Usefulness of Combined Sestamibi Scintimammography, Axillary Ultrasonography and FNA Cytology in Reducing the Number of Sentinel Node Procedures in Patients with Early-stage Breast Cancer*

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Abstract. *Background: Intraoperative analysis of the sentinel lymph node (SLN) status is currently performed in patients with breast cancer (BC) undergoing surgery. Axillary node (AN) metastases are present in up to 60% of cases, but the risk is only 30% in patients with early stage (T1) BC. The aim of this study was to evaluate the usefulness of ^{99m}Tc-sestamibi scintimammography (SSM), axillary ultrasonography (US) and US-guided fine-needle aspiration (FNA) cytology together in detecting axillary metastases preoperatively and their potential role in reducing the number of SLN procedures. Patients and Methods: A series of 86 consecutive women (median age 57 years, range 30-72) with confirmed BC and clinically negative nodes (T1N0) underwent both SSM and US prior to surgery. US-guided FNA cytology was performed in all the patients with suspicious AN on US, or positive SSM and ultrasonographically visualized enlarged nodes. Results: Final pathology showed 4 pT1bN0, 1 pT1bN1, 60 pT1cN0 and 21 pT1cN1 BC. The sensitivity, specificity, and accuracy were 59.1%, 93.7% and 84.9% for SSM, 63.6%, 90.6% and 83.7% for US, and 72.7%, 97.8% and 90.7% for SSM and US together. Using FNA cytology the specificity reached 100%, but the sensitivity did not increase. A combined method using radioisotope and blue dye was used for SLN biopsy. The procedure was omitted in patients with FNA cytology showing AN metastases (N=14, 16.3%) and they underwent level I-II axillary dissection, as well as those with positive SLN biopsy on frozen section (8 out of 72, 11.1%). Conclusion: In patients with BC, preoperatively selected by SSM and US in whom US-guided axillary FNA cytology has shown the presence of AN metastases, the SLN biopsy can be avoided and AN dissection should be the primary procedure.*

Breast cancer (BC) is the most common cancer in women, and axillary node (AN) status has, for decades, represented the best prognostic factor of primary BC (1). Overall, AN metastases are present in up to 60% of cases, but the risk of having AN metastases is only 30% in patients with BC less than 20 mm (T1) in size (2, 3). Sentinel node (SLN) biopsy has widely replaced axillary dissection and patients with negative SLN should not require further procedures to assess disease in the axilla. Moreover, SLN has been shown to be an efficient tool for reducing postoperative short- and long-term morbidity, without compromising the local control of the disease (4, 5).

The aim of this study was to evaluate the usefulness of ^{99m}Tc-sestamibi scintimammography (SSM), axillary ultrasonography (US) and US-guided fine-needle aspiration (FNA) cytology together in detecting axillary metastases and their potential role in reducing the number of SLN procedures.

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Patients and Methods

Study design. A series of 86 consecutive women (median age 57 years, range 30-72) with early-stage (T1) primary BC detected by screening mammography and clinically negative nodes (N0) were included in the study. The diagnosis was confirmed by FNA cytology, core-biopsy or open biopsy. In the patients with non-palpable lesions, the biopsy was performed using wire needle localization, under US or stereotactic guidance. Written informed consent was obtained from all the participants in accordance with Institutional Review Board approval.

^{99m}Tc-sestamibi scintimammography. A single dose (750 MBq) of ^{99m}Tc-sestamibi was injected intravenously in the arm contralateral to the side of the lesion, according to the procedure guidelines suggested by The Society of Nuclear Medicine (SNM) (6). A triple head gamma camera (Philips Irix) equipped with a parallel-hole low-energy high-resolution collimator (resolution 7.5 mm at 10 cm), a 140 keV (10% window) energy setting and a 256×256 matrix was used (7). Planar (prone lateral, anterior and posterior oblique) images combined with single-photon emission tomography (SPET) images (128×128 matrix, 64 steps, 30 s/step, 180˚ acquisition) were obtained. A focal uptake of the radiopharmaceutical and a mass-to-background ratio of more than 1.4 was considered as a positive result, as previously reported (7-9). To improve the visualization of the axilla, the patients were in the prone position, with arms raised above the head and the images were acquired 5-10 minutes after the injection of the ^{99m}Tc-sestamibi (3).

Axillary ultrasonography. US examination was performed using a Siemens Elegra scanner equipped with two real-time linear probes, with a frequency ranging between 5.1 and 9 MHz and between 9 and 12 MHz, respectively. Sonographic signs of malignancy included the replacement of an echogenic central sinus by hypoechoic tissue and eccentric thickening of the cortical region with humps on the profile of the AN. A longitudinal-to-transverse ratio >2, corresponding to oval shape of the node, was considered a sign of benignity, as previously reported (3). US-guided FNA cytology was performed in all the patients with suspicious AN on US, or positive SSM and ultrasonographically visualized enlarged nodes. All the smears of the FNA samples were spread on standard glass slides, air dried and stained with May-Grünwald-Giemsa stain, and were reviewed by the same cytologist (SB).

Statistical analysis and definitions. According to the TNM classification (10), the tumors were classified as: pT1a = between 0.1 and 5 mm; pT1b = more than 5 mm, but not more than 10 mm; pT1c = more than 10 mm but not more than 20 mm; pN0 = no lymph node metastases, and pN1 = metastases in at least one axillary node. Sensitivity was defined as true-positives (TP)/TP + false-negatives (FN), specificity as true-negatives (TN)/TN + false-positives (FP), positive predictive values (PPV) as TP/(TP + FP), negative predictive values (NPV) as TN/(TN + FN), and accuracy as (TN + TP)/overall number of patients.

The reported data are expressed as mean ± standard deviation (SD). Comparisons between groups were performed using the Student's *t*-test, when required. The Mann-Whitney *U*-test and the Pearson's correlation coefficient (R) calculation were used for the comparison of qualitative variables in the case of non-normal distribution and to evaluate the linear relationship between pairs of variables, respectively. A p-value <0.05 was considered statistically significant.

Results

The tumor size ranged between 8 mm and 19 mm. The pTNM staging was: 4 (4.7%) pT1bN0, 1 (1.2%) pT1bN1, 60 (69.7%) pT1cN0 and 21 (24.4%) pT1cN1 breast carcinomas. No pT1a BC was observed.

The sensitivity, specificity, PPV, NPV and accuracy of SSM and US are shown in Table I. AN metastases were histologically confirmed in all the patients with positive FNA cytology and thus the specificity reached 100%, but the sensitivity did not change because it was conditioned by the results of US and SSM. Both the age of the patients and the size of the tumor did not differ significantly (p=NS) between N1 and N0 patients and, similarly, between patients with TP and FN results of the preoperative studies (Table II). There was a linear relationship between age and size only among the patients with positive nodes (Table III).

A combined method using radioisotope and blue dye was used for SLN biopsy. The procedure was omitted in patients (N=14, 16.3%) with FNA cytology suggesting AN metastases. Thus, they underwent level I-II axillary dissection, as well as those (8 out of 72, 11.1%) with positive SLN biopsy on frozen section.

Discussion

With the onset of extensive mammographic screening, the rate of metastatic AN has declined, and currently 44% of patients with positive AN have only one-node metastases (11). When SLNs were positive, in over 60% of patients these were the only AN involved, indicating that SLN removal would be sufficient to remove metastases in the majority of patients (12, 13). Moreover, in patients with BC and positive SLN who did not undergo further axillary dissection, the risk of AN recurrence following breast conserving surgery and radiation therapy was about 2% (14). A relationship between lymphatic invasion in the primary tumor and metastases detection in the non-SLN was found (15).

The usefulness of SSM in detecting primary BC has long been reported (16-19). Although ^{99m}Tc-sestamibi is not really tumor specific it is currently used in performing SSM, according to the SNM guidelines (20, 21). The sensitivity and specificity of SSM alone in the detection of AN involvement range from 52% to 82%, and from 82% to 100%, respectively (7, 22, 23).

US-guided FNA cytology has good sensitivity, ranging between 71% and 89% and excellent specificity, ranging from 96% to 100% (24-26). The sensitivity is lower for AN of normal US appearance and increases with the increasing size of the primary tumor, but this technique may allow definitive management of the axilla and eliminate the need of SLN biopsy examination before AN dissection (27-28). A

Table I. *Results of ^{99m}Tc-sestamibi scintimammography (SSM), axillary ultrasonography (US) and fine-needle aspiration (FNA) cytology in detecting axillary node metastases.*

Procedure	TP	FP	TN	FN	Sensitivity	Specificity	PPV	NPV	Accuracy
SSM	13	4	60	9	59.1%	93.7%	76.5%	86.9%	84.9%
US	14	6	58	8	63.6%	90.6%	70.0%	87.9%	83.7%
SSM + US	16	2	62	6	72.7%	97.8%	88.9%	91.2%	90.7%
SSM + US + FNA	16	0	64	6	72.7%	100%	100%	91.4%	93.0%

TP, true-positive; FP, false-positive; TN, true-negative; FN, false-negative; PPV, positive predictive value; NPV, negative predictive value.

Table II. *Differences (mean ± standard deviation, SD) and relative p-value in age of the patients and size of the tumor between patients with involved nodes (N1) and negative nodes (N0) and between patients with true-positive (TP) and false-negative (FN) results.*

Parameter	N1	*p*-value	N0	TP	*p*-Value	FN
No. of patients	22/86 (25.6%)	-	64/86 (74.5%)	16/22 (72.7%)	-	6/22 (27.3%)
Age (years)	52.4±9.4	0.08	59.3±9.8	54.1±8.3	0.16	47.8±11.3
Size (mm)	16.0±2.7	0.10	14.8±3.0	16.2±1.9	0.60	15.5±4.4

recent meta-analysis (29) showed that both sensitivity and specificity of axillary US may differ according to methodology and criteria of AN positivity.

Cemrik *et al*. (30) found that the sensitivity of FDG PET for detecting AN metastases ranged between 41% and 67% in patients with pT1 and pT2 BC, respectively. In another study, performed in a group of patients with BC of 50 mm or less (mean 21 mm), the overall sensitivity was 95% and the specificity was 86%, but the diagnostic accuracy ranged from 86% to 94% in relation to primary tumor size (31). Similar results in patients with early-stage (pT1) BC were found in the present study, where the accuracy was 91% and the specificity 98%. Using US-guided FNA cytology the specificity reached 100%. Whal *et al*. (32) reported lower sensitivity (61%) and specificity (80%). They concluded that FDG PET had moderate accuracy for detecting AN metastases and was not recommended for axillary staging of patients with newly diagnosed BC. The results obtained with SSM and US in combination were better than those obtained with FDG PET, which is expensive and not available everywhere (3).

In conclusion, in patients preoperatively selected by SSM and US, in whom US-guided axillary FNA cytology has shown the presence of AN metastases, the SLN biopsy can be avoided and AN dissection should be the primary procedure.

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Table III. *Relationship between age of the patients and size of the tumor*

Groups of patients	R	*p*-Value
Overall	0.10	0.36
N1	0.43	0.04
N0	0.12	0.36

R, correlation coefficient; N0, patients with negative nodes; N1, patients with positive nodes.

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