experience was 100%, and false negative results were not observed.

Discussion

It has been found that, as much as 58% of the primary breast cancer patients have axillary involvement (24). With the improvement of the diagnostic tools and techniques, the rate of the detection of the early breast cancer patients has been rising (24-26). This will further decrease the probability of nodal metastases and eventually increase the frequency of unnecessary metastases-free axillary node dissection with no therapeutic benefit. In the patient group reported in this study, only 28.6% of the breast cancer patients had metastatic LNs. In other words, in about 70% of the patients (10 of the 14 patients), axillary dissection was not necessary as a curative intent. Because these patients are exposed to the considerable morbidity associated with the dissection procedure, it is understandable that less invasive approaches are sought for staging the axilla. When cancer develops in the breast, the axillary nodes are usually involved sequentially; first those in level I, then in level II, and at last in level III. However, isolated involvement of level II and/or level III nodes may infrequently occur (skip involvement). Level III nodal involvement alone is rare, occurring in less than 3% of patients. In the Milan study of 539 patients with carcinoma of the breast who underwent total axillary dissection, level I nodes only were involved in 58.2%, both levels I and II nodes in 21.7%, all 3 levels in 16.3%, and skipping distribution in only 1.5% (25). In other studies, the frequency of skip metastases was found between 0.1 to 2% (24-26). Although it is still a matter of considerable debate, the frequency of skip metastasis is very small, and to our belief, this rarity justifies the use of SLN as a reliable predictor of the presence or absence of LN metastasis. The number of patients included in our study is yet small, but no skip metastases were identified.

Lymphoscintigraphy is based on observation of Morton and coworkers who first used blue dye (29, 30). Since then, "sentinel lymph node" concept has gained increasing importance in the management of patients with various cancers. The SLN is defined as the first lymph node to receive drainage from a primary tumor. Therefore, lymphoscintigraphy is increasingly used to identify the SLNs in malignant diseases, such as malignant melanoma or breast cancer. Blue dye, which has been used for many years, has several drawbacks to identify SLN (31). Later, Giuliano *et al.* (32) have introduced radioactive tracer injection and using intraoperative gamma probe for localization of SLN, in addition to lymphoscintigraphy. Lymphoscintigraphy allows accurate preoperative visualization of SLN, while the utilization of intraoperative gamma probe precisely localizes the node(s). Although this technique has been established and approved for melanoma, there are several aspects to be improved to gain acceptance for staging and management of patients with breast cancer. Although optimum tracer, activity, injection volume and administration site are still investigated, consecutive studies have been reported in the literature which mentioned reproducibility and usefulness of this technique (33-40).

In the present study, we preferred to use ^{99m}Tc -nanocolloid for lymphoscintigraphy and intraoperative detection because almost 80% of particles in the nanocolloid are smaller than 30 nm, which warrants optimal lymph node depiction, and 20% of particles are between 30-80 nm, which enables prolonged retention (41, 42). Neuroprobe 1500 was used for surgical retrieval of the SLNs which is accepted to be one of the best gamma probes by Britten (43).

Lymphoscintigraphy revealed the SLN successfully in all patients. Non-visualization of SLNs on dynamic images could be explained by the administration site of the colloid, as mentioned by De Cicco and coworkers (36). In his article, intranodal uptake was demonstrated to become more prominent in late images with peritumoral injection of the tracer. We observed all SLNs in late static images, which should be obtained in anterior and anterior-oblique positions. Anterior views allow us to detect possible internal mammary chain drainage, whereas anterior-oblique views are the best to detect and differentiate SLNs from primary lesions. In the operation theatre, we used the hand-held gamma probe for SLN detection, and we proved to be successful in all cases.

Although our experience with this technique is yet limited, we were able to detect the SLN in 100% of the patients. The more important deduction of our results is that the SLN was predictive of the presence or absence of LN metastasis in all patients. In 10 patients, pathologic examination of the SLN revealed the absence of metastasis. In accordance, the rest of the axillary LNs were also tumor-free. In four patients, SLN was shown to harbour metastasis, as some of the other axillary LNs. One case was especially valuable to demonstrate a single LN metastasis, which was the SLN. There was not a single case where SLN was tumor-free but metastases existed in other LNs. Therefore, the predictive value of SLN biopsy was maximum in our initial experience with this method. Until we are completely satisfied with this system and team that our detection and evaluation of SLN in breast cancer patients are reliable enough to eliminate the need for full axillary dissection, we need to continue with the classical lymphatic clearance. If our future results accumulate to give the same success rate with no or very infrequent false evaluations, we will then proceed to targeting only the SLN as a reliable predictor of the axillary LN status.

Acknowledgment

The authors would like to thank Ömer Faruk Sabuncu and Ahmet Yeprem for their technological contributions to this study.

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