Sentinel nodes in complex areas: innovating radioguided surgery
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Chapter 3

SPECT/CT for preoperative sentinel node localization

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ABSTRACT

The value of SPECT/CT for detection and localization of sentinel nodes is reviewed. SPECT/CT depicts extra sentinel nodes and identifies non-nodal tracer accumulation. SPECT/CT is indicated in patients with complex lymphatic drainage as often present in patients with head, neck and scapular melanoma, breast cancer patients with extra-axillary sentinel nodes and patients with tumours draining to pelvic nodes. SPECT/CT also clarifies the drainage pattern of inconclusive conventional images (non-visualisation or unclear location of the nodes).
INTRODUCTION

Knowledge of the tumour status of the lymph nodes is relevant for staging and for prognostic and therapeutic reasons. Sentinel node mapping is widely used in patients with breast cancer or melanoma and its possible role in staging of other solid tumours is subject of ongoing research.

Conventional (planar) lymphoscintigraphy is routinely used to visualise the sentinel nodes and their afferent lymphatic vessels preoperatively, and to determine their number and their location. A new hybrid nuclear medicine and radiology technique has been developed for these purposes. This multimodal approach combines single photon emission computed tomography with CT (SPECT/CT). SPECT/CT is a more sensitive technique than conventional lymphoscintigraphy because it corrects for tissue attenuation and scatter. The CT visualises the anatomic surrounding of a sentinel node. SPECT/CT can be performed during or after conventional lymphoscintigraphy and will take approximately twenty minutes. When a hybrid system is used, the patient can usually stay in the same position on the bed of the gamma camera. Additional injection of the radiopharmaceutical is not required and no contrast medium is involved. A low dose CT is used limiting the radiation exposure of the patient to 1.3-5 mGy.

The purpose of this review is to report on the value of SPECT/CT for identification and localization of sentinel nodes in breast cancer, melanoma and in some specific other sites, based on a literature review and on our own experience. The PubMed database was searched for studies concerning SPECT/CT for lymphatic mapping. The following medical subject headings (MeSH terms) were used to find relevant articles: breast neoplasms, melanoma, sentinel lymph node biopsy, and tomography, emission-computed, single-photon.

First, conventional sentinel node imaging and detection techniques are discussed and then the value of adding SPECT/CT images is evaluated.

CONVENTIONAL IMAGING TECHNIQUES

Conventional lymphoscintigraphy is routinely used for preoperative sentinel node detection. In the late 1970's, Robinson et al. demonstrated visualisation of regional lymphatic drainage with colloidal gold scanning in melanoma of the trunk. Conventional lymphoscintigraphy after injection of a radiotracer has been widely applied since to visualise and localize sentinel
nodes preoperatively, also in breast cancer. But still no uniform guideline exists regarding this imaging technique.

Various radiopharmaceuticals are being used, most often technetium-99m albumin nanocolloid, technetium-99m rhenium colloid or technetium-99m sulfur colloid. Sentinel node visualisation depends on the transport of the radiopharmaceutical particles from the injection site through lymphatic channels towards sentinel nodes. The radiolabeled particles are then trapped within the node and absorbed by macrophages. The process of transport and accumulation can be influenced by several factors, such as particle size, particle concentration and injected dose. Continuous transport of the radiopharmaceutical towards the sentinel nodes enables visualisation with a gamma camera and intra-operative detection with a gamma ray detection probe for over 24 hours after injection.

In patients with melanoma, several intradermal tracer deposits are placed around the tumour or around the biopsy scar. In breast cancer patients, the tracer is often administered in or around the tumour, guided by ultrasonography in case of a non-palpable lesion. Some nuclear medicine physicians prefer injection superficial from the tumour or near the areola. Dynamic imaging immediately after the tracer administration demonstrates the lymph vessel(s) and is performed when immediate lymphatic drainage can be expected, for instance in patients with a tumour of the skin or mucosa. The visualisation of lymphatic ducts enables the distinction between sentinel nodes and nodes downstream. Sequential static images can visualise successive stages of drainage and can also help to distinguish sentinel nodes from second-tier nodes.

The location of a sentinel node can be marked on the patient’s skin after the late images by positioning an external radioactive point source over the sentinel node during real time imaging or with the aid of a gamma ray detection probe. Sentinel node biopsy based on conventional images has been carried out in breast cancer patients with good detection rates and rare false-negative results. In melanoma, identification rate is close to 100% but the false negative rate is typically between 10% and 20%.

**SPECT/CT IN PATIENTS WITH BREAST CANCER**

A review of the literature on SPECT/CT for visualisation and localization of sentinel nodes in patients with breast cancer revealed ten studies. An overview of these studies is given in table 1. The injected dose ranged from 37–148 MBq (1–4 mCi) and different injection techniques were used (intratumoural in three studies, peritumoural in three studies, combined
peritumoural and intracutaneous in two studies, and periareolar in two studies). Additional early sequential conventional images were made in six studies, three investigators only performed late static conventional images once and in one study no conventional images were obtained. The timing of the SPECT/CT differed from thirty minutes after injection of the tracer up to eighteen hours after injection.3,16-24 The visualisation rates were better with SPECT/CT (89–92%) than with conventional imaging (63%-88%) in all comparative studies.3,16-23

The first large study on SPECT/CT in breast cancer reported improved preoperative localization of hot nodes.18 Subsequent studies confirmed the value of SPECT/CT for this purpose.3,16,17,20-23 SPECT/CT also detected hot nodes that are not seen on conventional images. Non-nodal sites of tracer accumulation, typically due to contamination, could be identified as such, thereby avoiding surgical exploration to pursue a non-existing sentinel node.3,16-18,23 Sentinel nodes near the injection area are easily overlooked on conventional images because some 98% of the radioactivity does not travel and obscures the 0.16% of the tracer that on average ends up in the sentinel node.25 SPECT/CT can discern such a node and also depicts sentinel nodes in a substantial number of patients in whom the conventional images do not show enough uptake.21 Mapping of all direct tumour draining lymph nodes requires knowledge of the number and location of these sentinel nodes, which will be provided by SPECT/CT in addition to planar images. Some authors have argued that excision of a maximum of three sentinel nodes provides enough information for accurate staging.26-28 which would make the detection more then three sentinel node less relevant. Gallowitsch et al. reported that with the gamma probe even more sentinel nodes will be found then visualised on SPECT/CT.19 However, these authors do not clearly state their definition of a sentinel node. They may have considered all radioactive nodes to be sentinel nodes without requiring direct drainage from the primary tumour.19

SPECT/CT was also found to visualise lymphatic drainage in eight of fifteen breast cancer patients (53%) with non-visualisation on conventional images, including three tumour-positive sentinel nodes (figure 1). SPECT/CT may show the sentinel nodes in the axilla if conventional images only show drainage to a node elsewhere.21

SPECT/CT appeared to be of particular value in obese patients. Conventional images failed to visualise sentinel nodes in 28% of obese patients, while non-visualisation was 13% with SPECT/CT.3 The visualisation rate using conventional images decreased with an increasing body mass index, while the SPECT/CT results remained relatively stable.
Table 1 | Studies reporting on the value of SPECT/CT for lymphatic mapping of breast cancer.

<table>
<thead>
<tr>
<th>Study Authors</th>
<th>Year</th>
<th>N</th>
<th>Remarks</th>
<th>SN visualization</th>
<th>SPECT/CT</th>
<th>Additional SPECT/CT results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Husarik et al. [16] 2007</td>
<td></td>
<td>41</td>
<td>Value of SPECT/CT for lymphedema assessment also analyzed.</td>
<td>88% (clear: 62%)</td>
<td>91%</td>
<td>More accurate information in 82%. Improves localization and increases sensitivity and specificity of lymphoscintigraphy.</td>
</tr>
<tr>
<td>Pecking et al. [17] 2007</td>
<td></td>
<td>34</td>
<td>88% (clear: 62%)</td>
<td>91%</td>
<td>In 17%</td>
<td>Patients with non-vis. on planar images had a higher mean BMI. SPECT/CT has enhanced superiority in overweight patients.</td>
</tr>
<tr>
<td>Lerman et al. [3] 2007</td>
<td></td>
<td>220</td>
<td>Some patients also included in a previous study [11].</td>
<td>78%</td>
<td>91%</td>
<td>SPECT: 51 SN, CT: 65 SN, gamma probe: 68 SN. SPECT/CT provides more accurate localization but underestimates the number of SN.</td>
</tr>
<tr>
<td>Gallo-witsch et al. [19] 2008</td>
<td></td>
<td>51</td>
<td>Subgroup analyses: 15 non-vis. and 13 only extra-axillary SN (conventional images).</td>
<td>63%</td>
<td>90%</td>
<td>Provides valuable anatomical localization. Identical findings for planar images and SPECT/CT in the chemotherapy group.</td>
</tr>
<tr>
<td>Mucientes Rasilla et al. [20] 2008</td>
<td></td>
<td>25</td>
<td>No-op adjunct chemotherapy in 6 patients. Intra-operative findings used as gold standard.</td>
<td>63% (non-vis.)</td>
<td>53%</td>
<td>Provides exact anatomical localization (especially useful for extra-axillary SN). Surgical exploration is useful to detect SN in case of persistent non-vis.</td>
</tr>
<tr>
<td>Van der Ploeg et al. [21] 2009</td>
<td></td>
<td>28*</td>
<td>Subgroup analyses: 15 non-vis. and 13 only extra-axillary SN (conventional images).</td>
<td>63%</td>
<td>92%</td>
<td>Changed surgical approach on the basis of SPECT/CT: 42%.</td>
</tr>
<tr>
<td>Van der Ploeg et al. [22] 2009</td>
<td></td>
<td>134*</td>
<td>Some patients also included in a previous study [16].</td>
<td>84%</td>
<td>97%</td>
<td>Provides preoperative localization of SN. Atypical distribution of SN may suggest axillary positivity.</td>
</tr>
<tr>
<td>Ibusuki et al. [24] 2009</td>
<td></td>
<td>223</td>
<td>No comparison with conventional images.</td>
<td>84%</td>
<td>92%</td>
<td></td>
</tr>
</tbody>
</table>

Only the most recent study is mentioned in case of patient cohorts that have previously been analyzed in another study; *SPECT/CT was performed on indication only: in case of an unusual drainage pattern, difficult to interpret drainage on planar images or non-visualization; N: number of patients, BMI: body mass index, SN: sentinel node(s), non-vis.: non-visualization.
Figure 1 | A 67-year old patient with a non-palpable breast tumour. The radiotracer was injected in the tumour under ultrasonographic guidance. Conventional images after fifteen minutes, two hours and four hours did not show any lymphatic drainage. Additional conventional images were performed after six hours (A) but did not show a sentinel node. Subsequent SPECT/CT visualised an axillary sentinel node. Two dimensional fusion images (B) localized the node at the lateral margin of the pectoral muscles. Three-dimensional reconstruction (C) shows the node in relation to the injection area. During surgery, the radioactive sentinel node was found and was free of metastasis.

The value of SPECT/CT for the surgical approach was reported in a recent article. In 15% of all node positive patients, the involved sentinel nodes were depicted only on the SPECT/CT images. The initially planned surgical incision, which was made to approach the sentinel nodes, was changed on the basis of the anatomical information provided by SPECT/CT in 42% of the patients. The location of the incision was more precise in 36%, an extra incision was made in 4% and an incision was omitted in 1.5%. This study also showed the benefit of SPECT/CT images in patients with a sentinel node outside the axilla, for example in case of
parasternal sentinel nodes. The incision can be placed more precise in such patients, because SPECT/CT shows the exact intercostal space that should be explored or a location underneath a rib or behind the sternum.\textsuperscript{22}

Sentinel node mapping for breast cancer has been performed safely without SPECT/CT and the rate of axillary recurrence after a negative sentinel node biopsy has been very low.\textsuperscript{14} SPECT/CT should therefore be performed on specific indications only. In this way, the majority of patients who will not benefit from this imaging technique are spared unnecessary cost and inconvenience.

Based on the above-mentioned findings, one can conclude that current indications for SPECT/CT appear to be non-visualisation when conventional imaging is performed, obesity and presence of extra-axillary sentinel nodes or otherwise unusual drainage (e.g. in case of previous breast surgery). SPECT/CT might also be performed if the conventional images are difficult to interpret (e.g. suspicion of contamination or a sentinel node near the injection area).

**SPECT/CT IN PATIENTS WITH MELANOMA**

There are just a few case reports and cohort studies on SPECT/CT for lymphatic mapping in patients with melanoma and these are listed in table 2.\textsuperscript{29-35} The investigators of the cohort studies administered four intracutaneous deposits with a total dose of 74-185 MBq (2–5 mCi) of the radiopharmaceutical. Most investigators performed dynamic conventional imaging followed by sequential static imaging and subsequent SPECT/CT.\textsuperscript{31-33,35} Covarelli et al. only investigated patients with a head and neck melanoma and administered 10 MBq (0.3 mCi) when patients where operated on the same day and 50 MBq (1.4 mCi) if patients were operated the next day. They performed conventional imaging in half of the patients and SPECT/CT in the other half of the patients.\textsuperscript{34}

Several authors underlined the important additional anatomic information SPECT/CT can provide.\textsuperscript{31,33,35} Even-Sapir et al. found that a substantial number of additional sentinel nodes were depicted with SPECT/CT in patients with a melanoma on the head, in the neck or on the trunk, while in other areas of the body no additional value of SPECT/CT was established. In two out of the 15 patients with a head and neck tumour, a sentinel node only visualised with SPECT/CT was tumour-bearing.\textsuperscript{31} Ishihara et al. concluded that SPECT/CT is useful for exact localization of sentinel nodes in melanoma patients, regardless of their position, while Kretschmer et al. specifically mentioned its relevance for the identification of pelvic sentinel nodes in patients
Table 2 | Studies reporting on the value of SPECT/CT for lymphatic mapping in patients with melanoma.

<table>
<thead>
<tr>
<th>N</th>
<th>Remarks</th>
<th>SN visualization</th>
<th>SPECT/CT</th>
<th>Additional SPECT/CT results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Even-Sapir et al. [31] 2003</td>
<td>28 6 patients with squamous cell carcinoma also included.</td>
<td>Not mentioned</td>
<td>In 43% of patients with melanoma of trunk &amp; H&amp;N.</td>
<td>1 SN</td>
</tr>
<tr>
<td>Kretschmer et al. [32] 2003</td>
<td>31 Melanoma of lower extremity and lower trunk only. 31 out of 51 had SPECT/CT.</td>
<td>Planar images necessary to distinguish SN from second-tier node.</td>
<td>Successful fusion in 29 patients. Precise location of SN and identification of true pelvic SN.</td>
<td></td>
</tr>
<tr>
<td>Ishihara et al. [33] 2006</td>
<td>26 9 patients with tumours other than melanoma also included.</td>
<td>Blue dye: 85%</td>
<td>Blue dye: 85% SPECT/CT: 100%</td>
<td>Useful for anatomic localization of SN.</td>
</tr>
<tr>
<td>Covarelli et al. [34] 2007</td>
<td>23 Melanoma of H&amp;N only. 11 patients only planar imaging, 12 patients only SPECT/CT.</td>
<td>Planar images: 82%</td>
<td>Planar images: 82% SPECT/CT: 100%</td>
<td>Operation time was significantly shorter in the SPECT/CT group.</td>
</tr>
<tr>
<td>Van der Ploeg et al. [35] 2009</td>
<td>85* Some patients also included in a previous study [16].</td>
<td>Planar images: 99%* SPECT/CT: 100%</td>
<td>12 SN in 7 patients</td>
<td>Facilitates surgical exploration in difficult cases (change of surgical approach in 35%) and may improve staging.</td>
</tr>
</tbody>
</table>

* SPECT/CT was performed on indication only: in case of an unusual drainage pattern, difficult to interpret drainage or non-visualization on planar images; N: number of patients, SN: sentinel node, H&N: head and neck.
with a melanoma on the lower extremity.\textsuperscript{32,33} In our institution, SPECT/CT is performed only for certain indications. SPECT/CT was found to lead to a change in surgical approach in 35\% of the patients with an unusual drainage pattern on the conventional images, with conventional images that were difficult to interpret or with conventional images without sentinel node visualisation.\textsuperscript{35} On the basis of the SPECT/CT, a different incision was made in 20\% of the patients, an incision at another site was made in 9\% and 6\% of the patients received an extra incision. Additional value of SPECT/CT was present in all patients with a melanoma of the head and neck, in 71\% of the patients with a melanoma of the trunk (mainly tumours near the midline with drainage to multiple nodal basins) and in 27\% of the patients with a melanoma on the leg. Furthermore, three nodes (in two patients) that were only depicted on SPECT/CT appeared to contain metastasis.\textsuperscript{35} Figure 2 shows an example of a patient with complex drainage on the conventional images in whom SPECT/CT identified an additional subcutaneous sentinel node underneath the injection area. The value of SPECT/CT for lymphatic mapping of melanoma of the head and neck is underlined by Covarelli et al, who demonstrated that sentinel node biopsy based on SPECT/CT images took significantly less time than sentinel node biopsy based on conventional images.\textsuperscript{34} The authors argue that more precise preoperative localization of a sentinel node and knowledge of the relationship with anatomical structures facilitated surgical excision.\textsuperscript{34} They also mention that SPECT/CT can detect sentinel nodes in spite of scattered radiation of the injection site. This benefit is also present in lymphatic mapping of oral cavity carcinoma.\textsuperscript{36,37}

In patients with melanoma, SPECT/CT appears to be indicated in case of complex conventional images as is often the case in melanomas in the head and neck or in the scapular region. In these patients, SPECT/CT can detect additional sentinel nodes and the surgical approach can be planned based on the localization information SPECT/CT provides. In the future, the exact localization of second-tier nodes may have implications for the extent of a completion node dissection in case of a positive sentinel node and a SPECT/CT can then be useful in the identification of such nodes.\textsuperscript{38}

\textbf{SPECT/CT IN PATIENTS WITH OTHER MALIGNANCIES}

Various authors describe that SPECT/CT provides useful information as to the exact location of sentinel nodes in head and neck malignancies,\textsuperscript{31,34,36,37,39-41} as is exemplified in figure 3. SPECT/CT has been reported to visualise additional sentinel nodes in this anatomically complex area.\textsuperscript{31,36,39,41-43} Sentinel nodes located in the vicinity of the injection site are easily missed
on the conventional images and can often be discerned using SPECT/CT. Non-nodal tracer accumulation is often thought to represent a sentinel node on conventional images but its true nature, mostly contamination, can be identified with SPECT/CT.

Figure 2 | A patient who had undergone excision of a melanoma of the left abdominal wall. The radiopharmaceutical was injected intracutaneously around the scar. Conventional images after fifteen minutes (A: anterior, B: left lateral, C: right lateral) show complex drainage, with visualisation of several lymphatic channels and at least one sentinel node in each axilla. Late conventional images (D: anterior view) still show radioactivity in the lymphatic channels and also uptake in several nodes. Two-dimensional fused SPECT/CT (E) shows a subcutaneous sentinel node underneath the injection site that is not visible on the conventional images. The three-dimensional reconstruction (F) shows an overview of all hot spots. The hot spots with arrows were regarded as sentinel nodes, because they appeared to be on a direct drainage pathway: underneath the primary tumour site, in the left internal mammary chain and in each axilla. The node in the internal mammary chain could also be a second-echelon node from the subcutaneous sentinel node, but was considered as possible sentinel node because the presence of a separate lymphatic channel leading to this node could not be ruled out. One of the sentinel nodes (right axilla) contained metastasis.

The value of SPECT/CT for sentinel lymph node mapping in malignancies with pelvic or retroperitoneal drainage has been less extensively studied. Small studies have been performed
in patients with urological and gynaecological tumours and the investigators conclude that the new technique increases the yield of sentinel nodes.\textsuperscript{44-46} We examined the use of additional SPECT/CT in 46 sentinel node procedures for prostate cancer.\textsuperscript{47} SPECT/CT not only provided useful anatomical information about the location of the sentinel nodes but also revealed sentinel nodes that had not been depicted on the conventional images. This was especially relevant for sentinel nodes outside the pelvic area and nodes in close proximity to the prostate, where a substantial number of sentinel nodes would have been missed without SPECT/CT.\textsuperscript{47} Figure 4 shows an example of a presacral sentinel node that is only visualised on SPECT/CT images. Preoperative imaging of lymph drainage with SPECT/CT can also alter the targeted radiotherapy field and optimize pelvic irradiation.\textsuperscript{48}

\textbf{Figure 3} | A patient with an oral cavity carcinoma (localized medially in the floor of the mouth) with drainage to both sides of the neck on the conventional images (A: anterior, B: left oblique, C: right oblique), two hours after injection of the radiopharmaceutical. Three-dimensional SPECT/CT reconstruction (D) is comparable to the conventional images and can be rotated along its axis in order to see the location of all nodes visualised on the oblique conventional image (C). Scrolling down the two-dimensional SPECT/CT fusion images, the exact anatomic location of the caudally situated second-tier node (E) is shown as well as the more cranially depicted sentinel nodes (F). None of the sentinel nodes was tumour bearing.
CONCLUSION

Based on a review of the literature and on our own experience, we conclude that the use of SPECT/CT in addition to conventional lymphoscintigraphy leads to improved preoperative visualisation and localization of sentinel nodes, especially if performed for specific indications. Sequential conventional images remain useful to distinguish sentinel nodes from secondary nodes.
In breast cancer, SPECT/CT can depict sentinel nodes that are not visible on conventional images. Depiction of the exact location of extra-axillary nodes with SPECT/CT facilitates the planning and execution of the operation. In patients with melanoma, SPECT/CT adds relevant information in areas with a complex anatomy like head and neck and the scapular region, or when an unexpected drainage pattern is observed. SPECT/CT may be performed in every patient with lymphatic drainage to sentinel nodes in the pelvic and retroperitoneal regions, for instance in prostate cancer, to ensure complete and accurate staging.

SPECT/CT is indicated in all patients with conventional images that are difficult to interpret, because it facilitates accurate localization of sentinel nodes and differentiates these from non-nodal tracer accumulation sites.

REFERENCES


Chapter 3


