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
CHAPTER 14

The hidden sentinel node and SPECT/CT in breast cancer patients

Van der Ploeg IMC, Valdés Olmos RA, Kroon BBR, Rutgers EJTh, Nieweg OE
Eur J Nucl Med Mol Imaging, 2009; 36; 6-11
Abstract

Introduction: In a minority of breast cancer patients, lymphoscintigraphy shows no lymphatic drainage and ‘hidden’ sentinel nodes may remain undiscovered. The purpose of this study was to explore the additional value of the recently introduced hybrid SPECT/CT in breast cancer patients with axillary non-visualization on conventional images. The role of blue dye and careful palpation of the axilla was evaluated in patients in whom axillary sentinel nodes remained hidden after SPECT/CT.

Methods: Fifteen breast cancer patients with non-visualization on conventional lymphoscintigraphy and thirteen women with only extra-axillary sentinel nodes underwent SPECT/CT following late conventional imaging without re-injection of the radiopharmaceutical.

Results: SPECT/CT visualized lymphatic drainage in eight of the fifteen patients (53%) with non-visualization on conventional imaging, depicted nine of the fourteen harvested sentinel nodes (64%) and three of five tumour-positive sentinel nodes. In two of the thirteen patients (15%) with only extra-axillary sentinel nodes on their conventional lymphoscintigram, SPECT/CT showed an axillary sentinel node that appeared to be uninvolved. Careful exploration of the axilla with the combined use of blue dye, a gamma probe and intra-operative palpation revealed an axillary sentinel node in the remaining eighteen patients. SPECT/CT showed the exact anatomical location of all visualized sentinel nodes.

Conclusion: SPECT/CT discovered ‘hidden’ sentinel nodes in the majority of patients with non-visualization, but was less valuable in patients with only extra-axillary lymphatic drainage on the conventional images. Exploration of the axilla in patients with persistent non-visualization improved the identification of axillary (involved) sentinel nodes.
Introduction

Since the introduction of the sentinel node procedure and its integration in breast cancer management, it has been a challenge to optimize the technique.\(^1,2\) The combined use of a radiopharmaceutical, lymphoscintigraphy, blue dye and a gamma-ray detection probe was shown to lead to a high sentinel node retrieval rate.\(^3,4\) One of the aspects of the procedure that might be improved is the method of preoperative lymphoscintigraphic imaging. Lymphoscintigraphy is an important element of the lymphatic mapping providing essential information on the number and location of sentinel nodes and distinguishing these nodes from others further down-stream. Lymphoscintigraphy allows a sentinel node to be detected in more than 95% of breast cancer patients despite variations in technique.\(^1,5\) This means that there is a small minority of patients in whom no sentinel node is visualized. Several authors have discussed the lymphoscintigraphy strategy in patients with non-visualization and have described ways to discover such ‘hidden’ sentinel nodes.\(^6-9\) Recently, a hybrid imaging method has been introduced consisting of both a single photon emission computed tomography (SPECT)-camera and a CT scanner in one device.\(^10,11\) The patient can stay in the same position during imaging and fusion of the two images into one is easy. Furthermore, the correction for attenuation and scatter results in improved sentinel node visualization compared to SPECT alone.\(^12,13\) Initial studies suggest that SPECT/CT better specifies the anatomical location of the node and detects additional sentinel nodes.\(^14-16,17\) The purpose of this study was to explore these properties of SPECT/CT in breast cancer patients who have non-visualization or who have only sentinel nodes outside the axilla on conventional lymphoscintigrams. The role of blue dye, the gamma ray detection-probe and careful palpation of the axilla was evaluated in the patients in whom axillary sentinel nodes remained hidden after SPECT/CT.

Patients and methods

At the Netherlands Cancer Institute, lymphoscintigraphy is an integral element of lymphatic mapping. SPECT/CT was introduced in December 2006 and incorporated in the lymphoscintigraphy protocol. The indications for performing additional SPECT/CT images were conventional lymphoscintigrams with an unusual lymphatic drainage pattern, conventional images that were difficult to interpret or conventional lymphoscintigrams with non-visualization.\(^17\) Between December 1, 2006 and January 14, 2008, 317 breast cancer patients underwent lymphatic mapping of whom 105 patients (33%) met our criteria and received SPECT/CT after routine conventional
lymphoscintigraphy. Fifteen of these 105 patients (14% of the SPECT/CT patients, 5.0% of the whole group) underwent SPECT/CT because they had non-visualization, and thirteen patients (12% the SPECT/CT patients, 4.0% of the whole group) had only sentinel nodes outside the axilla on the conventional images. One patient was also subject of an earlier published pilot study. Histopathological proof of breast cancer was obtained preoperatively by fine-needle aspiration cytology or core biopsy. Ultrasonography of the axilla was routinely performed with fine-needle aspiration cytology in case of a suspicious node. A dosage of 120 MBq technetium-99-nanocolloid (Nanocoll®, GE- Healthcare, Eindhoven, the Netherlands) was injected into the tumour 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 made; additional images were obtained if needed. The patient was in the prone position with the hanging breast technique for the lateral images. A cobalt-57 flood source was placed behind the patient to outline the body contour. SPECT/CT images were made immediately after the four-hour conventional images. The SPECT/CT system (Symbia T, Siemens, Erlangen, Germany) consisted 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. For CT (130 KV, 17 mAs, B60s kernel), five millimetre slices were created. 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.). Two nuclear medicine physicians evaluated the images. 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 structures. A second, intratumoural injection of the radiopharmaceutical (100-120 MBq) was given to the patients with persistent non-visualization on the SPECT/CT images after which delayed conventional lymphoscintigraphy was done. This was not done in patients in whom extra-axillary sentinel nodes had been depicted. The number of sentinel nodes and their locations were determined after the conventional lymphoscintigraphic images as well as after the SPECT/CT images, and then compared. The location of a sentinel node was marked on the skin with indelible ink. The next day, 1 ml of patent blue dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) was administered in the primary lesion immediately before the operation. All procedures were performed by one of five experienced surgeons or under their
supervision by a resident or fellow. Sentinel nodes were pursued in all regions indicated by lymphoscintigraphy. The axilla was explored looking for a blue lymph vessel. If no lymphatic vessel was found, the gamma-ray detection probe (Neoprobe, Johnson & Johnson Medical, Hamburg, Germany) was used to search for a hot node. A sentinel node was defined as a lymph node to which the primary tumour drains directly.\textsuperscript{18} The axilla was carefully palpated and suspicious palpable nodes were routinely removed.

All harvested lymph nodes were fixed in formalin, bisected, embedded in paraffin, and cut at a minimum of six levels at 50 to 150 \( \mu \text{m} \) intervals. Pathological evaluation included both haematoxylin-eosin and immunohistochemical staining (CAM 5.2; Becton Dickinson, San Jose, CA, USA).

All patients were enrolled in the follow up program of the institution. At every clinic visit, special attention was paid to the axilla, which was examined by careful palpation and explored with ultrasound whenever the physical findings were uncertain.

**Results**

Conventional imaging failed to visualize any lymphatic drainage in fifteen breast cancer patients (figure 1). SPECT/CT demonstrated a sentinel node in eight of them.
(53%): an axillary sentinel node in six patients, an internal mammary sentinel node in one patient and both an axillary and an internal mammary sentinel node in the remaining patient (figure 2). Eight of these nine sentinel nodes were harvested (89%). Six axillary nodes were both blue and radioactive, the other two nodes were only radioactive. Three of these eight harvested sentinel nodes were tumour-positive and these three patients were classified in a higher stage. The internal mammary sentinel node depicted as the only node could not be found intraoperatively due to a minimal amount of radioactivity. Exploration of the axilla revealed no sentinel node. No axillary node dissection was performed based on the assumption that the internal mammary chain sentinel node was the only draining node.

Figure 2. A woman with right breast cancer. Conventional lymphoscintigraphy (A+B) shows no drainage on either the anterior or lateral images. The axial SPECT/CT fused image (C) shows one axillary sentinel node (arrow). The three-dimensional fused SPECT/CT maximum intensity projection (D) also shows an internal mammary sentinel node (ascending arrow) displayed just below the fourth rib.

Five of the seven patients with non-visualization on both conventional and SPECT/CT images received a second injection of the radiopharmaceutical. In one patient this was not possible for a logistic reason and another refused a re-injection. The second dose of the radiopharmaceutical failed to visualize lymphatic drainage in any of the five patients. In all seven patients with persistent non-visualization the axilla was
explored. A blue sentinel node was found in five patients, of which two were involved. In the sixth patient, a radioactive and blue node was harvested that was free of tumour. A non-radioactive, unstained, suspicious node was found in the remaining patient by palpation. This node was tumour-negative, but the patient refused to have a completion dissection. In the end, SPECT/CT visualized nine of the fourteen harvested sentinel nodes (64%) and three of five tumour-positive sentinel nodes (60%).

Thirteen women had only sentinel nodes outside the axilla depicted on the conventional images (figure 1). Subsequent SPECT/CT showed an axillary sentinel node in two of these patients (15%), and more clearly visualized the exact anatomical location of the 22 extra-axillary nodes than conventional lymphoscintigraphy (figure 3). All visualized sentinel nodes were identified intraoperatively using the probe. None were blue and none contained metastasis.

Figure 3. A woman with right breast cancer. Conventional lymphoscintigraphy (A+B) shows only extra-axillary drainage. On the anterior image (A) a sentinel node close to the injection site is visualized (lower horizontal arrow) as well as an internal mammary chain sentinel node (upper horizontal image). This latter node is also depicted on the lateral image (B). The axial SPECT/CT fused image (C) shows this same internal mammary chain node (descending arrow) and also visualizes an additional axillary sentinel node (horizontal arrow). The fused SPECT/CT maximum intensity projection (D) shows this axillary sentinel node (horizontal arrow) in a three-dimensional perspective.
The axilla was explored in the eleven patients with persistent axillary non-visualization after SPECT/CT. Eight sentinel nodes were removed in seven of these patients because they were radioactive (3), blue (2), or radioactive and blue (3). One blue, non-radioactive node was tumour-positive and prompted a completion dissection. In the other four patients, seven unstained, non-radioactive but suspicious and enlarged sentinel nodes were excised that appeared to be tumour-negative. In the end, SPECT/CT showed 24 of the 32 harvested sentinel nodes (75%) in the patients with initial drainage to nodes outside the axilla only. Two of these sentinel nodes (6%) were only depicted by SPECT/CT.

Two patients with visualization of only extra-axillary sentinel nodes had received previous treatment of the same breast. One patient had undergone a bilateral breast augmentation ten years earlier and breast-conserving therapy for an ipsilateral breast carcinoma six years thereafter. The other patient had undergone a bilateral breast reduction and breast lift five years before.

No patient recurred in or outside of the axilla in a mean follow-up time of nine months, ranging from one to fourteen months.

**Discussion**

SPECT/CT visualized lymphatic drainage in 53% of the patients in whom conventional lymphoscintigraphy had failed entirely. Three of the additionally visualized sentinel nodes were tumour-positive and prompted axillary node dissection. In two of the thirteen patients (15%) with only extra-axillary sentinel nodes on their conventional lymphoscintigram, SPECT/CT showed an axillary sentinel node that proved to be uninvolved.

Thus, SPECT/CT was more successful in the non-visualization group than in the patients with extra-axillary drainage only on conventional lymphoscintigraphy. This confirms the notion that some areas of the breast may drain only to a node that is outside the axilla. For instance, a watershed has been shown to run through the breast roughly from medio-ventral to latero-dorsal. Breast tissue dorsal from this plane drains (also) to the internal mammary nodes. Breast tissue ventral from this plane drains only to the axilla. If one looks carefully enough, nodes outside the axilla may be identified in more than half of the patients.

In other studies on the additional role of SPECT/CT in lymphatic mapping, SPECT/CT was performed in all consecutive patients eligible for sentinel node biopsy. Sentinel nodes were visualized in 89% to 100% by combined conventional imaging and SPECT/CT, with sentinel nodes depicted only by SPECT/CT in up to 14%.

The occurrence of non-visualization on conventional imaging has also been studied before the introduction of SPECT/CT. Initially, this occurred in 10% of the patients with the intra-lesional injection technique that we use. The visualisation rate improved by 5% with increasing experience, modifications in the colloid
particle concentration and the amount of tracer dosage.\textsuperscript{24,25} Delayed imaging (with an average of eight hours post-injection) showed sentinel nodes in 21% of patients with non-visualization, and a second injection of the radiopharmaceutical in 55% of the remaining patients.\textsuperscript{9} A sentinel node was surgically retrieved in 57% of the patients with persisting non-visualization in the same study. In another study this was 45%.\textsuperscript{26} Other techniques that may help detect hidden sentinel nodes are post-injection massage and injection of saline solution around the tumour. However, the advantage of increased volume in this matter is not clear and may even have a negative effect.\textsuperscript{7,20,27} These methods, designed to improve the identification of sentinel nodes, could probably have detected a fair number of the initially non-visualised nodes that have now been visualised by SPECT/CT, but it is difficult to determine how many. Especially the role of the gamma ray detection probe cannot be separated from the role of SPECT/CT in being decisive for the intraoperative discovery of axillary sentinel nodes. We can state that the extra-axillary sentinel nodes detected by SPECT/CT in two patients (13%) would not have been found otherwise, since regions outside the axilla are not routinely explored.

One study mentioned that non-visualized sentinel nodes that were identified intraoperatively appeared to be tumour-positive more often (50%) than sentinel nodes depicted by conventional imaging (38%).\textsuperscript{9} In another study, involved nodes were identified in 29% of patients with axillary drainage and in 63% of the patients without visualized axillary lymphatic drainage.\textsuperscript{28} These differences did not reach statistical significance, but it is conceivable that a sizeable metastasis may restrict inflow of lymph fluid and thus of radiolabelled colloids. Only the sensitive SPECT/CT will point out such a node.

In the present study, three of the six tumour-positive sentinel nodes were depicted by SPECT/CT only. The three other involved nodes were not visualized and only blue. This confirms the value of vital blue dye, as has been emphasized in literature before.\textsuperscript{9,26} In these studies, the harvested sentinel nodes were radioactive and blue in 43%, only radioactive in 9%, and only blue in 48% to 64%. In the current study, exploration of the axilla yielded fourteen sentinel nodes in thirteen of the eighteen patients (72%) with persistent (axillary) non-visualization on SPECT/CT. Thirty percent of these harvested sentinel nodes were blue and radioactive, 25% only radioactive and 45% were only blue. It has been suggested that the finding that some sentinel nodes were blue but not radioactive could be explained by replacement of nodal phagocytes by tumour, by differences in physiological behaviour between the vital blue dye and the radiopharmaceutical, or by variability in lymphatic flow.\textsuperscript{9} Eight uninvolved, clinically suspicious nodes were excised in five patients with persistent (axillary) non-visualization in whom axillary exploration with the help of blue dye and a gamma probe was also unsuccessful. In one patient this non-sentinel node was the only node excised. This patient refused the axillary dissection that is our routine policy in such cases. Extra-axillary drainage was present in the other four patients, which makes an axillary dissection unnecessary according to the guidelines at
our institute.
Sometimes non-visualization can be related to a patient’s medical history. Previous
treatment of the breast or the axilla is a controversial indication for lymphatic mapping
and sentinel node biopsy. For example, it has been reported that excisional biopsy
causes axillary non-visualization in more than a third of breast cancer patients. In the
current study, SPECT/CT was not of additional value in two previously treated patients
with visualization of extra-axillary sentinel nodes only.
Some surgeons will resort to axillary node dissection if no sentinel node is seen on the
lymphoscintigrams. The current study demonstrates that SPECT/CT depicts ‘hidden’
sentinel nodes in about half of the patients with non-visualization on conventional
imaging, but is less valuable in this respect in patients with visualization of extra-
axillary sentinel nodes only. SPECT/CT showed the exact anatomical location of
sentinel nodes in all patients. The anatomical location of extra-axillary sentinel nodes,
especially the intercostal location of internal mammary chain nodes, is depicted much
more accurately and this alone justifies an additional SPECT/CT. 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 intra-operative 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.

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