Abstract

BACKGROUND: Aim of the study was to assess the role of planar lymphoscintigraphy and fusion imaging of SPECT/CT in sentinel lymph node (SLN) detection in patients with various types of tumours and to estimate some factors influencing detection success — age and body mass index.

MATERIAL AND METHODS: Planar scintigraphy and hybrid modality SPECT/CT were performed in 550 consecutive patients (mean age 58.1 ± 13.1 years): 69 pts with gynaecological tumours (37 pts with cervical cancer, 25 pts with endometrial cancer, 7 pts with vulvar carcinoma; mean age 54.4 ± 13.2 years), 161 consecutive patients with melanomas (mean age 57.1 ± 14.8 years), and 320 consecutive women with breast cancer (mean age 59.4 ± 12.0 years). The radiopharmaceutical was injected around the tumour (gynaecological and breast cancers, melanomas), subareolarly (in some breast cancers), or around the scar (in melanomas after their removal). Planar and SPECT/CT images were interpreted separately by two nuclear medicine physicians.

RESULTS: Planar scintigraphy did not show SLN in 77 patients (14.0%): in 8 pts with gynaecologic tumours, in 23 pts with melanomas and in 46 pts with breast cancer. SPECT/CT was negative in 49 patients (8.9%): in 4 pts with gynaecologic tumours, in 12 pts with melanomas and in 33 pts with breast cancer. In 199 (36.2%) patients the number of SLNs captured on SPECT/CT was higher than on planar imaging. 35 foci of uptake (3.1% from totally visible 1134 foci on planar images) interpreted on planar images as hot LNs were found to be false positive non-nodal sites of uptake when further assessed on SPECT/CT. SPECT/CT showed the exact anatomical location of all visualized sentinel nodes. Influence of the age and BMI: The group of patients with higher number of detected SLN on SPECT/CT than on planar scintigraphy had lower average age than the group of patients with the same number of detected SLN on SPECT/CT and on planar scintigraphy, the difference was statistically significant (P=0.008). BMI did not differ between the two groups.

CONCLUSION: In some patients with gynaecologic and breast cancers and melanomas, SPECT/CT improves detection of sentinel lymph nodes. It can image nodes not visible on planar scintigrams, exclude false positive uptake and exactly localize axillary, inguinal, pelvic and paraaortic SLNs. It improves anatomical localization of SLNs. We have found the influence of the age on the difference in the number of SLNs detected by the fusion of SPECT/CT and planar lymphoscintigraphy. On the other hand, this difference was not influenced by BMI.

KEY words: sentinel node, gynaecologic cancers, breast cancer, melanoma, lymphoscintigraphy, planar scintigraphy, SPECT/CT
Background

Sentinel lymph node (SLN) has been incorporated in the routine management of various types of solid tumour [1–3]. Lymph node status in malignant tumours remains a most important prognostic factor for recurrence and survival and a major decision criterion for adjuvant therapy [4, 5]. Sentinel lymph node biopsy is the most accurate and the only reliable method for nodal staging which can diagnose microscopic tumour spread to the regional lymph nodes. Lymphoscintigraphy visualizes where lymph from the primary tumour site travels and, therefore, is an essential element of lymphatic mapping [6, 7]. The use of lymphatic mapping, SLN identification and biopsy in patients with some types of malignant tumours may help reduce the morbidity of surgery. Minimal invasive SLN biopsy can replace lymphadenectomy for staging. Planar lymphoscintigraphic imaging is an important element in lymphatic mapping, but interpretation of planar lymphoscintigrams is hindered by the absence of anatomical landmarks in the scintigraphic image [8]. An essential step in the procedure for SLN biopsy is to locate the first-echelon node of draining basin. In some patients, however, the lymphoscintigram shows a drainage pattern that is difficult to interpret and in a small minority no sentinel node is depicted at all [9]. Sentinel lymph node biopsy has an established role in malignant melanoma and breast cancer [3, 10]. A group of patients who might benefit from a SLN biopsy are those with cancer of the uterine cervix and other gynaecological malignancies.

In our study we compare hybrid SPECT/CT and planar lymphoscintigraphy in patients with various tumours and explore the value of SPECT/CT — mainly for detection of additional SLNs, the exact anatomical localization of SLNs, and differentiation of skin contamination. We estimated some factors influencing detection success of SLN — age and BMI.

Materials and methods

Patient population

Planar and hybrid SPECT/low-dose CT lymphoscintigraphy were performed in 550 consecutive patients (mean age 58.1 ± 13.1 years, BMI 27.8 ± 5.1): 69 pts with gynaecological tumours (37 with cervical cancer, 25 pts with endometrial cancer, 7 pts with vulvar carcinoma; mean age 54.4 ± 13.2 years, BMI 27.5 ± 5.0), 161 consecutive patients with melanomas (87 men, 74 women; mean age 57.1 ± 14.8 years, BMI 28.4 ± 5.1), and 320 consecutive women with breast cancer (mean age 59.4 ± 12.0 years, BMI 27.6 ± 5.1) with no clinical evidence of lymph node metastases (N0) and no remote metastases (M0).

Lymphoscintigraphic method

In patients with gynaecologic tumours (GROUP A), we performed preoperative lymphoscintigraphy utilizing Tc-99m-Tc-colloid, activity 40 MBq, on the operation day (one-day protocol). Gynaecologists made 4 injections of colloid around the tumour. Scintigraphy followed 25–60 minutes after injection. In melanoma patients (GROUP B) on the day of surgery (one day protocol), an activity of 100 MBq Tc-99m labelled colloid divided in four equal aliquots of 0.5 ml was injected by nuclear medicine physician in four intradermal injections around the tumour (79 pts) or around the scar (82 pts) after excision of the melanoma. In breast cancer patients (GROUP C) on the day prior to surgery (2 day protocol in 273 patients) or on the day of surgery (one day protocol in 47 women) an activity of 120 MBq of Tc-99m labelled colloid divided in four or five equal aliquots of 0.5 ml was injected by nuclear medicine physician. Women with palpable mass were injected in four peritumoral sites and one subdermal injection above the tumour (273 pts). Patients with nonpalpable tumour were injected in four subareolar sites (47 pts). We have used following Tc-99m-colloids: Nanocis (size of colloid particles 100 nm — 68 pts in all groups), Nanocoll (size of colloid particles to 80 nm — 379 pts), SentiScint (size of particles to 200 nm — 5 pts), NanoAlbumin (size of particles to 80 nm — 98 pts). The choice of radiopharmaceuticals (RF) was totally random. The type of RF was not important because we have compared planar scintigraphy and SPECT/CT performed with the same RF in individual patient.

We previously reported the success of SLNs detection by means of various RFs [3, 11–13] and this is not the aim of our present study.

In melanoma patients, the dynamic scintigraphy (parameters: matrix 128 × 128, 30 frames, 20 s per frame) was done. In all types of tumours, the planar scintigraphy (in melanoma patients planar scintigraphy was done immediately after dynamic scintigraphy) and SPECT/CT lymphoscintigraphy were performed using a hybrid system composed of a dual-head gamma camera with a low-dose CT installed in a gantry (Symbia T2 Siemens).

Planar lymphoscintigraphy was carried out in the anterior, posterior and lateral projections focusing on the area of interest. Acquisition time was 10 minutes. If SLN was displayed, to facilitate the surgical resection a reference mark was placed on the skin with the help of the 99mTc mark, corresponding to the position of the SLN visualized by lymphoscintigraphy. 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 collimators and a two-slice spiral CT scanner optimized for rapid rotation. SPECT acquisition (matrix 128 × 128, 60 frames at 25 s per view) was performed using steps of 6°. CT scan was a low-dose, noncontrast study (130 kV, 17 mAs, B60s kernel), 5 mm slices were created. The iterative reconstruction (OSEM 3D) was used for generating SPECT slices. Both SPECT images and CT axial slices were fused using an Essof 2000 application package (Siemens, Erlangen, Germany). Hybrid 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 localize SLNs in relation to anatomical structures.

Scintigraphic interpretation

Sentinel lymph node localization was interpreted separately on planar and SPECT/CT images. Image analysis was performed prospectively by two experienced nuclear medicine physicians in consensus reading. All images were analysed in two steps: 1. analysis of planar images; 2. analysis of coregistered SPECT/CT images. The location of SLNs was categorized as axillar, inguinal, pelvic, paraaortic and in other lymphatic basins.

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, if they excluded SLN suspected on...
planar images, or if they localized SLNs in additional or different basins than those suggested by planar images.

**Statistical test**

Student’s paired t-test was used for comparing numbers of nodes found by both techniques. F-test, Student’s t-test and Fisher’s exact test were utilized for age and BMI characteristics comparisons. P values < 0.05 were considered significant.

**Surgery**

On the basis of the scintigraphic findings on both planar and SPECT/CT images the surgeon or gynaecologist 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 in all patients before incision to identify the site with the highest counts of lymph nodes in the lymphatic basin. In some patients 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 parasternal (in intramammary chain — IMC) nodes which are not routinely harvested. If some SLNs in patients with breast cancer were metastatic, the axillary dissection was subsequently (in the same day or later) performed.

**Results**

On SPECT/CT images, hot nodes were detected in 501 of the 550 (91.1%) patients, with a mean of 2.9 ± 2.9 (range 1–11) nodes per patient. SPECT/CT showed the exact anatomical location of all visualized SLNs. There was a failure to detect SLNs in the remaining 49 (8.9%) patients. Planar images identified SLNs in 473 (86.0%) patients, with a mean of 2.4 ± 1.7 nodes (range 1–12) per patient. In the remaining 77 (14.0%) patients no SLNs were detected on planar images.

343 lymph nodes in 199 (36.2%) patients were missed on planar images, but identified on SPECT/CT. However, 35 (3.1%) foci of uptake in 29 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 31 (5.6%) patients, who had planar imaging negative, SPECT/CT visualized lymphatic drainage.

In GROUP A (pts with gynaecologic tumours), planar lymphoscintigraphy alone visualized SLN in 61 patients as compared to SPECT/CT imaging that identified SLN in 65 patients. The number of SLNs captured on SPECT/CT was higher than on planar imaging in 38 patients (55.1% of all patients of the GROUP A).

In GROUP B (pts with melanoma), the SLN detection rate by SPECT/CT lymphoscintigraphy was 92.5% (in 149 patients), by planar imaging 85.7% (in 138 patients), respectively. In 12 patients (7.5%) SPECT-CT failed to detect hot SLNs. In 12 patients (7.5%), SLNs were detected only by SPECT-CT and there was no patient with SLN detected only by planar images.

The overall SLN detection rate on SPECT/CT imaging in GROUP C (pts with breast cancer) was 89.7% (in 287 pts), and 85.5% (in 274 pts) by planar scintigraphy. In 33 patients (10.3%) SPECT-CT imaging failed to detect hot SLNs. In 15 (4.7%) patients, SLNs were detected only on SPECT/CT images.

We found the number of lymph nodes detected on SPECT/CT significantly higher than on planar scintigraphy (P < 0.001) both in all 550 patients and in each of three groups (A, B and C).

The age and BMI influencing detection rate by planar scintigraphy and fusion of SPECT/CT:

The group of patients with higher number of detected SLN on SPECT/CT than on planar scintigraphy (199 pts) had lower average age (56.4 ± 13.8 years) than the group of patients (351 pts) with the same number of detected SLN on SPECT/CT and on planar scintigraphy (59.2 ± 12.6 years), the difference was statistically significant (P = 0.008). BMI did not differ in these two groups (average BMI in the group of patients with higher number of detected SLN on SPECT/CT than on planar scintigraphy was 27.7 ± 5.1; average BMI in the group of patients with the same number of detected SLN on SPECT/CT and on planar scintigraphy was 27.9 ± 5.1). The difference was not statistically significant (P = 0.370).

Figures 1, 2, 3, 4, and 5 are the examples of planar scintigrams and fusion of SPECT/CT in 70 years old and obese man which illustrate the asset of SPECT/CT in older and obese patient.

**Discussion**

Sentinel lymph node was defined as the first lymph node draining the primary tumour, i.e. the first lymph node that is at risk for metastatic cells [14]. The histological status of the SLN has been found to be an indicator representative of the whole lymph node basin. It has turned out to be the strongest predictor for tumour recurrence and survival [15].

Lymphatic mapping has been applied extensively in breast cancer and melanoma patients [6, 16, 17]. Amongst gynaecological cancers, the SLN concept has been most accepted for vulvar cancers [18, 19]. A number of researchers have studied SLN detection in vulvar, endometrial and cervical cancer patients [19, 20–24].

The most important prognostic factor in melanomas, breast cancers and gynaecologic tumours is the state of the lymph nodes [13, 25, 26]. There is not suitable pre-surgery examination procedure for detection of affected lymph nodes. The most important benefits of the SLN procedure are avoidance of over treatment and prevention of morbidity [27, 28, 29, 30].

The use of lymphatic mapping and SLN identification may help reduce the morbidity of surgery without compromising the identification of higher-risk patients who require adjuvant treatment. The SLN protocol of enhanced pathologic evaluation of removed nodes may also provide a much more detailed evaluation of these nodes and
Figure 1. 70-year-old man (height 182 cm, weight 110 kg, BMI 33.2) with melanoma on his back in the region of left scapula. In the planar image in anterior, posterior and lateral projections three or four deposits on the left side are observed with no possibility of the exact localization of the SLNs.

Figure 2. The same patient as in the Figure 1. Fusion of SPECT and CT. Exact localization of SLN in the left axilla.
The potential for identifying micrometastasis that may have been missed with traditional pathologic evaluation [31].

Accurate visualization of the SLN is required for the best results. For example, in gynaecological tumours, the conventional lymphoscintigraphy provides planar images with views in only anterior or lateral projection and poor spatial information on the location of pelvic SLN. In melanomas, lymphoscintigraphy has been found to accurately predict the number of nodes in only 81% of the basins, overlooking nodes that were superimposed and could not be separated from other nodes or from the injection site or lymphatic channels and nodes that were beyond the resolution of the planar images [32]. The better anatomic definition and improved resolution that characterize SPECT images may overcome the above limitations of planar images. Localization of hot lymph nodes on SPECT images without anatomic landmarks is not possible.

A decade ago, hybrid imaging combining single-photon emission tomography (SPECT) with computed tomography (CT) was introduced for simultaneously acquiring functional and morphological information [33]. SPECT/CT was introduced in lymphatic mapping with the goal to show more SLNs and to show them more clearly, in order to improve nodal staging [34]. Hybrid SPECT/CT camera fuses tomographic lymphoscintigrams (physiological information) with anatomical data from CT [35, 36]. In comparison with traditional single-modality...
Imaging approaches, the dual-modality systems offer unique capabilities in combining data from two imaging modalities in a 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 [37]. Hybrid SPECT/CT provides better contrast and resolution than planar imaging with the possibility to correct an attenuation and scatter [38, 39]. SPECT/CT images provide the topographic landmarks that may further facilitate surgical exploration [36] 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 [37]. 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 [36, 40]. According to low-dose scanning protocol we evaluated the radiation exposure from spiral CT to about 1.5 millisieverts (mSv). 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 [8]. 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.

By visualizing SLN location and neighbouring structures by SPECT/CT information, less invasive treatment and thus a reduction of operative time, blood loss, and morbidity is likely to occur [33]. SPECT/CT has also been reported to reduce the false-positive interpretation of radiotracer accumulation in the event of contamination or radiotracer in lymphatic vessels [41]. One of the limitations of planar imaging in the detection of SLN is its inability to distinguish nodes that are superimposed [42]. A node close to the injection site can also be masked as the result of strong activity from the injection site (the „shine effect”) [43].

The use of SPECT/CT has been described in SLN lymphadenectomy for breast cancer, head and neck cancers, melanoma, prostate and bladder cancers, vulvar, cervical and endometrial cancers — the value of SPECT/CT for SLN identification and localization has been described in several reports [6, 31, 33, 44–49]. In special instances, SPECT/CT imaging allows for improved detectability and interpretation of lymphatic drainage. Contamination, nodes close to the injection site, and overweight patients are three noted instances in which SLN identification and localization are better with SPECT/CT than with standard planar methods.

The better resolution of SPECT itself, the improved quality of attenuation-corrected SPECT images and the improved anatomical localization 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 Leman et al. [50].

Nonvisualization of SLNs is higher in overweight patients with breast cancer [51]. Lerman et al. [51] 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 detection of SLNs 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.

Before the introduction of SPECT/CT, various methods were described to improve the visualization rate of sentinel nodes 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 visualized SLNs [52–55]. The combination of all
these improvements in the technique has led to a high sensitivity of lymphoscintigraphy. Some authors have stated that 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 [56]. 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 localization of 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 localization of SLNs. Especially SLNs outside the axilla and nodes close to the injection site were easier to identify using SPECT/CT [41, 50, 56]. Neither in the present study nor in studies by other investigators SPECT/CT did miss a sentinel node that was visualized by planar lymphoscintigraphy [34]. SPECT/CT was able to accurately bring to light sites of skin contamination with the radiopharmaceutical.

Thanks to the combined imaging techniques of SPECT and CT, it was possible to distinguish nodal uptake from injection site activity. 3-D SPECT/CT images may identify hidden nodes due to a good separation between counts related to the tracer injection and those of a closely located hot lymph node [57].

In this study, nodes were accurately located to the anatomic sites. Accurate anatomic localization of SLN nodes preoperatively can aid in probe-directed surgery and may reduce operator-dependent variation and time. It is reasonable to consider utilizing SPECT/CT in conjunction with planar imaging when feasible, especially in patients with negative planar imaging, in the hope of enhancing SLN detection and localization. If these data are confirmed, the routine use of SPECT in all patients may potentially have incremental value.

According to our information from literature, so far anybody has ever evaluated the effect of age on the difference in detection success of SLN using planar scintigraphy and SPECT/CT. The effect of the age was investigated only for planar scintigraphy by Birdwell et al. [58] and by Brenot-Rossi et al. [59]. Both authors investigated influence of age only in women with breast cancer and came to opposite results. Brenot-Rossi et al. [59] analysed different parameters, such as the number of positive LNs, presence of lymphovascular invasion, tumour size, tumour grade, histology, prior excisional biopsy, and patient age to determine whether they had any significant correlation with nonvisualization of SLNs in the axillary area. Patient age at diagnosis was stratified as < 70 or > 70 years. An increased risk of unsuccessful axillary mapping was statistically associated with the number of positive axillary nodes. The age showed a statistical trend with lymphoscintigraphy failure: age < 70 years old versus >70 years old (P < 0.096, Fisher exact test) — patient age showed no relation to unsuccessful lymphoscintigraphy. Birdwell et al. [58] compared patients with visualized and nonvisualized SLNs for age, tumour site, size, and histologic findings, injection guidance method, diagnostic biopsy type, interval between biopsy and lymphoscintigraphy, intraoperative identification method, and surgical identification rate. They proved different finding than Brenot-Rossi et al. [59] — there was a statistically significant difference between groups, with an age range of 29–79 years (mean age, 51.8 years) in patients with visualized SLNs and of 40–81 years (mean age, 60.2 years) in patients with nonvisualized SLNs. Patients with nonvisualized SLNs were older than those with visualized SLNs and patients with and those without visualization differed in age. This is similar to experience of Ng et al. [60], who reported an increase in failure to identify SLNs in women older than 50 years of age.

We have found that in people with lower average age, the higher number of SLNs on SPECT/CT than on planar scintigraphy has been detected in comparison with older patients. On the other hand BMI did not differ between the group of patients with higher number of detected SLN on SPECT/CT than on planar scintigraphy and the group of patients with the same number of detected SLN on SPECT/CT and on planar scintigraphy.

**Conclusion**

The addition of SPECT/CT to planar lymphoscintigraphy may improve the localization of preoperative draining nodes in patients with vulvar, cervical and endometrial cancers, melanomas, and breast cancers. It may detect SLNs nodes missed by planar imaging, exclude nonnodal false positive sites of uptake and accurately show the exact anatomical location of visualized sentinel inguinal, pelvic, paraaortic, axillary, and extra-axillary nodes in patients with inconclusive conventional lymphoscintigrams. Furthermore, hybrid imaging brought additional value, especially in the group of patients with scar after extirpation of melanoma, where SPECT/CT visualized higher number of SLNs in 20% more cases than in the group of patients prior the primary surgery. Some factors, for example lower age, may influence imaging of SLNs with better results on SPECT/CT compared to planar lymphoscintigraphy. According to our results BMI did not influence detection results with SPECT/CT in comparison with planar lymphoscintigraphy.

**References**


59. PMid:11425971.
