In search of the sentinel node: validation and sophistication of lymphatic mapping and sentinel node biopsy in breast cancer and melanoma
van der Ploeg, I.M.C.

Citation for published version (APA):
van der Ploeg, I. M. C. (2009). In search of the sentinel node: validation and sophistication of lymphatic mapping and sentinel node biopsy in breast cancer and melanoma Amsterdam: Nederlands Kanker Instituut - Antoni Van Leeuwenhoekziekenhuis

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 15

The yield of SPECT/CT for anatomical lymphatic mapping in patients with breast cancer

Van der Ploeg IMC, Nieweg OE, Kroon BBR, Rutgers EJTh, Baas - Vrancken Peeters MTFD, Vogel WV, Hoefnagel CA, Valdés Olmos RA
Eur J Nucl Med Mol Imaging, in press
Abstract

Introduction: The recently introduced hybrid single-photon emission computed tomography camera with integrated CT (SPECT/CT) fuses tomographic lymphoscintigrams with anatomical data of CT. The purpose of this study was to explore this sophisticated technique in lymphatic mapping in breast cancer patients.

Methods: We studied 134 patients who underwent SPECT/CT immediately after late conventional images when these showed an unusual drainage pattern (85 patients), a pattern that was difficult to interpret (27 patients), or non-visualization (22 patients).

Results: Conventional imaging suggested 271 sentinel nodes in 112 of the 134 patients (84%). SPECT/CT showed 269 of these same nodes and indicated that two sites of radioactivity were caused by skin contamination. SPECT/CT visualized nineteen additional sentinel nodes in fifteen patients of whom eleven had non-visualization on conventional images. Twenty-seven patients had one or more tumour-positive sentinel nodes. In four patients (15%), these were visualized only by SPECT/CT. SPECT/CT had no additional value for the surgical approach in eleven patients with persisting non-visualization (8%), and was of questionable value in 67 other patients (50%). Based on the SPECT/CT images, a more precise incision was made in 48 patients (36%), an extra incision in six (4%) and an incision was omitted in two patients (1.5%).

Conclusion: SPECT/CT detects additional sentinel nodes and shows the exact anatomical location of sentinel nodes in breast cancer patients with inconclusive conventional images. SPECT/CT is able to visualize drainage in patients whose conventional images do not reveal a sentinel node. Therefore, SPECT/CT facilitates surgical exploration in difficult cases and may improve staging.
Introduction

Conventional lymphoscintigraphic imaging is an important element in lymphatic mapping, identifying sentinel nodes in more than 95% of breast cancer patients. Occasionally, a conventional lymphoscintigram does not define the exact anatomical location of a sentinel node or displays a lymphatic drainage pattern that is unusual or difficult to interpret.

The recently introduced hybrid single photon emission computed tomography camera with integrated CT (SPECT/CT) fuses tomographic lymphoscintigrams with anatomical data of CT. The patient can stay in the same position during imaging and fusion of the two images into one is easy. Hybrid SPECT/CT provides better contrast and resolution than conventional imaging and has the possibility to correct for attenuation and scatter. This combination of imaging properties results in a clear depiction of the sentinel node within an anatomical landscape providing a valuable surgical roadmap.

The introduction of hybrid SPECT/CT into daily practice is associated with additional costs and requires extra time. The advantages of additional SPECT/CT may prevail when used in specific situations only. We perform SPECT/CT in addition to conventional imaging in patients with unusual lymphatic drainage on the conventional lymphoscintigrams, when there is a lymphatic drainage pattern that is difficult to interpret, and in case of non-visualization.

The purpose of this study was to explore the value of hybrid SPECT/CT in addition to conventional lymphoscintigraphy in breast cancer patients based on these indications. We focused on the detection of additional sentinel nodes by SPECT/CT, the anatomical localization of sentinel nodes and the resulting changes in the surgical approach.

Patients and methods

Between December 1, 2006 and July 14, 2008, 448 breast cancer patients underwent conventional lymphoscintigraphy of whom 134 patients (30%) met the criteria for subsequent SPECT/CT (figures 1-3). Some of these 134 patients had also been included in a previously published pilot study. Their mean age was 54 years. Before lymphatic mapping ultrasonography of the axilla was routinely performed with fine-needle aspiration cytology in case of a suspicious node. Node-positive patients did not undergo sentinel node biopsy.

A dosage of 120 MBq technetium-99m-nanocolloid (Nanocoll®, GE- Healthcare, Eindhoven, the Netherlands) was injected into the tumour in a volume of 0.2 ml shortly before lymphoscintigraphy. Conventional imaging was performed ten minutes, two hours and four hours after injection of the radiopharmaceutical. A dual-head gamma camera equipped with low-energy high-resolution collimators (Vertex®,...
Philips, Eindhoven, the Netherlands) was used. Both anterior and lateral images were routinely obtained and additional images if needed. The lateral views were made with the hanging breast technique to ensure an unobstructed view of the axilla. A cobalt-57 flood source was placed behind the patient to outline the body contour. Conventional lymphoscintigrams showed an unusual drainage pattern in 85 patients, a lymphatic drainage that was difficult to interpret in 27 patients and no sentinel node was visible in 22 patients.

SPECT/CT images were made immediately after the four-hour conventional images. The SPECT/CT system (Symbia T, Siemens, Erlangen, Germany) consists of a dual-head variable-angle gamma camera equipped with low-energy high-resolution collimators and a multislice spiral CT optimized for rapid rotation. SPECT acquisition (matrix 128x128, 60 frames at 25 seconds per view) was performed using six-degree-angle steps. After reconstruction, the SPECT images were corrected for attenuation and scatter. Both SPECT and CT axial five millimetre slices were generated using an Esoft 2000 application package (Siemens, Erlangen, Germany). Fusion of images was performed using an Osirix Dicom viewer (version 2.7) in a Unix-based
operating system (MAC OS X, Power G5, Apple Inc., Cupertino, CA, U.S.A.). The SPECT/CT images were also viewed using two-dimensional orthogonal reslicing in axial, sagittal and coronal orientation. Maximum intensity projections with a three-dimensional display were generated to localize sentinel nodes in relation to anatomic bone structures. A second, intratumoural injection of the radiopharmaceutical (100-120 MBq) was given at four hours in the patients with persistent non-visualization on the SPECT/CT images after which delayed conventional lymphoscintigraphy was repeated. This was not done in patients in whom extra-axillary sentinel nodes had been depicted.

The number and location of the sentinel nodes were determined and described after the conventional imaging as well as after SPECT/CT by a nuclear medicine physician. The location of a sentinel node was marked on the skin with indelible ink. The surgeons decided whether SPECT/CT had an additional value, such as the visualization of an extra sentinel node or a more precise anatomical localization, and whether this led to a more precise incision, an extra incision or the omission of an incision (figure 1 - 3). The precision of the incision was considered to be improved when SPECT/CT showed for instance, a sentinel node more deeply (interpectoral) or more superficially (intramammary) located than thought based on conventional images alone, or when SPECT/CT pointed out the exact location of an internal mammary chain sentinel node behind a rib or the sternum. SPECT/CT images were of questionable additional value when sentinel nodes were visualized that could have possibly been found with the help of blue dye and/or the gamma-ray detection probe.

![Figure 2. Additional value of SPECT/CT in patients with conventional images that were difficult to interpret. SN(s): sentinel node(s), +: additional value for surgeon, *: these axillary nodes were both radioactive and blue and could have also been found guided by blue dye and the gamma probe intraoperatively.](image-url)
The next day, 1 ml patent blue dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) was injected at the tumour site, immediately before the operation. The injection site was massaged for several minutes. The dye and a gamma-ray detection probe (Neoprobe®, Johnson & Johnson Medical, Hamburg, Germany) were used to identify the sentinel node(s). A sentinel node was defined as a lymph node upon which the primary tumour drains directly. Sentinel nodes were pursued in all regions indicated by lymphoscintigraphy. All harvested nodes were fixed in formalin, bisected, embedded in paraffin, and cut at a minimum of six levels at 50 to 150 μm intervals. Pathological evaluation included haematoxylin-eosin and immunohistochemical staining (CAM 5.2; Becton Dickinson, San Jose, CA, USA).

Figure 3. Additional value of SPECT/CT in patients with non-visualization on conventional images. SN(s): sentinel node(s), IMC: internal mammary chain, +: additional value for surgeon, *: these axillary nodes were both radioactive and blue and could have also been found guided by blue dye and/or the gamma probe intraoperatively, **: three axillary and one intramammary sentinel node(s) in four patients revealed a metastasis.
Results

Conventional imaging suggested 271 sentinel nodes in 112 of the 134 patients (84%) with conventional lymphoscintigrams that were difficult to interpret or that showed unusual or no lymphatic drainage. SPECT/CT showed 269 of these nodes and indicated that the other two sites of radioactivity were actually caused by skin contamination with the radiopharmaceutical. SPECT/CT depicted 19 additional sentinel nodes in 15 patients (11%). The mean number of visualized sentinel nodes was 2.4 with a range of one to five nodes after conventional imaging and 2.3 with the same range after additional SPECT/CT.

The additional visualized sentinel nodes were shown in the axilla in four patients with only internal mammary chain sentinel nodes on their conventional images. The other additional sentinel nodes were shown in eleven of the 22 patients (50%) with non-visualization on their conventional lymphoscintigrams. These nodes were situated in the axilla (seven patients), in the breast (three patients) and in the internal mammary chain (three patients).

The additionally visualized sentinel nodes were all harvested. The ones in the axilla were all radioactive and blue, and the ones elsewhere were only radioactive. Three of these axillary sentinel nodes in three patients and an intramammary sentinel node in another patient harboured macrometastases. These were the only involved sentinel nodes in these four patients, which led to upstaging and better tailored management. Surgical exploration of the axilla with the help of the gamma probe and blue dye revealed at least one sentinel node in all eleven patients with persistent non-visualization. Such a blue node was involved in three patients, which prompted a completion dissection.

In seven patients (5%), one intramammary, two infraclavicular, and four internal mammary chain sentinel nodes that were visualized by both imaging modalities could not be retrieved because of a lack of radioactivity during sentinel node biopsy.
Figure 4. A patient with right breast cancer with an unusual lymphatic drainage pattern. The anterior conventional lymphoscintigram (A) depicts an axillary sentinel node (descending arrow), and one internal mammary chain sentinel node (horizontal arrow) with a second-echelon node. The lateral conventional image also shows the axillary node (descending arrow), depicts the internal mammary chain sentinel node close to the injection site (horizontal arrow), and shows the second-echelon node in the internal mammary chain. An axial fused SPECT/CT image (C) shows the sentinel node presumed to be in the axilla (descending arrow) actually to be located between the pectoral muscles and determines the location of the internal mammary chain sentinel node (horizontal arrow) at the second rib. A fused SPECT/CT maximum intensity projection of the thorax (D) shows both these nodes in a three-dimensional perspective.
Figure 5. A patient with left breast cancer and a conventional lymphoscintigram that was difficult to interpret. The anterior conventional lymphoscintigram (A) visualizes a vague radioactive spot (horizontal arrow) above the primary tumour site. The lateral conventional lymphoscintigram (A) shows this same sentinel node (horizontal arrow) that is possibly located in the breast and another sentinel node below the clavicula (descending arrow). Axial fused SPECT/CT tomograms (C and D) show that both nodes are situated between the pectoral muscles (Rotter’s nodes).

In the end, SPECT/CT visualized lymphatic drainage in 123 of the 134 patients (92%) and improved the visualization rate compared to conventional imaging alone with 8%. Of the total of 34 tumour-positive sentinel nodes in 27 patients, four sentinel nodes in four patients (15%) were depicted only by SPECT/CT and three other nodes in three patients (11%) were not detected by either imaging technique but were identified with the help of blue dye. No patient recurred in the axilla or elsewhere in a mean follow-up time of ten months.
Figure 6. A patient with non-visualization on the conventional lymphoscintigram. Conventional lymphoscintigraphy (A and B) shows no (axillary) drainage on either the anterior or lateral image. An axial fused SPECT/CT tomogram (C) shows an axillary (ascending arrow) and an internal mammary chain sentinel node (descending arrow). The fused SPECT/CT maximum intensity projection of the thorax (D) displays both sentinel nodes in a three-dimensional anatomical view and shows the sentinel node in the internal mammary chain just inferior to the first rib (descending arrow).

The additional value of the SPECT/CT images (figures 4 – 6) for the surgical approach was evaluated per indication and is displayed in the flowcharts (figures 1 - 3). There was no additional value of SPECT/CT in eleven patients (8%) with persistent non-visualization. The additional value was considered questionable in thirteen patients (10%) with sentinel nodes in the axilla. It is possible that these sentinel nodes would also have been found with the help of blue dye or the gamma-ray detection probe and the incision was not changed based on the SPECT/CT images. The additional value for the surgical approach was also questionable in 54 other patients (40%) with radioactive internal mammary chain sentinel nodes in the intercostal space. SPECT/CT provided a precise location of such nodes but did not change the surgical approach since the probe...
easily guided the incision. There was an advantage of additional SPECT/CT imaging in the remaining 56 patients (42%). According to the operating surgeons, SPECT/CT images enabled a more precise incision in fourteen patients (10%) with internal mammary chain sentinel nodes underneath a rib, in ten patients (7%) with such nodes in close proximity to the sternum, in six patients (4%) with supraclavicular sentinel nodes, and in eighteen patients (13%) with intramammary or interpectoral sentinel nodes. Six patients (4%) had no visualization of lymphatic drainage on late conventional images, but did have both axillary and internal mammary chain sentinel nodes on SPECT/CT. The internal mammary chain region is not routinely explored and therefore an extra incision was performed based on SPECT/CT alone. In the two patients (1.5%) with two sites of radioactive contamination detected by SPECT/CT, an incision was avoided.

Discussion

SPECT/CT detected 19 additional sentinel nodes in 15 of the 134 patients (11%), of whom eleven had conventional images with non-visualization. SPECT/CT improved the visualization rate in our selected patient population from 84% to 92%. The visualization rate with SPECT/CT in our previously conducted pilot study was 100% in a small group of 31 breast cancer patients. The visualization rate with SPECT/CT in our previously conducted pilot study was 100% in a small group of 31 breast cancer patients. The current visualization rate is similar to the 91% in the series described by Lerman et al. These investigators performed additional SPECT/CT in consecutive breast cancer patients eligible for sentinel node biopsy whereas we restricted our study to patients with problematic lymphoscintigrams or no visualization. Their visualization rate after conventional imaging alone was 85%, which is relatively worse than our 84% since we selected patients with inconclusive lymphoscintigrams. The additional nodes in the study of Lerman et al, were mainly detected in the axilla (70%), a site that, in our study, was not of additional value for the surgical approach. This suggests that performing SPECT/CT in all breast cancer patients is unnecessary. Other studies evaluating the additional value of SPECT/CT in breast cancer patients showed an improvement in the sentinel node visualization rate of up to 17% and the percentage of nodes depicted by SPECT/CT alone was 14%. In four of the 27 patients (15%) with tumour-positive nodes of this series, these nodes were visualized only by SPECT/CT. One of these nodes was located intramammary in a region that would not have been explored without the information provided exclusively by SPECT/CT, the others were located in the axilla and could have been found with the help of the gamma probe and blue dye also. Their identification led to a higher disease stage and a better tailored management. SPECT/CT was of questionable value in 54 patients (40%) with internal mammary chain sentinel nodes located in the intercostal space, because the gamma probe easily guided the incision in these patients. The method was also considered to be of questionable value in thirteen other patients (10%) in whom SPECT/CT detected
axillary sentinel nodes, since these nodes might have been found intraoperatively with the help of the gamma-ray detection probe and blue dye as well. Some surgeons however, will find it of additional value to view such nodes in a two- or three-dimensional SPECT/CT image before starting the operation.

Since SPECT/CT was used in these patients in addition to the intraoperative techniques, the present study cannot definitively determine whether there is a difference in the value of each of these lymphatic mapping methods.

SPECT/CT was valuable in facilitating a more precise incision in 48 patients (36%), an extra incision based on the SPECT/CT images was made in six patients (4%), and an incision was avoided in two patients (1.5%). This assessment of the value of SPECT/CT for the surgical approach was based on the surgeons’ opinion and is somewhat arbitrary, especially in view of a more precise incision. Other investigators also concluded that additional SPECT/CT after conventional lymphoscintigraphy resulted in an improved anatomical localization of sentinel nodes. Especially sentinel nodes outside the axilla and nodes close to the injection site were easier to identify using SPECT/CT. In a study on its value in breast cancer patients not proceeded by conventional lymphoscintigraphy, SPECT/CT was also found to enable a precise characterization of the size, depth and anatomical location of the sentinel node.

Nor in the present study nor in studies by other investigators, SPECT/CT missed a sentinel node that was visualized by conventional lymphoscintigraphy. SPECT/CT accurately could bring to light sites of skin contamination with the radiopharmaceutical, that on conventional images were mistaken for sentinel nodes in two patients (1.5%). Other studies mentioned that 4 -17% of the radioactive spots that were thought to be sentinel nodes on the conventional scans were precisely classified by SPECT/CT as non-nodal sites of uptake, such as contamination.

Before the introduction of the SPECT/CT, various methods have been described to improve the visualization rate of sentinel nodes on conventional images. Alterations in the colloid particle concentration, in the amount of radiotracer, 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 sentinel nodes. The combination of all these improvements of 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 conventional images that are difficult to interpret or with no visualization on conventional images. In these cases, SPECT/CT appears to have additional value. Moreover, SPECT/CT provides an anatomical overview in two- and three-dimensional perspectives creating a surgical roadmap that cannot be provided by conventional images or intraoperative lymphatic mapping techniques. The present study confirms the additional value of SPECT/CT in the anatomical localisation of (additional) sentinel nodes and underlines its relevance for the surgical approach. SPECT/CT in our opinion therefore, facilitates surgical exploration in difficult cases and may improve staging.
References


