Sentinel node biopsy. Evolving from melanoma to breast cancer
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CHAPTER 10

CLINICAL RELEVANCE OF SENTINEL LYMPH NODES OUTSIDE THE AXILLA IN PATIENTS WITH BREAST CANCER

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SUBMITTED
ABSTRACT

Background: Lymphatic mapping in patients with breast cancer can reveal sentinel lymph nodes that are not located in level I-II of the axilla. Little is known about the clinical relevance of these nodes.

Methods: One hundred thirteen consecutive patients with clinical stage T1-3N0M0 breast cancer were included from October 1996 to June 1998 in two tertiary care hospitals in the Netherlands. Based on preoperative lymphoscintigraphy, sentinel node biopsy was performed guided by a gamma probe and patent blue dye. All sentinel nodes that were visible on lymphoscintigraphy were sought. Pathologic examination of the sentinel nodes included step-sections and staining with CAM 5.2. Axillary node dissection was performed regardless of sentinel lymph node status.

Results: Twenty-one (19 per cent) of 113 patients had sentinel lymph nodes outside level I-II of the axilla, mostly in the internal mammary chain. Twenty-two of the 30 sentinel nodes at those sites (73 per cent) were harvested. Three patients had only sentinel nodes outside the axilla. Four other patients had metastases outside the axilla. This changed postoperative treatment in three of them. No postoperative complications occurred.

Conclusion: Sentinel lymph nodes outside the level I-II of the axilla were present in 19 per cent of patients with breast cancer. Biopsy of these nodes was technically demanding. It was performed without additional morbidity. The clinical impact was limited: treatment changed in three per cent of patients.
Axillary lymph node dissection is important for staging patients with breast cancer and for regional control. Approximately 60 per cent of patients have uninvolved axillary nodes and will not benefit from this procedure. Since there is no viable alternative, axillary clearance is considered routine practice in the treatment of early breast cancer. Sentinel lymph node biopsy has been introduced recently and may be used to select patients for axillary treatment.

A sentinel lymph node is a lymph node that receives direct lymphatic drainage from the primary tumour. The sentinel node will therefore be the first site of metastasis if lymphatic dissemination occurs. Several studies have shown that the sentinel node can indeed be identified with blue dye, lymphoscintigraphy and a gamma probe, or with a combined technique. If the axillary sentinel nodes are free of tumour, the chance of having axillary lymph node metastases is probably so small that lymph node dissection can be omitted safely.

Although other investigators mention that sentinel nodes outside the axilla were visualised with lymphoscintigraphy in up to 38 per cent of patients, no report describes the systematical retrieval of such nodes. Biopsy of sentinel nodes outside level I-II of the axilla could improve staging and thus improve selection of patients for adjuvant radiotherapy and systemic therapy. This article describes the incidence of such nodes in patients with early stage breast cancer, the success of identification of these nodes, associated morbidity and the impact on staging and treatment.
PATIENTS AND METHODS

From October 1996 to June 1998, all consecutive patients with an operable palpable breast tumour that appeared malignant on clinical examination, imaging (mammography, ultrasound or both) and fine needle aspiration cytology were asked to participate in a study validating the sentinel lymphadenectomy concept. Patients were not enrolled when excisional biopsy had been performed, when there was clinical evidence of axillary lymph node metastases or when the patient was pregnant. The study was performed at two tertiary care hospitals in the Netherlands following the same protocol. This protocol was approved by the Ethical Committees of the participating centres and informed consent was obtained from all patients.

Sentinel node biopsy was performed as was described in more detail elsewhere. Lymphoscintigraphy was performed one day before surgery after intratumoural injection of 40 to 60 MBq of $^{99m}$Tc-labelled human albumen colloid (Nanocoll®, Sorin Biomedica Diagnostics S.p.A., Saluggia, Italy) in a volume of 0.2 ml. Dynamic and static images were obtained during 30 minutes after injection. Static images were repeated after four hours. A hot spot was regarded to represent a sentinel node if an afferent lymphatic vessel coming from the injection site was visualised. If no afferent vessels were seen, the surgeon was advised to search in both axilla and internal mammary chain for the first nodes that had appeared on the lymphoscintigraphy images.

Immediately prior to surgery, 1.0 ml of patent blue dye (Bleu Patenté V, Laboratoire Guerbet, Aulnay-sous-Bois, France) was injected into the tumour. Sentinel nodes were sought in the axilla through an incision at the border of the major pectoral muscle in all patients by following blue stained lymphatic vessels or by the gamma ray detecting probe (Neoprobe®, 1000/1500, Neoprobe Corporation, Dublin, Ohio, USA). Other sites than level I-II of the axilla were explored only when lymphoscintigraphy revealed hot spots at those sites. All sentinel lymph nodes which would not be removed in a routine level I-II axillary clearance are referred to in the

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Sentinel node biopsy was followed by level I-II (-III) axillary clearance regardless of sentinel lymph node status. Half of the patients were treated with mastectomy, the other half with breast conserving surgery.

All sentinel nodes were completely embedded for microscopic evaluation and stained with haematoxylin-eosin and immunohistochemistry for cytokeratin (CAM 5-2) at at least three levels. Nodes up to one centimetre were embedded in two halves in one block, larger nodes in parallel slices of 0.2 cm in more blocks. All blocks were cut at three levels at 100 micrometer intervals. All nodes removed during sentinel node biopsy that were considered to be non-sentinel nodes were processed the same way. Additional nodes from the axillary dissection specimen were evaluated at one or two levels including immunohistochemistry staining.

Table 1 Baseline characteristics of patients with sentinel lymph nodes in the axilla, outside the axilla or both

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 113)</th>
<th>SN axilla only (n = 79)</th>
<th>SN axilla and other site (n = 18)</th>
<th>SN outside axilla only (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>58 (33-89)</td>
<td>58 (33-89)</td>
<td>52 (34-79)</td>
<td>47 (44-49)</td>
</tr>
<tr>
<td>UICC clinical stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1N0</td>
<td>55 (49)</td>
<td>38 (48)</td>
<td>9 (50)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>T2N0</td>
<td>52 (46)</td>
<td>39 (49)</td>
<td>6 (33)</td>
<td>-</td>
</tr>
<tr>
<td>T3N0</td>
<td>6 (5)</td>
<td>2 (3)</td>
<td>3 (17)</td>
<td>-</td>
</tr>
<tr>
<td>Tumour location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UOQ</td>
<td>48 (42)</td>
<td>39 (49)</td>
<td>6 (33)</td>
<td>-</td>
</tr>
<tr>
<td>LOQ</td>
<td>20 (18)</td>
<td>14 (18)</td>
<td>3 (17)</td>
<td>-</td>
</tr>
<tr>
<td>UIQ</td>
<td>22 (19)</td>
<td>12 (15)</td>
<td>4 (22)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>LIQ</td>
<td>10 (9)</td>
<td>4 (5)</td>
<td>3 (17)</td>
<td>2 (67)</td>
</tr>
<tr>
<td>Central</td>
<td>13 (12)</td>
<td>10 (13)</td>
<td>2 (11)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Values are mean (range). All other values in parenthesis are percentages. SN, sentinel node; UOQ, upper outer quadrant; LOQ, lower outer quadrant; UIQ, upper inner quadrant; LIQ, lower inner quadrant
RESULTS

Sentinel node biopsy was performed in 113 patients. The sentinel node was identified in 100 of them. Twenty-one patients (19 per cent) had a sentinel node outside the axilla (level I-II). Eighteen of these 21 patients (86 per cent) had sentinel nodes both in the axilla and at another site. In the remaining three patients, all sentinel nodes were located outside the axilla (Fig. 1). Patient characteristics of each group are given in Table 1. Thirteen per cent (9/68) of patients with a tumour in the lateral quadrants of the breast had a sentinel node outside the axilla, against 27 per cent (12/45) of those with a tumour at a medial or central site.

The internal mammary chain was the most frequent location of sentinel nodes outside the axilla (17 patients). Three patients had sentinel nodes in the breast parenchyma (Fig. 2). In two patients, one of the sentinel nodes was located in the infraclavicular fossa (axilla level III) and in two other patients a sentinel node was found deep in the interpectoral fossa (Fig. 3).

Fig. 1 Lymphoscintigraphy of a 44-year old woman with a T1N0M0 breast cancer in the upper inner quadrant of the left breast. Sentinel nodes were located in the internal mammary chain(1) and in between the pectoral muscles(2). No metastases were found in the sentinel nodes nor in sixteen additional axillary nodes.
Fig. 2 Lymphoscintigraphy of a woman aged 34 with a T1N0M0 breast cancer in the lower inner quadrant of the right breast. The arrow marks the injection site. Drainage was visualised to the axilla(1) and through two intramammary nodes(2) to the internal mammary chain(3). The patient was treated with breast conserving surgery and did not consent to have the intramammary sentinel node explored. No metastases were found in the eighteen axillary nodes examined, including the sentinel node in the axilla.

Fig. 3 Lymphoscintigraphy of a 71-year old woman with a T1N0M0 breast cancer in the upper inner quadrant of the left breast. Sentinel nodes were located in the internal mammary chain(1), deep in the interpectoral fossa(2) and in the axilla(3). Metastases were found in the first two sentinel nodes but not in the eighteen axillary nodes, including the third sentinel node.
Intraoperative identification of sentinel nodes outside the axilla was found to be more difficult than for sentinel nodes in the axilla. Almost all axillary sentinel nodes were retrieved as seen on lymphoscintigraphy. The identification rate of sentinel nodes outside the axilla was only 73 per cent. Several problems occurred with blue dye mapping outside the axilla. In case of an internal mammary sentinel node, the blue lymphatic vessel could often not be followed into the intercostal space from the site where it penetrated the major pectoral muscle. The blue lymphatic vessel was often damaged. Sometimes the blue vessel entered an intercostal space below the level of the sentinel node. Only 55 per cent of sentinel nodes outside the axilla were found to be blue against 84 per cent in the axilla. Because the blue dye mapping was often not successful, gamma probe detection was relatively important. The skin mark placed by the nuclear medicine physician to indicate the location was accurate and helpful. Intraoperative gamma probe detection was still more difficult than in the axilla. The location of the sentinel nodes outside the axilla could often (65 per cent) not be established preoperatively with the gamma probe. This occurred in only 27 per cent of the operations in the axilla. The main cause was that the injection site was often close to the sentinel node. Most of the injected dose remains at the injection site which causes a high background radioactivity. The level of radioactivity in the lymph node is low, only about 0.16 per cent of the injected dose (L. Jansen, unpublished data). Besides that, the gamma probe is relatively large and could not be manipulated freely between the ribs. In nine patients, the search for radioactive lymph nodes outside the axilla was resumed after excision of the primary site which reduced the background level of radioactivity considerably. Retrieval of (one of) the sentinel nodes was then still not possible in six patients. A third group of problems that were encountered were general surgical difficulties. The overview on the area where the sentinel node was expected was limited through the narrow intercostal space. Sentinel nodes were sometimes located behind a rib. The sentinel nodes outside the axilla were small (1-5 mm). This made it sometimes difficult to recognise them as lymph nodes. Exploration of an intercostal space had to be performed cautiously to prevent damage to the pleura and the internal mammary artery.

The pleura was never opened when searching for an internal mammary node. In six patients, an extra incision in the skin had to be made to reach
all sentinel nodes. No postoperative complications were seen from removal of sentinel nodes outside the axilla.

Eight of 21 patients with sentinel nodes outside the axilla had regional metastases (Table 2). Four of them had no metastases in the sentinel nodes outside the axilla. One patient had metastases in sentinel nodes in the interpectoral fossa and in level I of the axilla (stage pT2N1). Biopsy of the sentinel nodes outside the axilla did therefore not influence staging in these five patients. Three patients had tumour-positive sentinel nodes in the internal mammary chain. They were upstaged to pT1cN3 (two patients) and pT3N3 (one patient) and received radiotherapy to the internal mammary chain. One of these three patients had no metastases in the axilla and also received adjuvant systemic treatment that would otherwise not have been given (Fig. 3).

### Table 2 UICC pathological nodal status per group

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 113)</th>
<th>SN axilla only (n = 79)</th>
<th>SN axilla and other site (n = 18)</th>
<th>SN outside axilla only (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>64 (57)</td>
<td>44 (56)</td>
<td>10 (56)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>N1</td>
<td>46 (41)</td>
<td>35 (44)</td>
<td>5 (28)</td>
<td>-</td>
</tr>
<tr>
<td>N3</td>
<td>3 (3)</td>
<td>-</td>
<td>3 (17)</td>
<td>-</td>
</tr>
</tbody>
</table>

SN, sentinel node. Values in parenthesis are percentages

**DISCUSSION**

This study demonstrated that sentinel nodes were located outside level I-II of the axilla in a substantial number of patients with breast cancer (19 per cent). Retrieval of these lymph nodes was technically demanding. Without additional morbidity, the majority of these nodes could be harvested. Systematical biopsy of these nodes improved staging in a few cases (3 per cent).
The proportion of patients with only tumour-positive lymph nodes outside the axilla was small as was expected (1/113). In most patients with sentinel nodes outside the axilla, drainage occurred both to the axilla and to the internal mammary chain. Dissemination to internal mammary nodes is common: approximately 30 per cent in patients with primary operable breast cancer\textsuperscript{15,16}. In only four per cent of patients, Urban found metastases limited to the internal mammary chain when performing radical extended mastectomy in the 1950's\textsuperscript{15}. Cody described Urban's last series of patients, selected for medial tumour location, and found that 11 per cent had metastases in the internal mammary nodes and not in the axilla\textsuperscript{16}. In contrast to dissemination to the internal mammary chain, dissemination to nodes in between the pectoral muscles (Rotter's nodes)\textsuperscript{17} or directly to axillary nodes at level III is relatively rare\textsuperscript{18,19}. The incidence of metastases only outside the axilla in the present series (1/113) was lower than the four per cent found by Urban. An explanation for this difference could be that Urban's population had more extensive disease and therefore more node-positive cases overall.

The impact on the indication for adjuvant systemic treatment is low because of two reasons. Firstly, the incidence of solitary metastasis outside the axilla is low. Secondly, prognostic characteristics of the tumour itself determine the indications for adjuvant systemic treatment nowadays\textsuperscript{20,21}. Consequently, most patients would have received adjuvant systemic treatment anyway. Metastasis in an internal mammary chain node is indeed an indication for systemic therapy because it is associated with worse prognosis\textsuperscript{16,22,23}. Half of the population presented in this paper had a T1-tumour. They would be given the option but not a strong advise to have adjuvant systemic treatment when the axilla was tumour-negative. Twelve of these 55 patients (11 per cent of all patients) had sentinel nodes outside the axilla, and in one patient this was the only site of metastases. Biopsy of sentinel nodes outside the axilla may be reserved for those patients with small tumours who would not be advised to have adjuvant systemic treatment when the sentinel node in the axilla is tumour-negative.

Whether the internal mammary chain nodes should be treated locally and, if so, how is a subject of long-standing controversy. Excision or
radiotherapy have not convincingly been shown to improve the survival rate when routinely applied\textsuperscript{24-26}. A limited survival benefit was seen in patients with axillary metastasis and a medial or central location of the primary cancer\textsuperscript{16,23}. This is understandable because these patients have the greatest incidence of tumour-positive nodes in the internal mammary chain. Treatment of these nodes could theoretically prevent locoregional recurrence. Isolated recurrences in the internal mammary chain is a rare event\textsuperscript{27}. Radiotherapy in the cardiac region may slightly increase the risk for myocardial infarction\textsuperscript{28}. Although benefit of radiotherapy to the internal mammary chain is not (yet) clearly shown, it is often given\textsuperscript{29}.

The impact of radiotherapy to the internal mammary chain on survival is the subject of an ongoing EORTC trial (#22922). Patients are included when the tumour is in a medial location or when the axilla is tumour-positive. These selection criteria are based on the results of radical extended mastectomy performed in the 1950's and 1960's\textsuperscript{15}. Lymphatic mapping could be a more sensitive tool to select patients because it provides insight in the individual lymphatic drainage pattern\textsuperscript{8,30}. The reliability of lymphoscintigraphy for indicating the first site of metastases has been established in many series in patients with melanoma or breast cancer\textsuperscript{5,31,32}. When no drainage to internal mammary chain nodes is visualised or when an internal mammary sentinel node is free of tumour, the chance of having metastases at that site is probably less than a few percent. Radiotherapy would then not be beneficial. The value of lymphatic mapping and sentinel node biopsy to select patients for adjuvant radiotherapy to the internal mammary chain should be further investigated.

\section*{Acknowledgements}

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REFERENCES


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