Sentinel Lymph Node Identification in Breast Cancer - Comparison of Planar Scintigraphy and SPECT/CT

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Abstract: *Aim*: Assess the role of planar lymphoscintigraphy and fusion imaging of SPECT/CT in sentinel lymph node (SLN) identification in patients with breast cancer.

Methods: Planar scintigraphy and hybrid modality SPECT/CT were performed in 223 consecutive women with breast cancer (mean age 59,5 yrs with range 25 - 82 years).

In 190 women with a palpable mass radiocolloid was injected in four peritumoral sites and one subdermal injection above the tumour (GROUP A), in 33 women with nonpalpable tumour radiotracer was injected in four subareolar sites (GROUP B).

Planar and SPECT/CT images were interpreted separately by two nuclear medicine physicians. Ability of these two techniques to image SLN was compared.

Results: In GROUP A the overall hot LN detection rate by planar and SPECT-CT lymphoscintigraphy was 87,9 % (167 patients). In 10 patients (5,3 %), hot LNs were detected only by SPECT-CT. 18 (5,3 %) foci of uptake in 13 (6,8 %) patients interpreted on planar images as hot LNs were found to be false positive non-nodal sites of uptake when further assessed on SPECT/CT.

In GROUP B the overall hot LN detection rate on planar and SPECT-CT was 97 % (32 patients). In one (3,0 %) patient hot LNs were identified only on SPECT/CT. Four (6,6 %) foci of uptake in four (12,1 %) patients were found to be false positive when further correlated with SPECT/CT. Differences in detection of SLNs between planar and SPECT/CT imaging in all 223 patients were statistically significant (P< 0.001).

Conclusion: In some patients with breast cancer SPECT/CT improves the detection of sentinel lymph nodes. It can image nodes not visible on planar scintigrams, exclude false positive uptake and exactly localize axillary and non-axillary SLN.

Keywords: Sentinel node, breast cancer, lymphoscintigraphy, planar scintigraphy, SPECT/CT.

INTRODUCTION

SLN biopsy is the most accurate and the only reliable method for nodal staging which can diagnose microscopic tumour spread to the regional lymph nodes [1]. Minimal invasive SLN biopsy replaced lymphadenectomy for staging [2, 3]. An essential step in the procedure for SLN biopsy is to locate the first-echelon node of draining basin. Planar lymphoscintigraphic imaging is an important element in lymphatic mapping, identifying sentinel lymph nodes (SLNs) in more than 95 % of breast cancer patients [4].

The disease status of the axillary lymph nodes is the most significant prognostic factor for patients with early-stage breast cancer [5]. Early and accurate identification of lymph node involvement enables the use of early systemic chemotherapy and local radiotherapy and may improve long-term survival. Incomplete detection of SLN results in inaccurate staging, and may lead to inadequate therapeutic

decisions [6]. Sentinel node biopsy in patients with clinically node-negative breast cancer is a valuable procedure for nodal staging [7-9] but also for treatment selection guiding [5]. Most patients with findings that were previously considered contraindications for the procedure of SLN detection and biopsy, such as palpable axillary nodes, large tumour size, multifocal or multicentric tumour, pregnancy, male gender, and prior breast or axillary surgery, have now been shown to benefit from the procedure. SLN biopsy following chemotherapy is feasible and accurate [10]. It allows the detection of clinically occult metastases by a meticulous histopathological examination. Accurate visualization of the SLN is required for the best results.

Interpretation of planar lymphoscintigrams is hindered by the absence of anatomical landmarks in the scintigraphic image [11]. SPECT/CT was introduced in lymphatic mapping with the goal to show more sentinel nodes and to show them more clearly than is possible with planar lymphoscintigraphy to improve nodal staging [12]. SPECT/CT is useful for finding the exact anatomic location of sentinel nodes and in detecting additional sites of drainage. These advantages facilitate surgical exploration. SPECT/CT may also obviate preoperative skin marking and

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may replace delayed lateral planar imaging. Whether SPECT/CT should be used on all patients or only for specific indications needs to be studied further [13]. The better anatomic definition and improved resolution that characterize SPECT images may overcome limitations of planar images. Localisation of hot lymph nodes on SPECT images without anatomic landmarks is not possible. However, it is possible by fusing the SPECT image with the anatomic data obtained by performing low-dose CT at the same setting as with the SPECT acquisition [14]. SPECT/CT can detect additional nodes not visualised on planar images and is especially useful in visualisation of SLN outside the axilla or nodes close to the injection site [12].

In this study, we compare hybrid SPECT/CT and planar lymphoscintigraphy in breast cancer patients with exploration the value of SPECT/CT - mainly for detection of additional SLNs, the anatomical localisation of SLNs, and differentiation of skin contamination. Added not high costs and extra time for SPECT/CT are more justified when the procedure is used for these indications. Extra radiation from „low-dose" CT is reasonable low.

MATERIALS AND METHODS

Patients' Population

Planar and hybrid SPECT/low-dose CT lymphoscintigraphy were performed in 223 consecutive women (mean age 59,5 yrs with range 25-82 years) with invasive breast cancer (T1a-T2) with no clinical evidence of axillary lymph node metastases (N0) and no remote metastases (M0).

Lymphoscintigraphic Method

On the day prior to surgery (2 day protocol in 184 patients) or on the day of surgery (one day protocol in 39 women) an activity of 120 MBq of ^{99m}Tc labelled colloid divided in four equal aliqouts of 0,5 ml was injected by nuclear medicine physician. Women with a palpable mass were injected in four peritumoral sites and one subdermal injection above the tumour (190 pts, GROUP A). Patients with nonpalpable tumour were injected in four subareolar sites (33 pts, GROUP B). We have used these ^{99m}Tc - colloids: Nanocis (size of colloid particles 100 nm - 40 pts), Nanocoll (size of colloid particles to 80 nm - 140 pts), SentiScint (size of particles to 200 nm - 4 pts), NanoAlbumon (size of particles to 80 nm - 39 pts). Choice of radiopharmaceuticals (Rf) was totally random. Type of Rf was not important because we have compared planar scintigraphy and SPECT/CT performed by the same Rf.

We previously reported the success of detection of SLNs by means of various [15-18] and this is not the aim of our present study.

Planar scintigraphy was done in anterior, posterior and lateral projections, ten minutes per projection. SPECT/CT images were acquired immediately after planar images. The SPECT/CT system (Symbia T2; Siemens, Erlangen, Germany) consisted of a dual-head variable-angle gamma camera equipped with low energy high resolution (LEHR) collimators and a two-slice spiral CT scanner optimised for rapid rotation. SPECT acquisition (matrix 128x128, 60 frames at 25 s per view) was performed using steps of 6^0. For CT (130 kV, 17 mA, B60s kernel), 5-mm slices were created. Both SPECT and CT axial 5-mm slices were generated using an Esoft 2000 application package (Siemens, Erlangen, Germany). The iterative reconstruction (OSEM 3D) was used for generating SPECT slices.

Both SPECT and CT slices were fused using an Esoft 2000 application package software (Siemens, Erlangen, Germany), too. Two nuclear medicine physicians evaluated the images. The SPECT/CT images were viewed using two-dimensional orthogonal re-slicing in axial, sagittal and coronal orientation. Maximum intensity projections with a three-dimensional display were generated to localise sentinel nodes in relation to anatomic structures.

The location of the SLN was marked on the skin with indelible ink.

Scintigraphic Interpretation

SLN localisation was interpreted separately on planar and SPECT/CT images. Image analysis was performed prospectively by two experienced nuclear medicine physicians in consensus reading. The number of SLNs and their locations were determined after the planar lymphoscintigraphic images as well as after the SPECT/CT images and then compared. The location of SLNs was categorised as axillar, parasternal and as other localisation.

In the analysis of the results, fused SPECT/CT images data were concluded to be clinically relevant if they identified SLNs which were missed on planar images or if they excluded SLNs suspected on planar images.

Statistical Test

Student's paired t-test was used for comparing numbers of found nodes by both techniques. Values were considered significant when P < 0.05.

Surgery

On the basis of the scintigraphic findings on both planar and SPECT/CT images the surgeon is guided during surgery. An intraoperative hand-held probe (NEO 2000, Neoprobe Corporation Dublin, Ohio, USA; detector: crystal of Cadmium Zinc Telluride; 12 mm collimated angulated probe) has been used before incision to identify the site with the highest counts of lymph nodes in the lymphatic basin. A patent blue dye (BLEU PATENTÉ V 2.5%, Guebert, France) has been injected similarly to the earlier colloid injection.

The surgeon removed all detected SLNs (excluding IMC nodes which are not routinely harvested). If some of SLNs was metastatic, axillary dissection followed (in the same day or later).

RESULTS

SLNs were detected on lymphoscintigraphy comprising planar and SPECT-CT images in 199 of the 223 (89,2 %) study patients; there was failure to detect SLNs in the remaining 24 patients.

SPECT/CT visualized lymphatic drainage in 11 (4,9 %) patients with non-visualisation on planar imaging. SPECT/CT showed the exact anatomical location of all visualised sentinel nodes.

Planar images identified 399 SLNs in 188 (84,3 %) women, with a mean of 2,1 ± 1,5 (range 0-12 nodes) per patient. In the remaining 35 patients no SLNs were detected on planar images. 91 lymphnodes in 64 (28,7 %) patients were missed on planar images, but identified on SPECT/CT. However, 22 (5,5 %) foci of uptake in 17 (7,6 %) patients interpreted on planar images as hot LNs were found to be false positive non-nodal sites of uptake when further assessed on SPECT/CT. On SPECT-CT images, 468 hot nodes were detected in 196 (87,9 %) patients with a mean of 2,4 ±1,7 (range 0-11) nodes per patient. In the remaining 27 (12,1 %) patients, SPECT-CT was negative.

In GROUP A the overall hot LN detection rate by planar and SPECT-CT lymphoscintigraphy was 87,9 % (167 patients). In remaining 23 patients (12,1 %) both imaging techniques failed to detect hot LNs. In 10 patients (5,3 %), hot LNs were detected only by SPECT-CT. 80 lymphnodes in 55 (28,9 %) patients were missed on planar images, but identified on SPECT/CT. 18 (5,3 %) foci of uptake in 13 (6,8 %) patients interpreted on planar images as hot LNs were found to be false positive non-nodal sites of uptake when further assessed on SPECT/CT.

In GROUP B the overall hot LN detection rate on planar and SPECT-CT was 97 % (32 patients). Both planar and SPECT-CT imaging failed to detect hot LNs in 1 (3,0 %) patient, hot LNs were detected only on SPECT/CT images in 1 (3,0 %) patient. 11 lymphnodes in 9 (27,3 %) patients were identified only on SPECT/CT. However, 4 (6,6 %) foci of uptake in 4 (12,1 %) patients were found to be false positive when further correlated with SPECT/CT.

Among the patients in whom SPECT-CT identified hot nodes, the location of these nodes was as follows (Tables **1** and **2**):

Parasternal (Internal Mammary Chain - IMC) Nodes

In 25 (11,2 %) patients, respectively in 22 (11,6 %) patiens in GROUP A and in 3 (9,1 %) patients in GROUP B, there were identified parasternal lymphnodes on SPECT/CT, however their localisation was ambiguous on planar images. As harvesting of IMC nodes is not routine procedure at our hospital, we do not know whether the hot nodes suggested preoperatively were involved with tumour.

Intraoperative SLNs detection (hot and blue positive; only hot; only blue) in these two groups of patients found 412 SLNs. SLN involvement was identified in 71 SLNs (17,2 % of 412 removed SLNs) in 58 patients (29,1 % of 199 patients). Thirteen of 71 positive SLNs presented a single micrometastatic deposit. Eleven SLNs with metastasis and four SLNs with micrometastasis were detected by SPECT/CT and not by planar lymphoscintigraphy, i.e. fifteen nodes identified only on SPECT/CT were positive for

Table 1.   Location of SLNs in the Group A

GROUP A	Patients	Axilla	Parasternal	Other	Static
Upper quadrants	15	23 (88,5%)	3 (11,5%)	0	18
Lower quadrants	4	6 (54,5%)	2 (18,2%)	3 (27,3%)	8
Inner quadrants	4	4 (57,1%)	2 (28,6%)	1 (14,3%)	7
Outer quadrants	16	31 (91,2%)	0	3 (8,8%)	26
Upper outer quadrant	76	120 (87,6%)	13 (9,5%)	4 (2,9%)	116
Upper inner quadrant	29	45 (84,9)	7 (13,2%)	1 (1,9%)	50
Lower outer quadrant	31	65 (73,9%)	20 (22,7%)	3 (3,4%)	74
Lower inner quadrant	11	21 (63,6%)	10 (30,3%)	2 (6,1%)	31
Central portion	4	11 (100%)	0	0	8

Table 2.   Location of SLNs in the Group B

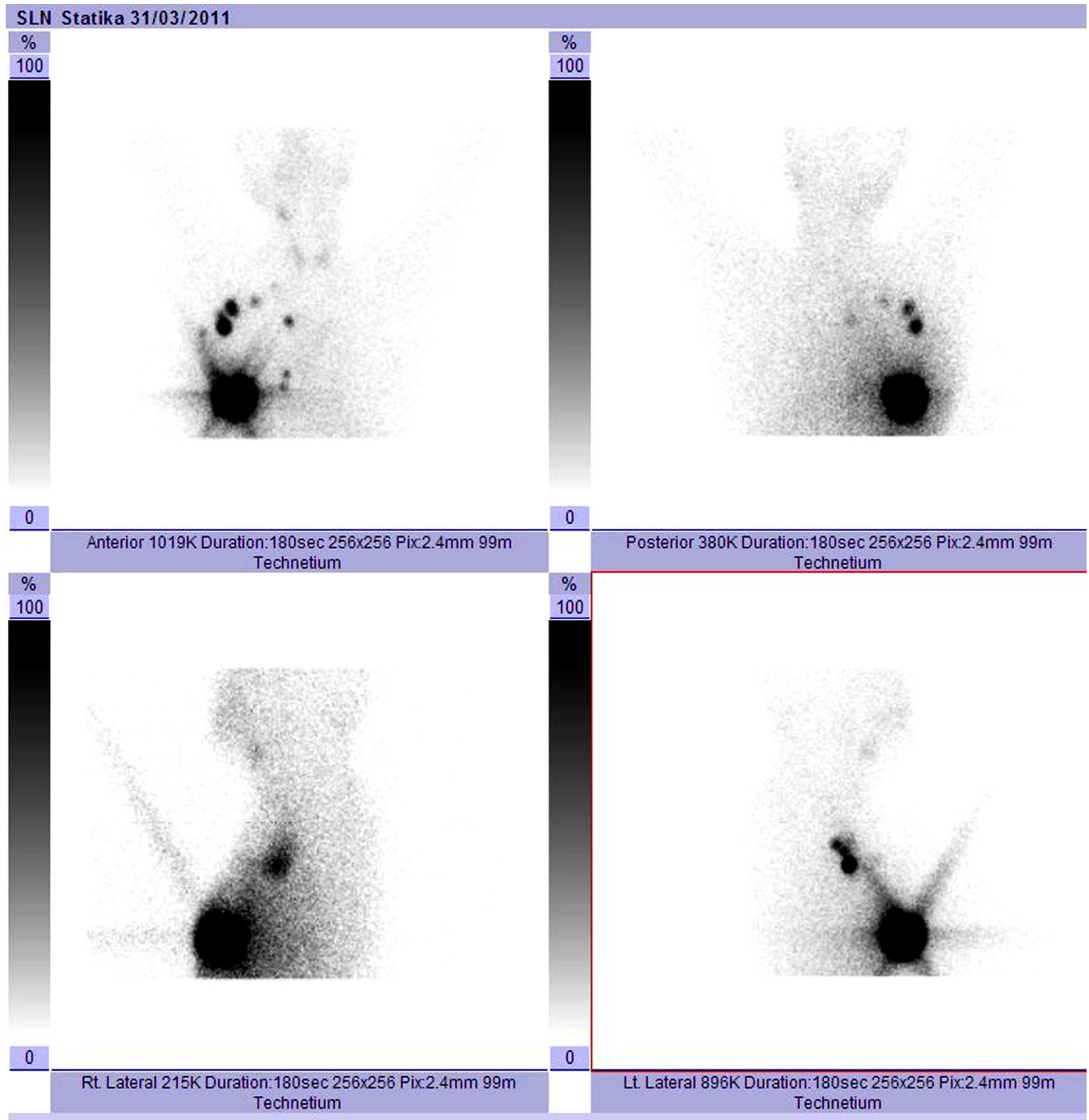| GROUP B	Patients	Axilla	Parasternal	Other	Static
Upper quadrants	4	8 (72,7%)	2 (18,2%)	1 (9,1%)	13
Lower quadrants	0	0	0	0	0
Inner quadrants	1	2 (100%)	0	0	2
Outer quadrants	7	14 (100%)	0	0	11
Upper outer quadrant	9	23 (95,8%)	1 (4,2%)	0	21
Upper inner quadrant	1	1 (100%)	0	0	1
Lower outer quadrant	0	0	0	0	0
Lower inner quadrant	1	1 (100%)	0	0	1
Central portion	10	13 (86,7%)	2 (13,3%)	0	12

Fig. (1). Static lymphoscintigram in 38 years old woman with right sided breast cancer in upper outer quadrant. On the planar scintigrams it is not possible to correct localise lymph nodes (axillary and parasternal).

tumour. Fifty-six metastatic SLNs were detected by means of SPECT/CT and planar scintigraphy.

Differences in detection of SLNs between planar and SPECT/CT imaging in all 223 patients were statistically significant (P< 0.001), in GROUP A also statistically significant (P< 0.001). In GROUP B differences were not statistically significant (P = 0.055).

DISCUSSION

In patients with a palpable mass we inject radiopharmaceutical in four peritumoral sites and one subdermal injection under the tumour because we as Cheng *et al.* [10] believe that both deep and superficial injection approaches are valid techniques and are complementary. The combination of both injection techniques (either peritumoral
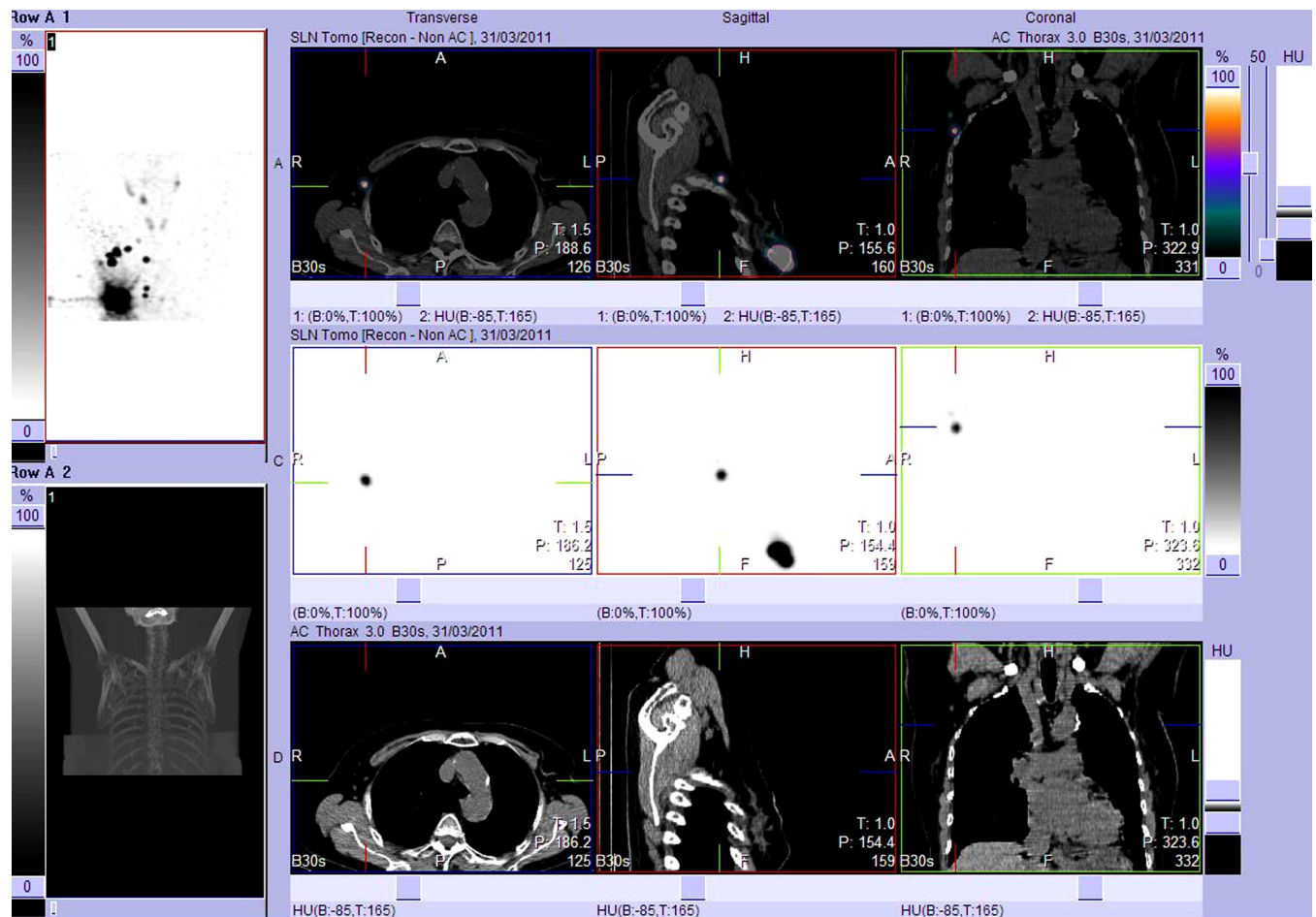
Fig. (2). Lymphoscintigram: fusion of SPECT/CT in 38 years old woman with right sided breast cancer in upper outer quadrant - axillary SLNs.

and subareolar injections or subdermal and peritumoral injections) may improve detection accuracy and decrease the false-negative rate [10].

Hybrid SPECT/CT camera fuses tomographic lymphoscintigrams (physiological information) with anatomical data from CT [19, 20]. In comparison with traditional single-modality imaging approaches, the dual-modality systems offer unique capabilities in combining data from two imaging modalities in way that simplifies, yet facilitates, image correlation with the goal of revealing useful diagnostic information that is not easily extracted when the imaging studies are performed independently [21]. Hybrid SPECT/CT provides better contrast and resolution than planar imaging with possibility to correct an attenuation and scatter [22, 23]. SPECT/CT images provide the topographic landmarks that may further facilitate surgical exploration [20] with improvement of surgical SLNs detection. If only used to correct the radionuclide image for photon attenuation, the CT data can be acquired with a considerably lower statistical quality and coarser spatial resolution than required for diagnostic-quality imaging and therefore can deliver a significantly lower radiation dose than that for a diagnostic CT study [21]. Planar nuclear medicine image fusion with CT topograms has been proven feasible and offers a clinically suitable compromise between improved anatomic details and minimally increased radiation dose [11].

Hybrid system allows transmission (low-dose CT) and emission (SPECT) scans to be performed without changing the patient´s position, thereby allowing for automatic and correct record of images obtained with two modalities. Fusion of two images into one image is easier [20, 24].

The introduction of hybrid SPECT/CT into daily practice is associated with additional costs and requires extra time [25]. But additional costs are not so high, because we use our hybrid camera for many other examinations. The advantages of additional SPECT/CT may prevail when used in specific situation only [13]. Contamination, nodes close to the injection site, and overweight patients are three noted instances in which SLN identification and localisation are better with SPECT than with standard planar methods [26, 27]. Lerman *et al*. [28] compared planar images to SPECT/CT in SLNs mapping of breast cancer in 157 patients. They found that 13% of the SLNs were only identified by lymphoscintigraphy on SPECT/CT due to obscuring by the scattered radiation from the injection site, two SLNs misinterpreted as one on planar images. Unexpected sites of drainage were found in 33 patients. A total of 4% of the hot lesions on planar images were false-
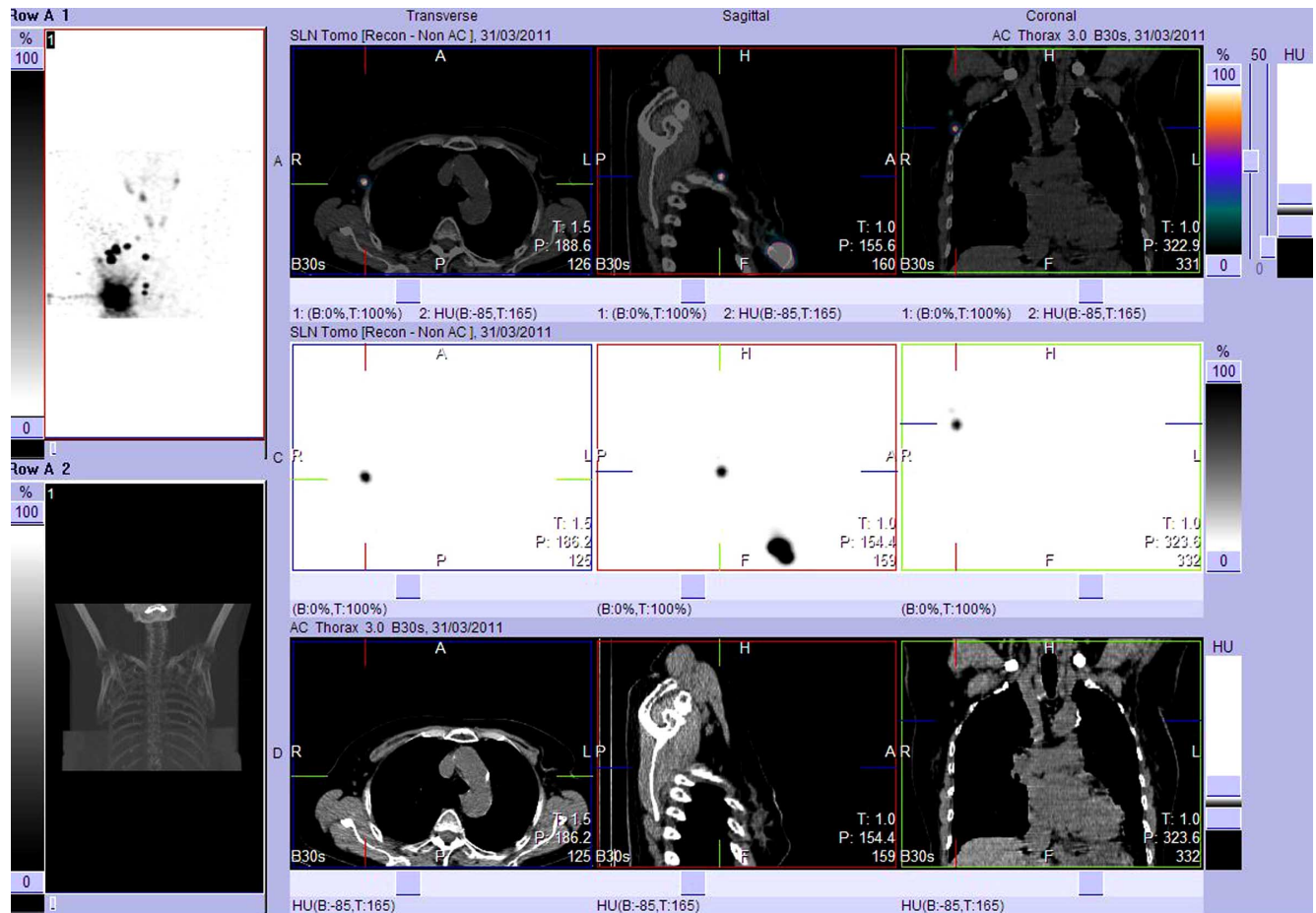
Fig. (3). Lymphoscintigram: fusion of SPECT/CT in 38 years old woman with right sided breast cancer in upper outer quadrant - SLNs in IMC.

positive nonnodal sites of uptake that could be correctly assessed by SPECT/CT imaging [28]. Beitsch *et al.* [14] reported that detection of axillary lymph nodes could be rendered difficult by "shine through" when using a peritumoral injection site, especially in patients with upper outer quadrant tumours. The authors consequently adapted the subareolar injection technique, moving the radioactive injection away from the axilla, where most draining nodes are supposed to be located [14]. Argon *et al.* [29] conclude that periareolar intradermal injection of radiocolloid combined with peritumoral intraparenchymal injection of blue dye is an accurate and easy method of locating SLN with very high detection rates but with low visualisation rate of the internal mammary nodes.

Besides breast cancer, the use of SPECT/CT has been described in SLN lymphadenectomy for head and neck cancer, melanoma, prostate cancer, bladder cancer, vulvar, cervical and endometrial cancer - the value of SPECT/CT for SLN identification and localization has been described in several reports [30-40]. In special instances, SPECT/CT imaging allows for improved detectability and interpretation of lymphatic drainage.

Low radiation dose is added to the scintigraphic mapping by the low-dose CT, ranging from 1,3 mGy at the centre to 5 mGy at the surface of the body [20]. We use „low dose" CT

with reasonable low radiation with sufficient anatomical details. According to our scanning protocol we evaluated the radiation exposure from spiral CT to about 1.5 millisieverts (mSv). It is still a half of exposure from standard two views breast mammogram (avg. 3 mSv). Because of hybrid system, CT scanning following SPECT acquisition directly, there is not additional manipulation with patient needed, so the total acquisition time is not prolonged considerably.

The better resolution of SPECT itself, the improved quality of attenuation-corrected SPECT images and the improved anatomical localisation of nodes offered by the three-dimensional data of the SPECT reconstructed planes as well as the anatomical landmarks on CT may have contributed to the better nodal identification by SPECT/CT found in the study of Lerman *et al.* [28].

After the ipsilateral axilla, the second most frequent drainage basin from breast tumour sites is the internal mammary chain (IMC) with wide variability in the rate of detection of this drainage [41]. In our study, SLN in IMC were detected in 25 of the 223 patients (11,2 %). These LNs were clearly identified on SPECT/CT. In 24 patients in our study (10,4 %), lymphoscintigraphy failed to detect hot nodes. Possible cause can be SLN involvement [42], altered lymphatic drainage pathways in patients with breast implants, post reduction mammoplasty or after axillary

surgery, previous neoadjuvant chemotherapy and radiation therapy. Nonvisualisation of SLNs is higher in overweight patients [43] and in older patients. Lerman *et al*. [43] stated that the rate of false-negative planar imaging results for 122 overweight and obese patients was 28%, higher than that for the general study population. The rate of false-negative SPECT/CT results for these 122 patients was also higher than that for the general study population, 11%; however, the latter modality identified hot nodes in 18 additional patients (53%) and had a statistically higher rate of SLNs detection in overweight patients. The addition of SPECT/CT to the acquisition protocol for lymphoscintigraphy in overweight and obese patients with breast cancer improves the identification of SLNs and avoids false-positive interpretations of sites of nonnodal uptake. In our next study we would like to verify these facts in groups of overweight, obese and older patients.

Ploeg *et al*. [44] showed that SPECT/CT visualised lymphatic drainage in 53% of the patients in whom planar lymphoscintigraphy had failed entirely. Three of the additionally visualised sentinel nodes were tumour-positive and prompted axillary node dissection. In two of the 13 patients (15%) with only extraaxillary sentinel nodes on their planar lymphoscintigram, SPECT/CT showed an axillary sentinel node that proved to be uninvolved. In our present study we proved that from seventy-one metastatic SLNs eleven with metastasis and four with micrometastasis were detected by SPECT/CT and not by planar lymphoscinti-graphy, i.e. fifteen nodes identified only on SPECT/CT was positive for tumour. Fifty-six metastatic SLNs were detected by means of SPECT/CT and planar scintigraphy.

Before the introduction of SPECT/CT, various methods were described to improve the visualization rate of SLNs on planar images. Alterations in the colloid particle concentration, in the amount of radiotracer and in the time of imaging (early versus delayed), a second injection of the radiopharmaceutical, and post-injection massage have all been advocated to enhance the number of visualised SLNs [45-48]. The combination of all these improvements in the technique has led to a high sensitivity of lymphoscintigraphy. SPECT/CT, therefore, should only be performed in selected patients, i. e. those with an unusual lymphatic drainage pattern, with planar images that are difficult to interpret or with no visualization on planar images. In these patients, SPECT/CT appears to have additional value [13]. Moreover, SPECT/CT provides an anatomical overview in two- and three-dimensional perspectives creating a surgical road-map that cannot be provided by planar images or intraoperative lymphatic mapping techniques. The present study confirms the additional value of SPECT/CT in the anatomical localisation of (additional) SLNs and underlines its relevance for the surgical approach. SPECT/CT in our opinion, therefore, facilitates surgical exploration in difficult cases and may improve staging. Other investigators have also concluded that additional SPECT/CT after planar lymphoscintigraphy resulted in an improved anatomical localisation of SLNs. Especially SLNs outside the axilla and nodes close to the injection site were easier to identify using SPECT/CT [13, 28, 49]. In a study of its value in breast cancer patients not preceded by planar lymphoscintigraphy, SPECT/CT was also found to enable a precise characterisation of the size,

depth and anatomical location of the sentinel node [50]. Neither in the present study nor in studies by other investigators did SPECT/CT miss a sentinel node that was visualized by planar lymphoscintigraphy [12]. SPECT/CT was able to accurately bring to light sites of skin contamination with the radiopharmaceutical that on planar images were mistaken for sentinel nodes in 17 patients (7,6 %). In other studies, 4-17% of the radioactive spots that were thought to be SLNs on the planar scans were precisely classified by SPECT/CT as nonnodal sites of uptake, such as contamination [12, 28, 49]. Even if SPECT/CT is not successful, it seems worthwhile to not give up. By careful exploration of the axilla with the combined use of blue dye, a gamma probe and intraoperative palpation, a fair number of patients can be identified as node-positive and undergo the axillary clearance they need and others can be spared such a procedure that does not benefit them [48].

Ploeg *et al*. [13] limited the use of SPECT/CT to difficult and unusual cases because they believe planar lymphoscintigraphy is an excellent preoperative mapping technique for most patients. They added nonvisualisation as a new indication, because SPECT/CT visualized drainage in patients whose planar images did not reveal a SLN. They believe that the added costs and extra time for SPECT/CT are more justified when the procedure is used for this new indication. The potential benefit of using SPECT/low-dose CT technology for SLN identification is derived from the improved lesion detectability of SPECT, from the improved quality of the CT attenuation-corrected SPECT images, and from the improved anatomic localisation of nodes, achieved by the 3-D data of SPECT as well as the anatomical data of CT. Pitfalls of planar lymphoscintigraphy interpretation may be avoided by adding SPECT/CT to the acquisition protocol of scintigraphic SLN mapping. Two close SLNs can be clearly separated on SPECT images. SLNs showing only faint activity on planar images, if deeply located, may be better identified on SPECT. SPECT/CT may reduce the false-positive rate by differentiating between nodal and extranodal foci such as skin folds or radioactive contamination, which can be misinterpreted as hot lymph nodes on planar images [24] (Figs. **1-3**).

CONCLUSION

The addition of SPECT/CT to planar lymphoscintigraphy may improve the localisation of preoperative draining nodes in patients with breast cancer. It may detect SLNs nodes missed by planar imaging, exclude non nodal false positive sites of uptake and accurately localise axillary and extra-axillary nodes.

ACKNOWLEDGEMENT

CONFLICT OF INTEREST

Declared none.

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