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Results of a prospective multicenter IAEA sentinel node trial on the value of SPECT/CT over planar imaging in various malignancies

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Short running foot line: SPECT/CT over planar imaging

ABSTRACT

We aim to assess the additional value of SPECT/CT over planar lymphoscintigraphy (PI) in sentinel node (SN) detection in malignancies with different lymphatic drainage like breast cancer, melanoma and pelvic tumors.

METHODS.

From 2010 to 2013 1508 patients were recruited in a multicenter study: 1182 breast cancer, 262 melanoma and 64 pelvic malignancies (prostate, cervix, penis, vulva). PI was followed by SPECT/CT 1-3 hours after injection of ^{99m}Tc-colloid particles. Surgery was performed the same or next day.

RESULTS

Significantly more SNs were detected by SPECT/CT for breast cancer (2165 vs 1892), melanoma (602 vs 532) and pelvic cancer (195 vs 138), all $p<0.001$. The drainage basin mismatch between PI and SPECT/CT was 16.5% for breast cancer, 11.1% for melanoma and 51.6% for pelvic cancers. Surgical adjustment was 17% for breast cancer, 37% for melanoma and 65.6% for pelvic cancer.

CONCLUSION

SPECT/CT detected more SNs and changed the drainage territory, leading to surgical adjustments in a considerable number of patients in all malignancies studied but especially in the pelvic cancer group due to its deep lymphatic drainage. We recommend SPECT/CT in all breast cancer patients with no SN visualized on PI, all patients with melanoma of head and neck or trunk, all patients with pelvic malignancies, as well as those breast cancer and melanoma patients with unexpected drainage on PI.

Key words: sentinel node, SPECT/CT, breast cancer, melanoma, pelvic cancer

INTRODUCTION

The status of regional lymph nodes is a major prognostic factor in many malignant tumors. Sentinel lymph node (SN) biopsy in patients with clinically node-negative tumors is a validated technique for accurate staging of nodal disease in breast cancer *(1,2)* and melanoma *(3,4)* and is being used with promising results in other solid tumors including pelvic malignancies *(5,6)*. The use of SN mapping in an increasing list of tumors shows a variety of lymphatic drainage basins containing the SN *(7).* SNs are the lymph nodes draining the primary tumor and therefore the most likely to contain tumor cells spreading to the drainage basin *(8)*. Assuming an orderly progression of lymph flow, the tumor status of the SN predicts the status of the regional draining basin *(1)*. Selective SN biopsy enables the detection of metastatic and occult micrometastatic nodal involvement by thorough histopathologic examination in the intraoperative setting, sparing patients a systematic regional lymphadenectomy when the node is negative.

Planar lymphoscintigraphy (PI) following local injection of radiocolloid is well suited for mapping of regional lymph nodes but occasionally no SNs are visualized, for instance in obese patients or when SNs are located too close to the injection site. In addition, the anatomical information provided by planar scintigraphy is limited and the exact SN location is difficult to define in deeply located nodes *(9,10).* Unexpected basin drainage sites and unpredictable pathways also hinder interpretation of planar images (PI). Single Photon Emission Computed Tomography coupled with X-ray Computed Tomography (SPECT/CT) can overcome most of these limitations due to its superior contrast, resolution and display of exact anatomical landmarks *(11-18).*

In the present study we aim to assess the additional value of SPECT/CT over PI in a large series of patients with tumors draining to different lymphatic drainage basins throughout the body.

MATERIALS AND METHODS

From December 2010 to September 2013, 1508 patients were recruited in a prospective multicenter research project of the International Atomic Energy Agency (IAEA) conducted at 15 centers from 10 different countries. Each institutional review board approved this study and all subjects signed a written informed consent. Tables 1 and 2 display patient characteristics and patients per site. Inclusion criteria were invasive/in situ breast cancer (T1-4); melanoma with Breslow thickness 0.75-4 mm and pelvic carcinoma with tumor size ≤3 cm; all N0, M0. Exclusion criteria were pregnancy, inflammatory breast cancer, palpable node, age below 18 years and refusal to give consent.

General Protocol

Dual-head SPECT/CT gamma cameras with low-energy high-resolution collimators were used (Infinia-Hawkeye GE Medical Systems, Symbia T2-T16 Siemens and Precedence 6 Philips). PI was performed with 5-minute (min) static images obtained in anterior, posterior, oblique and lateral views as deemed adequate (matrix 256x256, prostate cancer 512x512). A ^{57}Co flood source was placed to delineate the body contour. SPECT/CT was performed immediately after planar acquisition, comprising between 80 and 120 20-40 second(s) views (matrix 128x128, cervix cancer 64x64). Patient position for SPECT/CT was supine with the arms above the head in breast cancer, and along the body sides in the rest. Reconstruction was iterative using OSEM algorithms. CT data was used for attenuation correction and anatomical localization of lymph nodes. First draining nodes in a basin, and all lymph nodes visualized with a lymphatic duct draining from the injection site were considered as SNs. Lymph nodes depicted in different basins than those of the first draining nodes were also considered as SNs. The number of SNs and their draining basin localization was evaluated separately on planar and SPECT/CT images to establish the incremental value of SPECT/CT over planar scintigraphy (additional SNs and/or mismatch in localization). In patients with superficial drainage the site of SNs was marked on the skin with a felt-tip pen. Planar and SPECT/CT images were discussed with the surgeon.

Lymphoscintigraphy was performed following injection of ^{99m}Tc-labeled colloid particles, Nanocoll (GE Healthcare) in most cases (breast carcinoma 39.8%, melanoma 36.5%, pelvis 100%). Gentle massaging of the injection site was performed for a few minutes immediately after injection in breast cancer and melanoma patients and movement of the ipsilateral arm was encouraged before imaging in breast cancer patients. Table 3 displays the injected doses and volumes.

Breast Cancer

Breast cancer was present in 1182 patients. Axillary ultrasonography was performed in patients with clinically negative axillae, and suspicious nodes underwent fine-needle aspiration cytology. Radiopharmaceutical injection was periareolar, peritumoral or both in 58.2%, 28.2% and 13.6% of patients respectively. Injection was guided by ultrasonography in 26.2% of cases.

Melanoma

Melanoma of intermediate thickness (Breslow 0.75-4 mm) and no evidence of palpable lymph nodes was present in 262 patients. The radiopharmaceutical was administered intradermally within 1 cm from the tumor or biopsy site. A 20-30 min dynamic study comprising 0.5-1 min frames was acquired immediately following injection. For head and neck melanomas the dynamic acquisition comprised 15 s frames for 15 min. Subsequently, planar images and SPECT/CT were acquired. Surgery was the same day in 47.2% of patients and the day after in 52.8%.

Pelvic Cancer

Pelvic cancer with no evidence of abnormal enlarged lymph nodes was present in 64 patients. In prostate cancer patients intraprostatic injections (two into each lobe) were given under guidance of transrectal ultrasound followed by flushing with 0.7 ml saline. Patients received antibiotic therapy to prevent prostatitis.

Planar images were acquired 15 minutes and 2 hours post-injection and SPECT/CT after the late planar views. Surgery was performed the same day in all patients. Cervix cancer patients received superficial peritumoral (intradermal/submucosal) injections of radiopharmaceutical. In patients with penile or vulvar cancer, ^{99m}Tc-labeled colloid particles were injected following preparation with anesthetic spray. A 45 min dynamic study comprising 1 min frames was acquired immediately following injection. Next, PI and SPECT/CT were acquired. Surgery was the same day in 83.3% of the patients and the day after in 16.7%.

Statistical Methods

Results were presented as the mean $\pm$ SD for continuous variables and frequencies (proportions) for categorical variables. Comparisons were performed using paired t-test. Two tailed p–value <0.05 was considered significant for all tests. Calculations were performed using IBM SPSS Statistics (version 20).

RESULTS

Significantly more SNs were detected by SPECT/CT when compared to PI in the three groups of patients, p<0.001 (Table 4). There were no significant differences in age and body mass index (BMI) between patients with and without sentinel node detection on either PI or SPECT/CT. Patients´ age and BMI did not differ significantly among the different tumor groups. Tables 4 and 5 summarize results on a SN and patient basis respectively.

Breast Cancer

Planar images failed to visualize a SN in 146 patients (12.3%). Of these, SPECT/CT depicted one or more SN (Fig. 1) in 44 patients, with persistent non-visualization in 102 patients (8.6%). Of these, 56 patients (54.9%) had metastatic nodes on the axillary lymphadenectomy. The location of the 273 additional SNs found in 232 patients was axillary in 134 patients, interpectoral in 34, internal mammary in 27, intramammary in 20, clavicular in 15, contralateral axillary in 1 and contralateral internal mammary in 1. SPECT/CT showed additional SNs in 112 of the 195 patients with drainage mismatch, the remaining 83 patients showing the same number of SNs on either modality. In the latter the most frequent adjustments in drainage territory from PI to SPECT/CT were from axillary to interpectoral (44.6%) and intramammary (21.7%) locations.

The locations of the positive for metastases SNs depicted only by SPECT/CT in 38 patients were axillary, intramammary, interpectoral and infraclavicular in 27, 4, 4 and 3 patients respectively. In 33 of these patients the SN depicted only on SPECT/CT was the only positive node. Internal mammary and other extra-axillary SNs (Fig. 2) were not routinely excised in all centers.

Melanoma

No SN was visualized on PI in 3 patients. SPECT/CT revealed an axillary SN in a trunk melanoma patient and persistent non-visualization in 2 patients with head and neck melanoma. In the latter cervical lymphadenectomy was positive for metastases. The locations of the 70 additional SNs revealed by SPECT/CT in 53 patients were: levels IB, IIB, III, intraparotid and occipital in 6 patients with head and neck melanoma (25%); axillary and clavicular in 11 patients with upper limb melanoma (25.5%); axillary, clavicular and scapular in 29 patients with trunk melanoma (20.5%); and inguinal and popliteal in 7 patients with lower limb melanoma (12.9%). SPECT/CT showed additional SNs in 13 of the 29 patients with drainage mismatch. The 2 patients with a positive SN depicted only by SPECT/CT had trunk melanomas. The locations were axillary and inguinal, the latter being the only positive node in the patient. The surgical approach was modified in 97 patients (37%): 41.6%, 39.7%, 33.3% and 30.2% of head and neck, trunk, lower limb and upper limb lesions respectively.

Pelvic Cancer

In the prostate cancer group no SNs were depicted on PI in 4 patients while SPECT/CT revealed one or more SNs. Locations were obturator in one patient, and internal iliac and obturator in the other three. The locations of the 57 additional nodes revealed in 33 patients, with mismatch versus PI in 32, were: obturator (17), common iliac (13), pararectal (6), presacral (6), internal iliac (4), paravesical (2), paraaortic (2), psoas muscle (2), near the abdominal wall (2), external iliac (2) and aortocaval (1) (Fig. 3). In the 7 patients with the same number of SNs on planar and SPECT/CT imaging the latter provided a more precise localization of the SN in the obturator fossa, common iliac and external iliac basin. SPECT/CT information modified the surgical approach in 33 patients (82.5%).

In the cervix cancer group PI didin´t show SNs in 4 patients, of whom SPECT/CT showed a SN in one patient and persistent non-visualization in the other three. The localization of this additional SN was left mesorectal at the level of the sacro-coccygeal joint. In the remaining 11 patients there were no additional SNs visualized on SPECT/CT. Although SPECT/CT information only changed the surgical approach in the case with the additional SN on SPECT/CT, it increased surgeon confidence in all other cases. PI and SPECT/CT showed SNs in all cases in the penile cancer group. SPECT/CT depicted an extra right inguinal SN in a patient with two inguinal nodes (bilateral) seen on PI. The surgical incision was modified in this and in 5 additional patients (total 85%) without extra SNs due to better localization of the SNs leading to a more precise incision. In the vulva patients, inguinal SNs were seen on PI with no extra SNs visualized with SPECT/CT, nevertheless, the surgical incision was changed due to better localization.

DISCUSSION

Planar lymphoscintigraphy is a robust technique able to provide a roadmap for surgeons by tracing the direct lymphatic pathway from the tumor site to the sentinel node. Its validation in malignancies with simple and superficial lymphatic drainage patterns such as melanoma, breast cancer, penile and vulvar cancer has been easier than for gastrointestinal, urological and gynecological malignancies with deeply located SNs *(12)*. For melanomas of head and neck or trunk, SN localization in the operating room may become difficult due to a more complex anatomy. Also, extra-axillary SNs in breast cancer represent a surgical challenge and cannot always be resected *(13)*. Obesity and SN location near the tumor injection site are additional factors that hamper detection by planar images *(16)*. In the past decennium hybrid cameras enabling SPECT/CT were introduced and are now widely available, enabling fusion images that clearly depict the sentinel nodes in an anatomical relationship with the neighboring vascular structures and surrounding tissues. SPECT/CT however, has a higher cost, increases camera time with related patient discomfort and limited workflow, and delivers a small but non-negligible radiation dose *(16,19)*. In addition, the benefit of retrieving additional SNs has been questioned as more than 3 SNs increases surgery time and pathology costs without significant improvement in diagnostic accuracy in breast cancer patients *(14,20)*.

In our multicenter study PI identified SNs in 87.6%, 98.8% and 87.5% of breast cancer, melanoma and pelvic cancer patients respectively. These visualization rates are in accordance with the reported 63%-88% for breast cancer *(14,16,17)*, 82%-99% for melanoma *(18)* and 84-91% for gynecologic and prostate cancer *(6,7,21)*. SPECT/CT improved the visualization rates to 91.3% for breast cancer, 99.2% for melanoma and 95.3% for pelvic cancer, again in agreement with the reported rates of 81%-97.3% for breast cancer *(16-18)*, near 100% for melanoma *(18)*, and 92.2%-100% for gynecologic and prostate cancer *(6,7,21,22)*. SPECT/CT depicted SNs in 3.7% of breast cancer, 0.4% of melanoma and 4.7% of pelvic cancer patients respectively with no SNs visualized on PI; representing a considerable number of patients that would have undergone lymphadenectomy if only PI was performed. In addition, the metastatic involvement of SNs depicted only by SPECT/CT in 3.2% of breast cancer, 0.8% of melanoma and 3.1% of pelvic cancer patients is also relevant as these patients would have been inadequately staged if SPECT/CT was not performed.

In breast cancer patients it is important to note that SPECT/CT indicated the location of the interpectoral, intramammary, internal mammary and other extra-axillary SNs. Interpectoral lymph nodes are in many cases the primary drainage station in breast cancer, representing a pathway by which skip metastasis may occur, and a potential site of recurrence. The identification of intramammary nodes has clinical implications as they may contain metastases in approximately 10% of operable breast cancers and have been associated with poor disease free survival and outcome. The internal mammary chain is the second most frequent drainage basin from breast cancer after the axilla *(23)* but excision of these nodes is difficult and many surgical teams don´t resect them. Nevertheless, awareness of such drainage is important as it can alter the patient´s management (inclusion in the area of irradiation, systemic therapy) *(24).* However, due to the particular drainage of the breast, the detection of internal mammary nodes has clinical relevance only if dose injection is near the primary tumor *(25)*.

Melanomas of the limbs have predictable drainage patterns to the axilla or groin. In a limited number of cases they drain to popliteal or epitrochlear lymph nodes. However, head and neck melanomas and melanomas located near the midline and in the posterior trunk have variable and unpredictable drainage patterns with pathways not always leading to the nearest basin or leading to multiple basins *(18,26)*. In 5 of our cases the identification of additional scapular and occipital SNs was only possible with SPECT/CT, a notable fact as they must be considered as true SNs *(27)*.

Lymphatic drainage from the prostate is generally to the pelvic nodes but direct drainage outside the pelvic area is a frequent finding *(6)*. Paraaortic nodes are difficult to locate with precision by PI *(7)* and abdominal wall nodes may not be seen at all *(26)*. In our study SPECT/CT identified drainage outside the pelvic area (presacral, aortocaval, paraaortic, abdominal wall and psoas muscle), not visualized by PI in 22.5% of patients; the aortocaval node was one of the metastatic SNs depicted only by SPECT/CT. Furthermore SPECT/CT showed SNs outside the obturator fossa in 82.5% with drainage exclusively outside the obturator area in 22.5%, information relevant to the extension of pelvic lymphadenectomy. Also the depiction of paravesical and presacral SNs, exclusively identified by SPECT/CT, is important as these basins are not included in the area of extended pelvic lymphadenectomy which is frequently considered as the modality of choice to stage the pelvis *(28)*.

The information provided by SPECT/CT modified the surgical approach in 17% of breast cancer, 37% of melanoma and 65.6% of pelvic cancers. The lower than reported *(10)* adjustment rate in breast cancer patients may be explained by the fact that internal mammary and other extra-axillary SNs were not excised routinely in all centers. The global melanoma adjustment rate agrees with previous study results, *(19,26,29)* together with the finding of the greatest benefit for patients with head and neck *(30)* and trunk *(26)* locations. This is not surprising as prediction of the lymphatic drainage pathways of melanoma of the head and neck is very difficult in a region with more than 350 small lymph nodes and fast tracer uptake *(31)*. SPECT/CT excluded non-nodal false positive sites of uptake in 21 breast cancer and 10 melanoma patients, avoiding unnecessary surgical search. Although the global surgical adjustment rate of pelvic cancer patients was 65.6% it was actually higher for prostate (82.5%), and for penile and vulvar cancer (88.8%) patients.

The advantage of this study is that it has been performed prospectively by different institutions around the world, using different techniques. In spite of this, the results are similar to previously published results, confirming the accuracy of the research. A limitation of the study is the small number of patients with pelvic malignancies; there were no patients with testicular or endometrial cancer and only 2 patients with vulvar cancer.

We conclude that SPECT/CT is of great benefit in patients showing no lymphatic drainage on PI, in patients with malignancies located in areas expected to show unpredictable drainage, and in cases expected to drain to deep intraabdominal or retroperitoneal drainage. Based on the results of this study we recommend that SPECT/CT be performed in all patients with breast cancer and no planar SN visualization, all patients with melanoma of head and neck or trunk and all pelvic cancer patients, as well as those breast cancer and melanoma patients with unexpected drainage on PI.

DISCLOSURE

None

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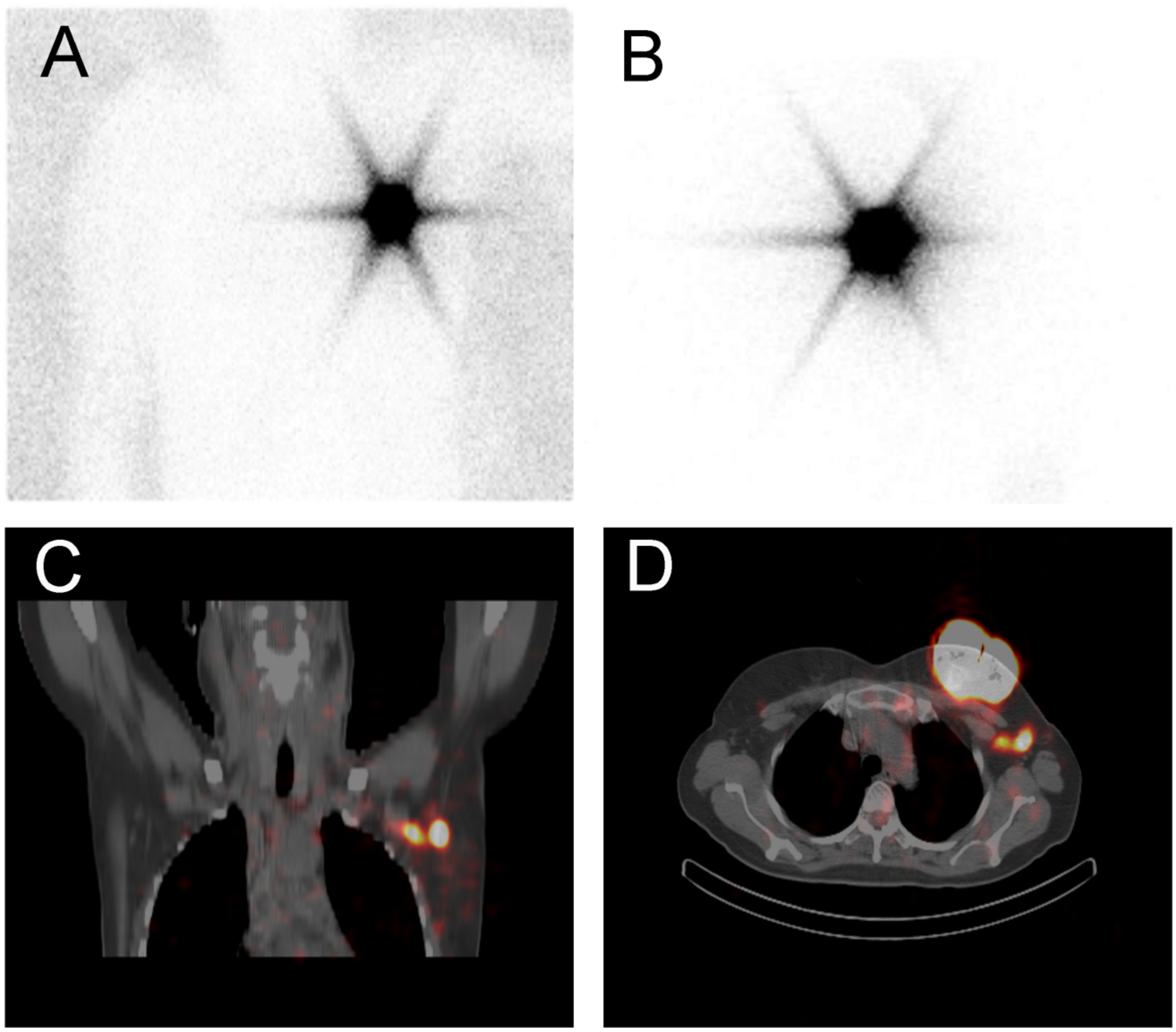

Figure 1. Patient with left breast cancer in the upper inner quadrant of a small breast. No lymphatic drainage is seen on anterior (A) and lateral (B) planar images. SPECT/CT reveals 2 sentinel nodes right behind the tumor (C-coronal and D-transaxial views).

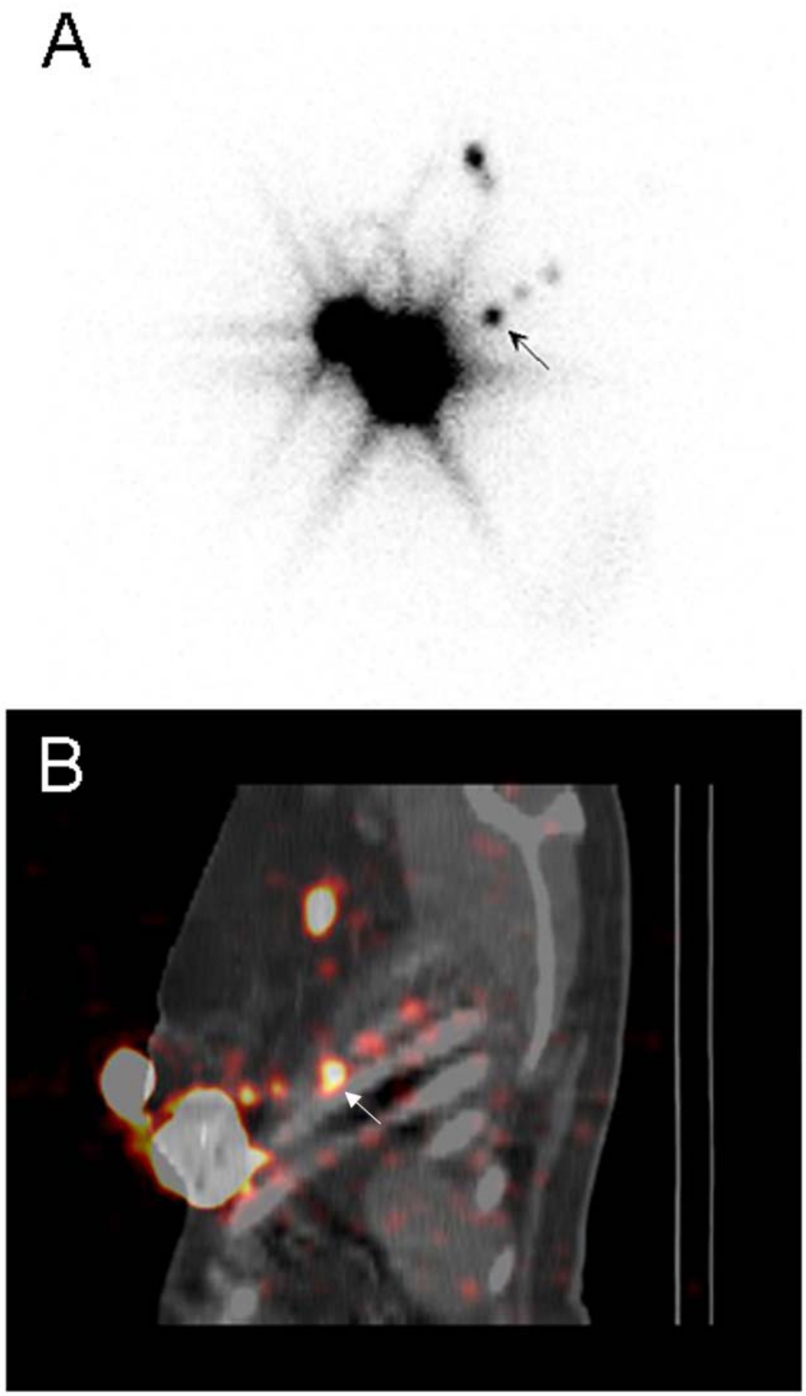

Figure 2. Patient with left breast cancer in the lower outer quadrant. The lateral planar view reveals axillary drainage and lateral nodes of uncertain location (arrow) (A). SPECT/CT clearly depicts three consecutive costal nodes (arrow) in addition to the axillary nodes (B-sagittal view).

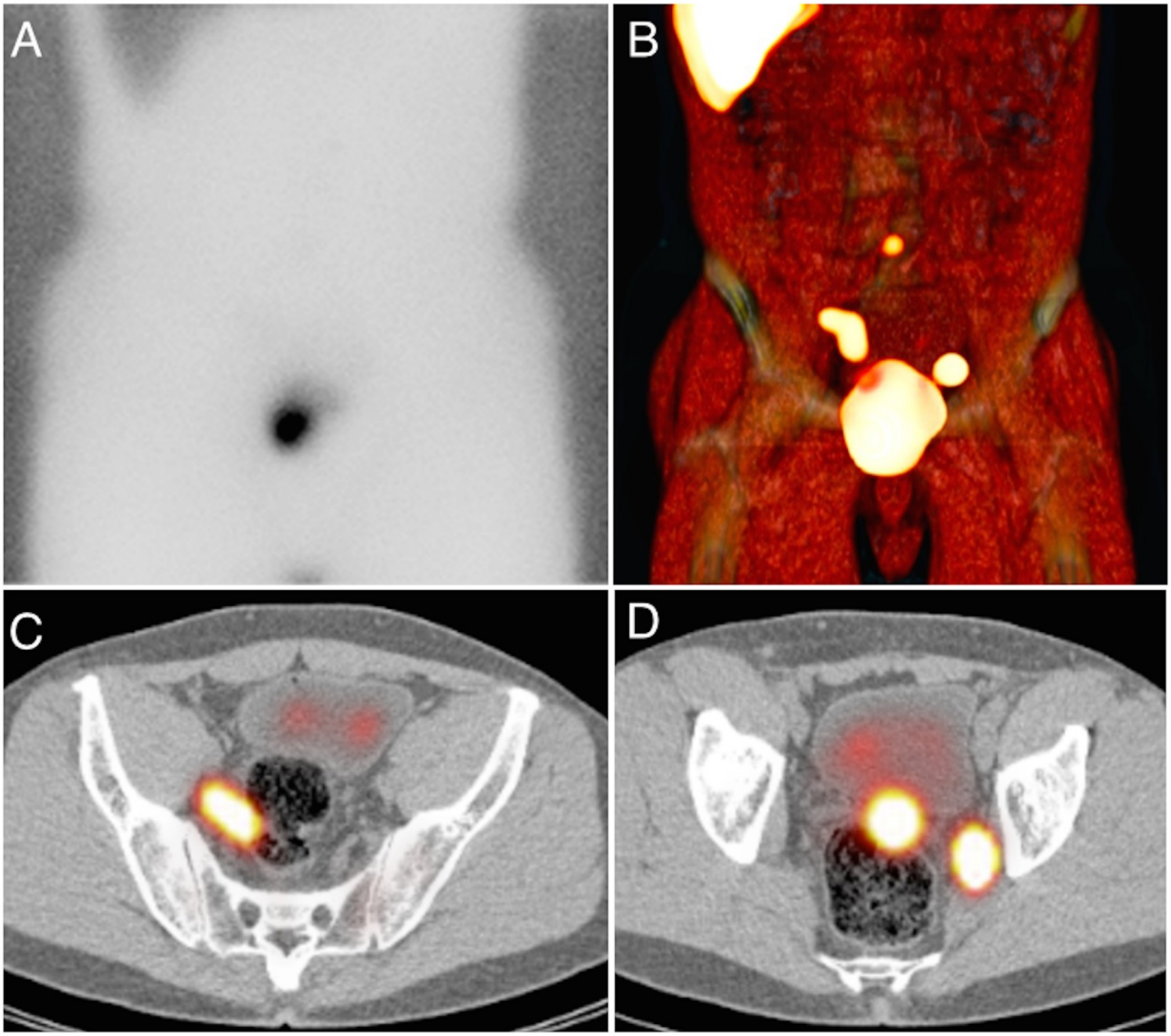

Figure 3. Patient with prostate cancer without evident lymphatic drainage on anterior planar image (A). SPECT/CT displayed with volume rendering (B) shows bilateral drainage to obturator lymph nodes in the pelvis and to a sub-aortic lymph node. The iliac sentinel nodes are seen as hot spots on transversal SPECT/CT fusion images (C, D).

Table 1. Patient characteristics

Characteristic	Breast	Melanoma	Pelvis	
N patients	1182	262	prostate	40
			cervix	15
			penis	7
			vulva	2
Mean age, years	55.2 ± 12.3	53.9 ± 15.2	60 ± 11.3	
Male:female	7:1175	117:145	47:17	
BMI	25.1± 8.2	24.6± 8.7	27± 3.9	

N: number

Table 2. Patients per site

SITE	Breast	Melanoma	Pelvis
Brazil[1]	230	40	
Spain	268		
India[1]	135		
Croatia	79	38	
India[2]	109		
Chile	53	42	1
Bulgaria[1]	48	44	
South Africa[1]	38	38	
Brazil[2]	36	40	
Philippines	72		
India[3]	59		
Bulgaria[2]	46	9	
The Netherlands			40
Colombia	9	11	8
South Africa[2]			15

Superscripted numbers are sites per country

Table 3. Dose and injection details

Patients	Breast	Melanoma	Pelvis	
Injected dose (MBq)	61.4 ± 28.2	50.4 ± 27.4	prostate	214.2 ± 11.6
			cervix	67.6 ± 18.8
			penis/vulva	40.2 ± 9.8
Injected volume (ml)	0.38 ± 0.34	0.49 ± 0.31	prostate	0.4 ± 0.0
			cervix	0.4 ± 0.3
			penis/vulva	0.5 ± 0.2
N injection sites	N patients (%)			
1	824 (69.7)	7 (2.7)	-	
2	212 (17.9)	16 (6.1)	-	
3	53 (4.5)	13 (5.0)	7 (10.9)	
4	80 (6.8)	223 (85.1)	57 (89.1)	
5	13 1.1)	1 (0.4)	-	
6	-	2 (0.8)	-	

N: number

Table 4. PI and SPECT/CT sentinel node findings

Sentinel node detection	Breast cancer	Melanoma	Pelvic cancer
Planar	1892	532	138
SPECT/CT	2165	602	195
Planar and SPECT/CT	1871	522	138
Mean planar SN	1.6±1.3	2±1.3	2.1±1.3
Mean SPECT/CT SN	1.8±1.4	2.3±1.4	3 ±1.65
Positive SNs with SPECT/CT but not planar	44	3	4

Table 5. Patient's sentinel node details and surgical impact

Number of patients (%) with:	Breast cancer 1182	Melanoma 262	Pelvic cancer 64
SN found	1080 (91.4)	260 (99.2)	61 (95.3)
No SN found	102 (8.6)	2 (0.8)	3 (4.7)
Planar detection rate*	1036 (87.6)	259 (98.8)	56 (87.5)
SPECT/CT detection rate*	1080 (91.4)	260(99.2)	61(95.3)
At least one SN SPECT/CT but none planar	44 (3.7)	1 (0.4)	5 (7.8)
Equal SNs planar and SPECT/CT	929(78.6)	199(75.9)	29(45.3)
More SNs planar vs SPECT/ CT†	21 (1.8)	10 (3.8)	0
More SNs SPECT/CT vs planar	232 (19.6)	53 (20.2)	all 35 (54.6) prostate 33 (82.5) cervix 1 (6.6) penis 1 (14.2) vulva 0
No drainage basin mismatch	987 (83.5)	233 (88.9)	31 (48.4)
Drainage basin mismatch	195 (16.5)	29 (11.1)	33 (51.6)
At least one SN positive for metastasis	366 (31)	34 (13)	16 (25)
At least one SN positive for metastasis planar	328 (29.7)	34 (13)	13 (20.3)
At least one SN positive for metastasis SPECT/CT	366 (31)	33 (12.6)	16 (25)
At least one SN positive for metastasis planar but not SPECT/CT	0	0	0
At least one SN positive for metastasis SPECT/CT but not planar	38 (3.2)	2 (0.8)	2 (3.1)
Surgical adjustment ‡	200 (17)	97 (37)	42 (65.6)
Without changes in management if only SPECT/CT performed	0	0	0

*At least one SN found

† Planar SN finding revealed by SPECT/CT to be skin contamination or hold up in lymphatic channels

‡ Patients without changes in management if only planar imaging had been performed