Sentinel lymph node biopsy in breast cancer and melanoma
Doting, Meintje Hylkje Edwina

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Immediate dynamic lymphoscintigraphy delivers no additional value to lymphoscintigraphy three hours after tracer injection in sentinel lymph node biopsy in breast cancer patients

M.H. Edwina Doting¹, H.M. Annemiek Stiekema², Jakob de Vries¹, Clara Lemstra², Harald J. Hoekstra¹, Mirjam Vrieling², Lianne Rietman², Pieter L. Jager²

Departments of Surgical Oncology¹ and Nuclear Medicine and Molecular Imaging², University Medical Center Groningen, University of Groningen, Groningen, the Netherlands

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Introduction
In 1993 Krag et al. published the first study of sentinel lymph node biopsy in patients with invasive breast cancer.\(^1\) \(^{99m}\)Tc-labeled colloid was injected intraparenchymally around the primary tumour 1-4 h prior to surgery to map the lymphatic tract and to identify the sentinel lymph node by a hand-held gamma ray detection probe. Giuliano and co-workers published in 1994 their initial work of intraoperative lymphatic mapping with a vital blue dye.\(^2\) Both techniques were combined by Albertini and co-workers in an effort to improve the detection rate and to reduce the ‘learning curve’.\(^3\) Veronesi and co-workers documented in a randomized comparison of sentinel lymph node biopsy with routine axillary lymph node dissection in breast cancer patients, that sentinel lymph node biopsy is a safe and accurate method of screening the axillary lymph nodes for metastasis in women with small breast cancer.\(^4\) Within a decade sentinel lymph node biopsy has become the standard of care for axillary lymph node staging in clinically T1-T2 node-negative breast cancer patients in the Netherlands and other western countries. Preoperative lymphoscintigraphy, blue dye injection at the time of surgery, and intraoperative use of a gamma ray detection probe are the three methods to locate sentinel lymph nodes. Preoperative lymphoscintigraphy can be obtained in a dynamic study, e.g. in the first period after tracer administration (‘immediate’ lymphoscintigraphy) as well as three hours later (‘3 h post-injection’ lymphoscintigraphy). In theory the immediate images would be more accurate because it allows direct identification of sentinel lymph nodes, whereas in 3 h post-injection imaging differentiating first- from second-echelon nodes is difficult and generally all hot spots are considered sentinel lymph nodes. Intraoperative detection of gamma radiation is objective, whereas detection of blue staining of a node at the time of surgery can be difficult and operator dependent and thus less reliable. However, blue dye may help to distinguish first-echelon nodes from nodes with secondary drainage. This is particularly useful when lymphoscintigraphy shows accumulation of radioactive tracer in a multitude of nodes without indicating the drainage sequence. The three methods are best used in a complementary fashion rather than independently.\(^5\)

This study was performed to define the value of immediate dynamic versus 3 h post-injection lymphoscintigraphy in sentinel lymph node biopsy in breast cancer patients, and in particular whether immediate imaging could safely be omitted.

Patients and methods
Patients
One hundred and sixty-two women with proven invasive breast cancer (T1-T2) and a clinical negative axilla underwent immediate and 3 h post-injection lymphoscintigraphy. Three patients suffered from bilateral breast cancer and these women underwent a sentinel lymph node biopsy procedure at both sites resulting in 165 sentinel lymph node biopsy procedures. Patient characteristics are presented in Table 1. Patients with
multicentric breast cancer, suspected axillary involvement, prior major breast or axillary surgery that could interfere with lymphatic drainage and/or distant metastases were excluded for sentinel lymph node biopsy. An experienced team of specialists in nuclear medicine, surgery and pathology treated all patients.

Table 1.  
**Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)*</td>
<td>58</td>
<td>(32-88)</td>
</tr>
<tr>
<td>Affected breast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>74</td>
<td>45</td>
</tr>
<tr>
<td>Right</td>
<td>91</td>
<td>55</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1N0M0</td>
<td>113</td>
<td>68</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>52</td>
<td>32</td>
</tr>
<tr>
<td>Breast quadrant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper outer</td>
<td>66</td>
<td>40</td>
</tr>
<tr>
<td>Upper inner</td>
<td>36</td>
<td>22</td>
</tr>
<tr>
<td>Lower outer</td>
<td>26</td>
<td>16</td>
</tr>
<tr>
<td>Lower inner</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Central</td>
<td>13</td>
<td>8</td>
</tr>
</tbody>
</table>

*values in parenthesis are ranges.

Lymphoscintigraphy

A 2-day protocol was used. Lymphoscintigraphy was performed on the day preceding the operation. A single dose of 40-60 MBq $^{99m}$Tc-nanocolloid (Nanocoll; Amersham Cygne, Eindhoven, the Netherlands) in 1 mL saline was injected intraparenchymal in four depots around the primary tumour or biopsy scar site, in case of a previously performed excisional biopsy, for both lymphoscintigraphy and intraoperative lymph node detection. The particles of $^{99m}$Tc-nanocolloid are smaller than 80 nm in size, which meets the criteria for optimal inert colloids for interstitial lymphoscintigraphy. In case of non-palpable breast cancer, injection was preceded by stereotactic needle localization. For imaging a single headed gammacamera (Diacam, Siemens, Hoffmann Estates, IL, USA) was used equipped with Low Energy All-Purpose collimator. The energy window was centered on the $^{99m}$Tc photopeak of 140 KeV, using a 15% window. Zoom factor was 1, image matrix 128 x 128 pixels for dynamic and 256 x 256 pixels for static acquisition. Anterior dynamic imaging (30 seconds images) to visualize the lymph flow was started immediately after the injection and continued for 30 minutes. Subsequently, anterior and lateral static lymphoscintigrams in an acquisition time of 5 minutes were obtained. A radioactive $^{57}$Cobalt-flood source was used to outline the body contour. These images were considered ‘immediate’. Another set of five-minute late static images was made at three hours after injection and again the body contour was outlined by a radioactive $^{57}$Cobalt-flood source. If no focal accumulation of radioactive tracer in the lymph node
basin(s) was seen, a repeat injection was given intracutaneously and imaging was repeated three hours after this second injection. The position of sentinel lymph nodes was marked on the skin with waterproof ink.

Criteria to distinguish the sentinel lymph node from second-echelon lymph nodes were the visualization of an afferent lymphatic channel leading from the injection site to the sentinel lymph node or, if no afferent channels were seen, the first lymph node appearing in each basin.

The lymphoscintigrams were discussed with the surgeon before the sentinel lymph nodes were excised. Immediate and 3 h post-injection lymphoscintigrams were evaluated with regard to location of draining lymph node basins and location, number and sequence of appearance of sentinel lymph nodes. Surgical results were compared with the lymphoscintigrams.

**Surgery**

After induction of general anesthesia, a dose of 1.0 mL Patent blue dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) was injected peritumourally. Ten minutes after injection all nodal basins identified by lymphoscintigraphy were explored surgically through limited incisions. Surgical dissection was guided by a hand-held gamma ray detection probe (Neoprobe® 1000 and 1500, Johnson & Johnson Medical, Hamburg, Germany) and by looking for blue-stained afferent lymphatic vessels that led to blue-stained sentinel lymph nodes. Once the sentinel lymph nodes had been excised the probe was used to search the resection bed to ensure that there were no residual areas of high radioactivity. Sometimes, multiple lymph nodes were blue and/or radioactive.

Lymph nodes with an afferent blue lymphatic channel coming from the direction of the breast were considered to be sentinel lymph nodes. Lymph nodes that received blue dye from another lymph node were considered to be second-echelon nodes. After excision of the sentinel lymph nodes, the final probe survey of the draining lymph node basin should reveal only background radioactivity (less than 10% of that of the most radioactive resected sentinel lymph node).

Extra-axillary regions were explored only in case of lymphoscintigraphic visualization. Extra-axillary sentinel lymph nodes were identified by the combined detection technique, in the same manner as axillary sentinel lymph nodes were identified. Internal mammary chain sentinel lymph nodes were explored either through the incision made for the removal of the primary tumour or through a small separate transverse incision over the intercostal space concerned. After splitting the pectoral muscle fibres, the intercostal muscles were separated from the lower rib to expose the fatty tissue along the internal mammary vessels on the surface of the parietal pleura without dividing ribs. If no radiocolloid or blue dye drainage was observed to any region, the sentinel lymph node biopsy procedure was considered to have failed and a level I and II axillary lymph node dissection was performed.
Pathology

All sentinel lymph nodes were formalin-fixated, bisected, paraffin-embedded, and cut at a minimum of six levels at 50- to 150-μm intervals. Pathologic evaluation included HE and immunohistochemical staining (CAM 5.2, Becton Dickinson, San Jose, CA). All lymph nodes from the axillary lymph node dissection were evaluated using routine HE staining.

Results

Visualization of sentinel lymph nodes occurred in immediate lymphoscintigraphy with dynamic imaging in 50 patients (30%) and in immediate static imaging in 63 patients (38%). 3 h post-injection lymphoscintigraphy showed sentinel lymph nodes in 163 procedures (99%) (Table 2).

<table>
<thead>
<tr>
<th>Table 2.</th>
<th>Sentinel lymph node visualization on preoperative lymphoscintigraphy (n=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Visualization</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Immediate lymphoscintigraphy</td>
<td></td>
</tr>
<tr>
<td>Dynamic images (0-30 min p.i.)</td>
<td>50</td>
</tr>
<tr>
<td>Early static images (30-40 min p.i.)</td>
<td>63</td>
</tr>
<tr>
<td>3 h post-injection lymphoscintigraphy</td>
<td></td>
</tr>
<tr>
<td>Late static images (180 min p.i.)</td>
<td>146</td>
</tr>
<tr>
<td>Late static images after repeat injection (360 min p.i.)</td>
<td>17</td>
</tr>
<tr>
<td>Overall visualization</td>
<td>163</td>
</tr>
<tr>
<td>Overall non-visualization (failures)</td>
<td>2</td>
</tr>
</tbody>
</table>

In two procedures (1%) lymphoscintigraphy revealed no uptake of radioactivity despite repeat injection. These were considered failures and level I and II axillary lymph node dissection was performed. In one of these two patients no metastases were found on pathologic evaluation. In the other patient eight out of 16 lymph nodes contained metastases, including five lymph nodes with macrometastases.

In 17 procedures (10%), in which immediate lymphoscintigraphy had visualized sentinel lymph nodes, additional lymph nodes were seen on 3 h post-injection lymphoscintigraphy. In nine procedures (5%) these additional lymph nodes were seen in a second draining lymph node basin and these nodes were considered first-echelon nodes, i.e. sentinel lymph nodes. In the remaining eight procedures (5%) the sentinel lymph nodes and additional lymph nodes were seen in the same draining lymph node basin. It is possible that not all of these additional nodes, i.e. one to two per patient, were first-echelon but in fact second-echelon nodes. Due to lack of visible lymphatic channels and limited resolution of the gamma camera, the improvement of interpretation of
preoperative sentinel lymph node imaging by immediate lymphoscintigraphy was minimal (Figure 1, Figure 2, Table 3).

**Figure 1.**
Lymphoscintigraphy reveals transport of the tracer from the injection site (large spot) along an invisible lymphatic channel towards one axillar sentinel lymph node (small spot) at immediate dynamic anterior imaging; ant=anterior view; min=minutes; SLN=sentinel lymph node; Injection=Injection site of $^{99m}$Tc-nanocolloid.

**Table 3.**
Value of immediate lymphoscintigraphy

<table>
<thead>
<tr>
<th>Additional hot spots in 3 h post-injection lymphoscintigraphy compared to early</th>
<th>n (%)</th>
<th>Value of early LS</th>
</tr>
</thead>
<tbody>
<tr>
<td>lymphoscintigraphy</td>
<td>17 (10)</td>
<td></td>
</tr>
<tr>
<td>In different lymph node basins</td>
<td>9 (5)</td>
<td>no</td>
</tr>
<tr>
<td>In same lymph node basin</td>
<td>8 (5)</td>
<td>minimal</td>
</tr>
</tbody>
</table>

*n = procedures; LS = lymphoscintigraphy.*
Immediate dynamic lymphoscintigraphy delivers no additional value to lymphoscintigraphy three hours after tracer injection in sentinel lymph node biopsy in breast cancer patients.

Figure 2.
Anterior and lateral view lymphoscintigrams of immediate and 3 h post-injection static imaging confirming drainage to the axilla with visualization of one sentinel lymph node (small spot); min=minutes; p.i.=post-injection.

Non-axillary sentinel lymph nodes were seen in 28 lymphoscintigrams (17%) together with axillary sentinel lymph nodes, except for one isolated intraparenchymal sentinel lymph node. The internal mammary chain was the most frequent location of sentinel lymph nodes outside the axilla. These nodes counted for 61% of all non-axillary sentinel lymph nodes. Intraparenchymal, infraclavicular and supraclavicular sentinel lymph nodes were seen in respectively seven (25%), three (11%) and one (3%) non-axillary sentinel lymph node biopsy procedure(s) (Table 4). Intraoperative identification of sentinel lymph nodes outside the axilla was found to be more difficult than for sentinel lymph nodes in the axilla, but without additional morbidity, the majority of these lymph nodes could be harvested (68%).
In six patients (4%) the sentinel lymph nodes that were visualized by preoperative lymphoscintigraphy could not all be identified during operation with blue dye and/or a gamma ray detection probe. Axillary sentinel lymph nodes could not be identified in three procedures and internal mammary chain sentinel lymph nodes could not be identified in another three procedures (Table 5).

If non-axillary sentinel lymph nodes could be identified successfully, staging was improved in three patients (3 out of 63 tumour-positive sentinel lymph node procedures (5%)). These patients were upstaged and received radiotherapy to the internal mammary chain.

**Discussion**

The goal of this study was to investigate if immediate lymphoscintigraphy could be omitted in lymphoscintigraphy in breast cancer management. This study showed that in 17 procedures (10%) additional lymph nodes were seen on 3 h post-injection lymphoscintigraphy. In nine procedures (5%) these additional lymph nodes were seen in a second draining lymph node basin and these nodes were considered first-echelon nodes, i.e. sentinel lymph nodes. So, in these patients immediate lymphoscintigraphy did not contribute to distinguish first-echelon from second-echelon nodes. In the remaining eight procedures (5%) the sentinel lymph nodes and additional lymph nodes were seen in the same draining lymph node basin. Due to lack of visible lymphatic channels and limited discriminating power of the gamma camera, the interpretation of preoperative sentinel lymph node imaging was not really improved by immediate imaging in these procedures. Therefore we conclude that the added value of immediate imaging is minimal and that immediate lymphoscintigraphy can safely be omitted in sentinel lymph node biopsy in breast cancer patients at the expense of removing a few second-echelon nodes. This is in agreement with previous studies.6-9
### Table 5.

**Characteristics of six patients in who visualized sentinel lymph nodes could not be identified during operation**

<table>
<thead>
<tr>
<th>UICC clinical stage (quadrant)</th>
<th>Tumour location (quadrant)</th>
<th>Age (years)</th>
<th>Axillary IMC (n)</th>
<th>IMC (n)</th>
<th>Axillary IMC (n)</th>
<th>IMC (n)</th>
<th>Pathology</th>
<th>SLN identified by LS</th>
<th>SLN identified by surgery</th>
<th>Pathology</th>
<th>Adjuvant treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0</td>
<td>UO</td>
<td>67</td>
<td>1</td>
<td>n.i.</td>
<td>-</td>
<td>-</td>
<td>0/7*</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T2N0</td>
<td>LO</td>
<td>47</td>
<td>1</td>
<td>n.i.</td>
<td>-</td>
<td>-</td>
<td>4/15</td>
<td>-</td>
<td>-</td>
<td>Chemotherapy and radiotherapy</td>
<td></td>
</tr>
<tr>
<td>T1N0</td>
<td>UO</td>
<td>60</td>
<td>1</td>
<td>1</td>
<td>n.i.</td>
<td>1</td>
<td>Tumour-negative</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T1N0</td>
<td>UI</td>
<td>60</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>n.i.</td>
<td>Tumour-negative</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T2N0</td>
<td>UI</td>
<td>38</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>n.i.</td>
<td>Tumour-positive</td>
<td>-</td>
<td>0/17</td>
<td>Chemotherapy and radiotherapy</td>
<td></td>
</tr>
<tr>
<td>T1N0</td>
<td>UO</td>
<td>64</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>n.i.</td>
<td>Tumour-negative</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

SLN = sentinel lymph node; LS = lymphoscintigraphy; ALND = axillary lymph node dissection; UICC = International Union Against Cancer; IMC = internal mammary chain; n = number; UO = upper outer; UI = upper inner; LO = lower outer; n.i. = not identified; *number of tumour-positive lymph nodes out of the total number of axillary lymph nodes that were excised by ALND.

By contrast, immediate dynamic lymphoscintigraphy is considered an essential feature as part of the sentinel lymph node biopsy procedure in melanoma. Dynamic imaging in melanoma allows for identification of all draining lymph node basins at risk, sentinel lymph nodes in unexpected locations and to distinguish first-echelon nodes from nodes with secondary drainage. However, in breast parenchyma lymph flow appears to be relatively slow, when compared to the rapid flow seen in (intra)dermal lymphatics. Consequently, lymphatic channels are rarely visualized in the breast and nodal uptake is usually not apparent before a period of two to three hours. Besides, lymphatic drainage from the breast parenchyma is less efficient than from the skin, resulting in a significantly lower uptake in sentinel lymph nodes in patients with breast cancer. For these reasons some breast surgeons even do not use preoperative lymphoscintigraphy at all in breast cancer treatment. These surgeons identify the sentinel lymph nodes intraoperatively by the gamma probe and/or blue dye without using lymphoscintigraphy as ‘road map’. Goyal advocates preoperative lymphoscintigraphy just for surgeons in the learning
phase to decrease the learning curve and in patients who have an increased risk of intraoperative failure of sentinel lymph node localization (obese or old patients).\textsuperscript{19} We are not in favor of these arguments. We still recommend routine use of 3 h post-injection preoperative lymphoscintigraphy in all breast cancer patients to pursue non-axillary sentinel lymph nodes because of the improved staging,\textsuperscript{20-22} the therapeutic implications and the minimal morbidity. Especially in patients with a small tumour who would not be advised to have adjuvant systemic treatment when the sentinel lymph node in the axilla was tumour-negative.\textsuperscript{23} Another argument in favor of preoperative lymphoscintigraphy is the chance that too many second-echelon nodes would be removed if lymphoscintigraphy is not performed. This would defeat the main purpose of the sentinel lymph node biopsy procedure, which is to be selective and to avoid unnecessary disturbance of non-sentinel lymph nodes and their afferent and efferent lymphatics. Besides that, the patient can be informed better preoperatively with respect to the localization of the sentinel lymph nodes. The lymphoscintigraphy images and skin markings are a road map in assisting the sentinel lymph node biopsy procedure and appear to yield more favorable morbidity outcomes for the patients compared to performing sentinel lymph node biopsy with only the probe or performing sentinel lymph node biopsy with dye alone.\textsuperscript{24-26}

Whether a 1-day protocol (i.e. lymphoscintigraphy and surgery on the same day) or a 2-day protocol is used is often a matter of logistic preference. A 2-day protocol has advantages both in scheduling multiple patients for lymphoscintigraphic imaging as well as in planning the operating room schedule, facilitating the planning of multiple sentinel lymph node procedures at the same day.\textsuperscript{27} Moreover, a 2-day protocol has radiation safety advantages, showing a significantly decreased dosage of radioactivity in the resected specimen\textsuperscript{28} and a smaller absorbed radiation dose to the hands of the medical staff due to radioactive decay.\textsuperscript{29} In patients undergoing the 2-day protocol, the visualization rate of sentinel lymph nodes on lymphoscintigraphy is higher due to the possibility of delayed images on the following day if the lymphoscintigraphy was negative.\textsuperscript{30}

For visualization of non-axillary sentinel lymph nodes intraparenchymal tracer administration is essential, because intradermal or subdermal injections rarely visualize drainage to the internal mammary chain. A recent study of MD Anderson Cancer Center, in which lymphoscintigraphy images were obtained at 1 to 2 hours after peritumoural injection, showed internal mammary drainage in only 4%. Findings on lymphoscintigraphy did not enhance sentinel lymph node identification or alter management in their series of 136 patients with early breast cancer.\textsuperscript{31} However, in our series sentinel lymph nodes were located outside the axilla in a substantial number (n=28) of patients with breast cancer (17%) and staging was improved in three patients (5%).

The identification rate of sentinel lymph nodes outside the axilla in our series was lower
than in the axilla. Preoperatively the location of non-axillary sentinel lymph nodes could often not be established with the gamma probe, because the injection site was often close to the sentinel lymph nodes. Intraoperative gamma probe detection was more difficult than in the axilla; the gamma probe is relatively large and could not be manipulated freely between the ribs. The overview on the area where the small non-axillary sentinel lymph node was expected was limited through the narrow intercostal space. Besides that, the blue lymphatic channel could often not be followed into the intercostal space from the site where it penetrated the major pectoral muscle. In conclusion, immediate lymphoscintigraphy delivers no additional value to lymphoscintigraphy 3 h post-injection in sentinel lymph node biopsy in breast cancer patients and can therefore safely be abandoned in breast cancer management.
References


