Clinical relevance and refinement of the sentinel node procedure in breast cancer and melanoma
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CHAPTER 2

THE SENTINEL LYMPH NODE IN SURGICAL ONCOLOGY:
BREAST CANCER

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The standard procedure in breast cancer patients used to be a radical mastectomy with axillary lymph node dissection. As time went by, more conservative methods were studied and a selection of patients was identified to undergo a wide local excision of the primary breast tumor. Therefore, it is not strange that new methods have been developed for staging and treatment of the axilla as well.

Axillary lymph node dissection comes with a substantial morbidity (Tables 1 and 2). Although these complaints are usually not severe, the incidence is high. However, staging of the axilla is too important to omit. Together with the size and the grade of the primary tumor, the axillary lymph node status is an important parameter that indicates the need for adjuvant systemic therapy. Effective adjuvant treatment is available and widely accepted. It leads to around 25% reduction in mortality. Lymph node dissection also assures regional tumor control and improves survival.

Table 1. Postoperative complications from axillary lymph node dissection.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Haematoma (%)</th>
<th>Wound infection (%)</th>
<th>Seroma (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes 1977^1</td>
<td>126</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Urist 1983^4</td>
<td>98</td>
<td>1</td>
<td>7</td>
<td>27</td>
</tr>
<tr>
<td>Bowsher 1986^5</td>
<td>15</td>
<td></td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>combined</td>
<td>239</td>
<td>1</td>
<td>6</td>
<td>15</td>
</tr>
</tbody>
</table>

Table 2. Late complications from axillary lymph node dissection.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patients</th>
<th>Serious edema (%)</th>
<th>Functional disorder (%)</th>
<th>Pain (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes 1977^1</td>
<td>126</td>
<td>0</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Urist 1986^4</td>
<td>98</td>
<td>1</td>
<td>7</td>
<td></td>
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<tr>
<td>Kissan 1986^6</td>
<td>94</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Danforth 1986^7</td>
<td>136</td>
<td>6</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Bowsher 1986^5</td>
<td>15</td>
<td>3</td>
<td>6</td>
<td>6</td>
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<tr>
<td>combined</td>
<td>469</td>
<td>4</td>
<td>6</td>
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</tr>
</tbody>
</table>

Some 60% of the patients nowadays have no metastases in the axilla and derive no therapeutic benefit from such an invasive surgical procedure. Sentinel node biopsy looks promising as a replacement of axillary clearance for staging breast cancer. Only the sentinel nodes and occasionally suspicious other nodes are harvested during this procedure. The associated morbidity is thought to be much less when compared to complete axillary dissection. A recent study showed that the differences in overall complaints, number of symptoms, pain, range of motion of the operated upper extremity, numbness, paresthesia, and arm swelling as well as perceived disability in activities of daily living are significantly in favor of the sentinel node procedure. The length of hospital stay was also significantly shorter for sentinel node patients. At the Memorial Sloan-Kettering Cancer Center, the sentinel node procedure is associated with a significant sensory morbidity among women undergoing breast-conserving therapy, although it is approximately half that of women undergoing axillary clearance. Despite the observation that it improved in the first three months after surgery, patients continued to report sensory morbidity at one year.
A second reason to replace the complete axillary dissection by the sentinel node procedure is the improved staging. Instead of having to examine up to twenty lymph nodes, the pathologist can focus on one node or a few at the most: the node(s) most likely to contain metastatic disease. These nodes can then be evaluated more intensively by means of techniques such as serial sectioning. The role of immunohistochemistry staining is currently a contentious issue, as is the use of this information to guide recommendations for patient care. This more intensive histopathologic evaluation identifies previously occult tumor in 7-33% of the cases. A number of studies have been published on the benefits of an axillary clearance after harvesting a sentinel node with a micrometastasis. Unfortunately, many of these studies are underpowered to detect a significant difference in overall survival. While retrospective data suggest that occult micrometastases detected with routine hematoxylin and eosin are associated with decreased survival, the clinical significance of micrometastases detected with immunohistochemistry is uncertain. The value of adjuvant therapy can then be questioned for patients with otherwise good prognostic factors.

**Inclusion Criteria**

So now it is clear why to perform the sentinel node biopsy, the next question is on whom. Which group of patients should be selected? Patients with a T1-3N0 breast cancer can be included. Some investigators think that it is more difficult in T3 lesions to imitate the true drainage from the primary tumor site with the tracers. Also, the incidence of tumor-positive lymph nodes in the axilla increases in this subgroup of patients and by that, the chance of failure could increase as well. This remains to be shown. This same problem exists in patients with multifocal breast lesions.

Before considering the sentinel node procedure, the N0 stage should be confirmed by preoperative evaluation of the axilla preferably including ultrasonography and fine needle aspiration cytology of suspicious nodes. This will reduce the risk of false negative results due to obstruction of the lymph flow by tumor within the node. Uptake of the radioactive tracer and the patent blue dye will not occur if a sentinel node is completely invaded by tumor. The lymph flow will be rerouted from the original sentinel node to a neo-sentinel node and so will the tracers. Even after meticulous preoperative evaluation, an occasional N1 patient might slip through. How can we recognize this phenomenon? Sometimes it is possible to intra-operatively identify a blue lymphatic vessel approaching a node and stopping right in front of it, without actually staining the node. In these cases, blocking of the dye by tumor inside the node must be considered and such a node should be named the sentinel node. We have experienced that intra-operative palpation of the biopsy wound is also helpful. In this way solid lymph nodes might be detected which could not be felt through the skin at preoperative physical examination. Further reduction of the incidence of false negative sentinel node biopsies may be accomplished by excluding patients who have undergone recent therapy of the breast. Some institutes have already enrolled breast cancer patients after prior excisional biopsy in their sentinel node protocols. Others are reluctant to do so because of the possible failure of the technique due to the potential disruption of breast lymphatics. Retrospective analysis of studies in which these patients were included can tell us more, or a study of the reproducibility of the lymphoscintigraphy. The first method has been used in several studies. Haigh et al. concluded that sentinel lymph node dissection has a high success rate in breast cancer patients regardless of the biopsy method or the excision volume removed before the sentinel lymph node procedure. A study by Wong et al. does not support concerns regarding sentinel node biopsy
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after excisional biopsy of the primary tumor either.²² This sounds promising, but these retrospective analyses lack certain reliability. A study of the reproducibility of the lymphoscintigraphy before and after excisional biopsy should be done. At The Netherlands Cancer Institute, such a study is being performed (Figure 1). More patients have to be enrolled in this study though before any conclusions should be drawn.

**Figure 1.** *The difference in drainage before and after an excisional biopsy in a patient with DCIS.*

**DRAINAGE**

Where can we expect the sentinel nodes to be other than in the axilla?²⁵ The development of lymphatic mapping has generated a renewed interest in drainage patterns because a sentinel node may be located outside the axilla. A Dutch surgeon named Camper was the first to identify lymphatic drainage to lymph nodes along the internal mammary vessels in 1770.²⁹ These nodes extend upwards from the fifth intercostal space to the retroclavicular glands. Injection studies with vital dyes showed that the internal mammary nodes receive their lymph from deep lymphatics.²⁷²⁹ These lymphatics arise from the breast lobules, leave the posterior surface of the breast and pass through the pectoral and intercostal muscles to reach the internal mammary chain. Other investigators confirmed that the internal mammary chain represents an important pathway of lymph drainage from both the medial and lateral quadrants of the breast.²⁸³⁰³¹ Other less frequently encountered drainage routes have been described. Lymphatics sometimes pass through lymph nodes on their way to the axilla or internal mammary chain, so-called interval nodes. These are the interpectoral nodes (situated between the pectoralis major and pectoralis minor muscles) or lymph nodes in the breast parenchyma (intramammary nodes). Mornard first described occasional direct drainage from the breast parenchyma to supraclavicular nodes.³² Retrosternal lymphatic drainage to the contralateral internal mammary chain occurs sporadically.

Lymphatic drainage patterns from various regions within the breast have been studied once before the sentinel node era. In 1972, Vendrell-Torne and coworkers used an intraparenchymal radioactive gold administration and a conventional scanner that depicts less detail than the now ubiquitous gamma cameras.³¹ Their study, performed in normal individuals without breast cancer, showed frequent drainage to the internal mammary chain. Tracer administered in the
upper outer quadrant traveled there in 36% of the cases and for the lower outer quadrant this was 64%. The lower inner quadrant drained even more frequently to the internal mammary nodes than to the axilla, 86% vs. 68%. Vendrell-Torne and coworkers did not observe drainage to intramammary or interpectoral nodes, perhaps due to the primitive equipment that was used at the time and the lack of intra-operative confirmation of the exact location of the sentinel node seen on the scan. Paganelli and others have shown that tracer administration deep in the parenchyma of the inner quadrants travels to internal mammary nodes in 66% of the cases, whereas these nodes are seen in just 10% when the tracer is administered in an outer quadrant. Drainage to nodes elsewhere around the breast was not observed. Byrd and coworkers also found that 10% of upper outer quadrants drain to the internal mammary chain. For the lower outer quadrant, upper inner quadrant and lower inner quadrant these percentages were 27, 17 and 25 respectively. No nodes outside the axilla or the internal mammary chain were described. Uren and others found drainage to sentinel nodes outside the axilla in a surprisingly high 56%.

A study at The Netherlands Cancer Institute described the lymphatic drainage patterns from the five ‘quadrants’ of the breast in 700 women. Radiolabeled colloid was administered into the primary tumor. The overall identification rate of sentinel nodes was 678 out of 700 (97%). Drainage to the axilla from the upper outer quadrant, upper inner quadrant, lower outer quadrant, lower inner quadrant and center was 95.8%, 93.1%, 97.7%, 88.0% and 100% respectively. A sentinel node in the internal mammary chain region was seen in 10.4%, 32.4%, 29.5%, 52.0% and 23.7% respectively. Both palpable and non-palpable lesions drained towards the internal mammary chain, although the latter more frequently ($P=0.001$). Drainage was occasionally observed to supraclavicular, infraclavicular, interpectoral and intramammary sentinel nodes. The drainage patterns of all 678 patients combined are presented in Figure 6 on page 53.

**RESULTS**

Although a clear consensus has been obtained on the technique of sentinel node biopsy in melanoma patients, this is not yet the case for breast cancer. Several issues are still subject of debate. Different institutes favor different identification and injection techniques. The nuclear medicine aspects of the sentinel node procedure and the injection techniques have been described earlier in this chapter. It is becoming clear that a radioactive tracer alone will not do to identify the sentinel node. The administration of blue dye should also be performed. Several studies have shown benefits of the use of both techniques, as they are complementary. In a study by Tanis et al., exploration of the axilla after injection of blue dye revealed a sentinel node in 24 of the 42 patients in whom no sentinel node was visualized on the preoperative images. In a similar study, a sentinel node was identified during surgery in 21 of 47 patients who were unsuccessfully imaged by lymphoscintigraphy. In nineteen of these cases the sentinel node was harvested with the aid of blue dye.

Now that we know where to expect the sentinel nodes and how to visualize and surgically identify them, what about the published results? When comparing the data on the learning phase studies, one should be aware of the fact that no standardized technique exists. Surgical identification and false negative rates obtained by various investigators are shown in Table 3. The surgical identification rates were between 41% and 98% and the false negative rates between 0% and 40%. Nowadays, many learning phases have been closed and no confirmatory axillary lymph node dissections are performed in sentinel node negative patients. The identification rates now generally exceed 95% and the reported false negative rates have not been alarming so far.
Table 3. Results of sentinel lymph node biopsy obtained by various investigators. The percentage of false negative procedures is calculated over the patients with a tumor-containing axilla. \(S=\)preoperative lymphoscintigraphy, \(D=\)blue dye, \(P=^{99m}\text{Tc} \) labeled colloid and gamma detection probe.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Technique</th>
<th>Identification (%)</th>
<th>False negative (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Offodile 1998(^{25})</td>
<td>41</td>
<td>P</td>
</tr>
<tr>
<td>2</td>
<td>Giuliano 1996(^{41})</td>
<td>107</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>Albertini 1996(^{44})</td>
<td>62</td>
<td>D, P</td>
</tr>
<tr>
<td>4</td>
<td>Kapteijn 1998(^{45}) *</td>
<td>30</td>
<td>D</td>
</tr>
<tr>
<td>5</td>
<td>Barnwell 1998(^{46})</td>
<td>42</td>
<td>D, P</td>
</tr>
<tr>
<td>6</td>
<td>De Vries 1998(^{47})</td>
<td>48</td>
<td>S, D, P</td>
</tr>
<tr>
<td>7</td>
<td>Krag 1994(^{48})</td>
<td>22</td>
<td>P</td>
</tr>
<tr>
<td>8</td>
<td>Cox 1998(^{49})</td>
<td>466</td>
<td>S, D, P</td>
</tr>
<tr>
<td>9</td>
<td>Van der Ent 1999(^{50})</td>
<td>60</td>
<td>S, D, P</td>
</tr>
<tr>
<td>10</td>
<td>Roumen 1997(^{51})</td>
<td>83</td>
<td>S, P</td>
</tr>
<tr>
<td>11</td>
<td>Veronesi 1997(^{52})</td>
<td>163</td>
<td>S, P</td>
</tr>
<tr>
<td>12</td>
<td>Borgstein 1998(^{53})</td>
<td>130</td>
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<td>13</td>
<td>Koller 1998(^{54})</td>
<td>98</td>
<td>D</td>
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<td>14</td>
<td>Gill 1997(^{55})</td>
<td>36</td>
<td>S, P</td>
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<tr>
<td>15</td>
<td>Guenther 1997(^{56})</td>
<td>145</td>
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<td>16</td>
<td>Krag 1998(^{57})</td>
<td>443</td>
<td>P</td>
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<tr>
<td>17</td>
<td>Giuliano 1994(^{58})</td>
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</tr>
<tr>
<td>18</td>
<td>O'Hea 1998(^{59})</td>
<td>60</td>
<td>S, D, P</td>
</tr>
<tr>
<td>19</td>
<td>Crossin 1998(^{60})</td>
<td>50</td>
<td>P</td>
</tr>
<tr>
<td>20</td>
<td>Miner 1998(^{61})</td>
<td>42</td>
<td>P</td>
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<tr>
<td>21</td>
<td>Horgan 1998(^{62})</td>
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<tr>
<td>22</td>
<td>Flett 1997(^{63})</td>
<td>68</td>
<td>D</td>
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<td>23</td>
<td>Schneebaur 1996(^{64})</td>
<td>15</td>
<td>S, D, P</td>
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<tr>
<td>24</td>
<td>Reuhl 1998(^{65})</td>
<td>96</td>
<td>S, P</td>
</tr>
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<td>25</td>
<td>Fölscher 1997(^{66})</td>
<td>79</td>
<td>D</td>
</tr>
<tr>
<td>26</td>
<td>Sandrucci 1997(^{67})</td>
<td>37</td>
<td>P</td>
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</table>

* Ex vivo study.

In determining the rate of false negative results, a mistake that is sometimes made is to calculate this rate over the entire group of patients, both those who are axilla-positive and those who are axilla-negative. The outcome is too flattering with this approach, for it is not possible to miss metastasis in a patient who has no metastasis. The false negative rate should be calculated over the entire group of axilla-positive patients. But how should we define a false negative result? In learning phase studies, the definition of a false negative result followed the original definition of the sentinel node, which is based on direct drainage from the primary lesion site. This node is identified by lymphoscintigraphy, by a probe, or a blue dye. The sole purpose of the procedure is the identification of this particular lymph node. The result of this procedure would be false negative if this sentinel node is disease-free at initial pathologic evaluation, but tumor is established in any axillary lymph node at any time. Lately, however, we sense a shift towards the use of a definition based on the finding of an axillary recurrence during follow-up. In our opinion, this definition is too broad. The best definition lies in between and encourages removal of apparently tumor-positive, non-sentinel nodes while discouraging the indiscriminate removal
of non-sentinel nodes. This best serves the clinical purpose, which is to establish metastatic disease but in the least disruptive manner.

All the false negative cases in breast cancer patients at The Netherlands Cancer Institute have been reviewed. The axillary sentinel node revealed metastasis in 204 (36.1%) of the 565 patients in whom it was identified and was false negative in eight patients. Two false negative results came to light by confirmatory axillary lymph node dissection during the learning phase. Tumor-positive lymph nodes were incidentally found in the axillary tail of the simple mastectomy specimen in two patients. Excision of a firm, non-radioactive, unstained but tumor-positive non-sentinel node occurred in three other patients. One patient developed an axillary recurrence 22 months postoperatively. Presumptive causes for these failures were surgical delay, pathological sampling error and lymphatic blocking by massive tumor infiltration.

CLINICAL RELEVANCE OF EXTRA-AXILLARY SENTINEL NODES

The existence of lymphatic drainage of the breast to axillary and extra-axillary sites has been known for centuries. Although also these latter nodes are known to sometimes contain metastatic disease, their removal has never been pursued enthusiastically. Preoperative lymphoscintigraphy is mandatory to detect non-axillary sentinel nodes. As discussed above, intraparenchymal tracer injection is essential because intradermal or subdermal injection will rarely visualize drainage to the internal mammary chain. Harvesting lymph nodes outside the axilla is often a technically challenging procedure. Internal mammary nodes are very small and sometimes located behind a rib. The probe is difficult to handle in the intercostal space, because it is sometimes inaccessible due to bony deformation or location of the ribs close to each other. Increasing experience of the surgeons and possibly the increase in radioactivity dose and colloid particle concentration result in the improvement of identification. Morbidity is usually limited to an occasional injury to the internal mammary artery or pleura. In a few patients, a separate incision of a few centimeters is necessary (Figure 2). Long-term sequelae have not been encountered so far.

Figure 2. Additional incision to harvest a sentinel node in the internal mammary chain. The intercostal space is opened after detaching the intercostal muscles.
At The Netherlands Cancer Institute, a sentinel node in at least one extra-axillary basin was depicted in 183 out of 600 sentinel node procedures (31%). Visualized internal mammary chain nodes could be harvested in 111 of the 132 cases (84%) and contained metastasis in 18 out of 111 (16%). Other visualized extra-axillary sentinel nodes, such as the supraclavicular, subclavicular, interpectoral and lateral and medial intramammary nodes, were excised in 61 out of 81 cases (75%) and harbored metastasis in 12 of these procedures (20%). In 15 of the 183 patients with a visualized sentinel node in an extra-axillary basin (8%), this node was tumor-positive while the axilla was tumor-free. There was a change in the management of 31 out of these 183 patients (17%) such as institution or omission of radiotherapy to the internal mammary chain, adjuvant systemic therapy or omission of an axillary lymph node dissection. If lymphoscintigraphy had been omitted, a tumor-positive extra-axillary sentinel node would have been missed in 2.5% of all 600 patients.

There are therapeutic implications because it is generally accepted that metastases in these lymph nodes are of prognostic significance. The overall survival rates of patients with isolated internal mammary chain metastases are similar to those with isolated axillary lymph node involvement. The lowest survival rates are observed in patients with both axillary and internal mammary node metastases. Whether these ramifications of improved staging result in a survival benefit is unknown.

**CONCLUSIONS ON LYMPHATIC MAPPING IN BREAST CANCER**

The technique of lymphatic mapping in breast cancer is certainly not as standardized as in melanoma. The clinical relevance of both extra-axillary sentinel nodes and micrometastastic disease is not yet clear. However, axillary staging by means of the sentinel node procedure with the aid of radioactive tracer, lymphoscintigraphy and blue dye has proven its surplus value over the axillary lymph node dissection.

Genetic analysis should enable us soon to determine the biology of the disease based on analysis of the primary lesion. Meaningful predictions of the course of the disease will be the result and the tailoring of treatment to the needs of an individual patient. Such tests will, for instance, tell us that a particular patient may benefit from adjuvant chemotherapy because his or her particular tumor has a tendency for dissemination to distant sites. One study has already shown that this may be possible. If these results are confirmed, the conservative management of breast cancer has been taken yet another step ahead and the need for axillary staging - and sentinel node biopsy – may be less urgent.

This chapter is also published in Nieweg OE, Estourgie SH, Valdés Olmos RA: Lymphatic mapping and sentinel node biopsy. In: Nuclear medicine in diagnosis and treatment. Ell PJ, Gambhir SS. Eds. Elsevier.

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