Clinical relevance and refinement of the sentinel node procedure in breast cancer and melanoma
Estourgie, S.H.

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CHAPTER 7

SHOULD THE HUNT FOR INTERNAL MAMMARY CHAIN SENTINEL NODES BEGIN?
AN EVALUATION OF 150 BREAST CANCER PATIENTS

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INTRODUCTION

The existence of lymphatic drainage from the breast to axillary and extra-axillary sites has been known for centuries. Although the latter may contain metastatic disease, their removal has never been pursued enthusiastically. One of the reasons is that the clinical relevance of removing internal mammary chain (IMC) nodes is questionable. A survival benefit has not been observed after complete dissection of this region. Whether radiotherapy to the IMC or adjuvant systemic therapy can improve survival is yet unclear. However, the tumor-status of IMC lymph nodes does have an impact on survival, which is comparable to that of the status of the axillary lymph nodes.

Sentinel node biopsy is considered to be a valuable method for staging the axilla. Identification of IMC sentinel node metastases may improve staging further and may enable additional node-positive patients to receive adjuvant systemic therapy or radiotherapy. The aim of this study was to determine the incidence of IMC sentinel nodes, their identification rate, the associated morbidity and the implications of their tumor-status on staging and treatment.

MATERIALS AND METHODS

Between January 1999 and December 2002, 681 breast cancer patients underwent a sentinel node procedure at The Netherlands Cancer Institute. Part of this group of patients has been evaluated previously by Tanis et al. Ten patients had a bilateral tumor and 179 patients had a non-palpable tumor. Pathologic proof of breast cancer was routinely obtained by core biopsy or fine needle aspiration. The primary tumor was still present in all patients.

A two-day protocol was used. On the day before surgery, \(^{99m}\)Te-nanocolloid (Nanocoll\(^\circledR\), Amersham Cygne, Eindhoven, the Netherlands) was injected into the lesion in a mean volume of 0.2 ml and a mean radioactivity dose of 114.9 MBq (3.1 mCi). In case of non-palpable breast cancer, the intratumoral injection was guided by ultrasound or stereotaxis. Static imaging was performed at 30 minutes and four hours post-injection with simultaneous transmission scanning using a \(^{57}\)Co flood source to outline the body contour. Since July 1999, additional views were obtained after two hours. Both anterior and lateral images were obtained using a dual-head gamma camera (ADAC Vertex\(^\circledR\), Milpitas, California, USA). The location of the node was marked on the skin with indelible ink. In patients with non-palpable breast cancer, a localization procedure was performed after the last scintigraphic image including placement of a catheter for intratumoral administration of patent blue dye. A more extensive description of this technique has been published elsewhere.

The option of having the internal mammary sentinel node removed was presented to the patient. It was explained that a more accurate staging could be accomplished, often at the cost of an additional incision. It was made clear that the impact on survival was unknown. The next day, 1.0 ml of patent blue dye (Blue Patenté V, Laboratoire Guerbet, Aulnay-sous-Bois, France) and a gamma ray detection probe (Neoprobe\(^\circledR\), Johnson & Johnson Medical, Hamburg, Germany) were used to identify the sentinel node. All procedures were performed by one of four experienced surgeons or under their supervision by a resident or fellow. A hot spot on the lymphoscintigram was considered to be a sentinel node if either an afferent lymphatic channel was visualized, or the hot spot was the first one seen in a sequential pattern, or the hot spot was the only one depicted in the basin. An afferent blue lymphatic vessel originating in the tumor area also defined a node as sentinel node. Exploration of the axilla was always performed, even
if no axillary hot spot was visualized. The parasternal region was explored only in case of lymphoscintigraphic visualization.

IMC sentinel nodes were explored either through the incision made for the removal of the primary tumor or through a small separate transverse incision over the intercostal space concerned. After splitting the pectoral muscle fibers, 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. Never was a rib divided.

All sentinel nodes were formalin-fixated, bisected, paraffin-embedded and cut at a minimum of six levels at 50 to 150-μm intervals. Pathological evaluation included hematoxylin-eosin and immunohistochemical staining (CAM 5.2, Becton Dickinson, San Jose, California, USA).

If no radiocolloid or blue dye drainage was observed to any region, the sentinel node procedure was considered to have failed and formal axillary lymph node dissection was performed. Otherwise, only patients with a tumor-positive axillary sentinel node received an axillary lymph node dissection. At our institution, the indication for radiotherapy to the IMC was traditionally a positive axillary lymph node, irrespective of the size and location of the primary tumor. In the lymphatic mapping era, a patient will only receive radiotherapy to the parasternal area if an excised IMC sentinel node is tumor-positive or such lymphoscintigraphic visualized sentinel node cannot be harvested. If no drainage to the IMC is observed on lymphoscintigraphy, the decision of whether to irradiate the IMC or not is based on the axillary status. Adjuvant systemic therapy was instituted if the patient had stage N1a disease or higher or if the primary tumor is larger than three cm. In N0 or N1mi patients with a primary breast cancer of 1-3 cm, adjuvant systemic therapy was considered if the tumor was poorly differentiated (grade III, mitotic index over nine).

Patient characteristics and both lymphoscintigraphic and surgical results were recorded prospectively. Patients with sentinel nodes in other locations than the axilla or the IMC were not subject of this study. The χ²-test was performed to evaluate differences in drainage between various patient groups.

RESULTS

Every patient who was offered the option wanted to have her IMC sentinel node pursued. IMC sentinel nodes usually take up a small amount of the radioactive tracer but the interpretation of the images was nevertheless straightforward (Figure 1). Lymphoscintigraphy demonstrated an IMC sentinel node in 150 of the 691 lymphatic mapping procedures (22%). In 38 patients, more than one IMC sentinel node was visualized.
The location of the IMC sentinel nodes within the intercostal spaces is shown in Table 1. In 27 of the 150 patients, no hot spot was visualized in the axilla (18%). In eleven of these 27 patients, a sentinel node could still be identified in the axilla with the aid of blue dye. The remaining sixteen patients were presumed to have drainage restricted to the IMC and did not undergo an axillary lymph node dissection.

The IMC sentinel node could be harvested intra-operatively in 130 of the 150 patients (87%). A median number of 1.4 IMC sentinel nodes were harvested (range: 1-4). The majority were only radioactive (70%), the remainder were both blue and radioactive. None were only blue.

There were occasional complications while pursuing an IMC sentinel node. The internal mammary artery was damaged in three patients. Hemostasis could be secured without having to resort to more extensive exposure. The pleural cavity was accidentally opened in another seven patients. In the first two patients, a drain was inserted into the thoracic cavity to be removed the next day. In the subsequent patients, the thorax was closed while the lung was inflated. No pneumothorax or other postoperative complications were observed. There was no long-term morbidity.

The IMC sentinel node contained metastatic disease in 22 patients (17%). Nine patients had a tumor-negative axilla but a tumor-positive IMC sentinel node (7%). The axilla was tumor-positive in 28 of the 134 patients in whom an axillary sentinel node was harvested (21%) (Table 2). Tumors with IMC drainage metastasize less frequently to lymph nodes compared to tumors draining to the axilla only (27% vs. 38%, \( P=0.008 \)), while the average tumor size was similar (1.7 cm vs. 1.8 cm) (Table 2). More non-palpable tumors were present in the group of patients with IMC drainage (35% vs. 23%, \( P=0.006 \)).

<table>
<thead>
<tr>
<th>Table 1. Locations of the internal mammary chain sentinel nodes within the intercostal spaces.</th>
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<tr>
<td>Intercostal space</td>
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<th>Table 2. Comparison between patients with and without drainage to the internal mammary chain (IMC) region. (NS=not significant)</th>
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<tr>
<td>IMC drainage (n=150)</td>
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<tr>
<td>Tumor-positive axillary sentinel node</td>
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<tr>
<td>Tumor-positive IMC sentinel node</td>
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<tr>
<td>Tumor-positive sentinel node</td>
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<tr>
<td>Non-palpable tumor</td>
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<td>Size primary tumor</td>
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The primary tumor was excised by means of a simple mastectomy in 38 patients. No additional incision had to be made in these patients to reach the IMC. Of the remaining 112 patients, the intercostal space could be reached through the incision necessary for the excision of the primary tumor in 19 patients (17%).

The locations of the primary tumors of all 150 patients are shown in Figure 2. The chances of an IMC sentinel node for each quadrant of all 691 patients are shown in Figure 3. The chances of a tumor-positive IMC sentinel node for each quadrant in case of identification are shown in Figure 4.

Upstaging occurred in all 22 patients with a tumor-positive IMC sentinel node (17%) according to the latest TNM-classification (Table 3). One patient had a tumor-positive contralateral IMC sentinel node and was staged as pM1(LYM).

The tumor-status of the IMC sentinel node resulted in a change in management in 38 patients (29%) (Table 4). Radiotherapy to the IMC region was given in ten patients with a tumor-free axilla and a tumor-positive IMC sentinel node. Radiotherapy to the IMC region was omitted in eleven patients because of a tumor-free IMC sentinel node despite a tumor-positive axilla. As described above, sixteen patients did not receive an axillary lymph node dissection because drainage was presumed to be to the IMC only. Finally, adjuvant systemic therapy was given to fourteen patients due to a tumor-positive IMC sentinel node in the absence of axillary metastases or with only micrometastatic involvement of the axilla.

<table>
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<th>Stage migration</th>
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<tr>
<td>pN0 → pN1b</td>
<td>8</td>
</tr>
<tr>
<td>pN0 → pM1(LYM)</td>
<td>1</td>
</tr>
<tr>
<td>pN1mi → pN1c</td>
<td>5</td>
</tr>
<tr>
<td>pN1a → pN1c</td>
<td>6</td>
</tr>
<tr>
<td>pN2a → pN3b</td>
<td>2</td>
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**Table 4.** Fifty-one changes in management in 38 out of 130 patients (29%).

<table>
<thead>
<tr>
<th>Changes in management</th>
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<tr>
<td>Institution of radiotherapy to the internal mammary chain region</td>
<td>10</td>
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<tr>
<td>Omission of radiotherapy to the internal mammary chain region</td>
<td>11</td>
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<tr>
<td>Omission of an axillary lymph node dissection</td>
<td>16</td>
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<tr>
<td>Institution of adjuvant systemic therapy</td>
<td>14</td>
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**Discussion**

**Technique**

Removing a sentinel node from the IMC is a feasible procedure with a minimal risk of morbidity although it is often technically challenging. It is generally more difficult than finding a sentinel node in the axilla as is illustrated by the 87% identification rate which was lower than our 98% for sentinel nodes in the axilla. Blue dye is not of much help since a mere 30% of these nodes are blue. Even if the node is blue, the colored lymphatic channel can rarely be dissected underneath the internal intercostal muscle. IMC nodes are small, on average some three millimeters. A sentinel node here takes up just a small amount of the radioactive tracer, which makes it hard to find with the probe. The probe is difficult to handle in the narrow intercostal space, which can be inaccessible due to bony deformation. The node is sometimes situated underneath a rib, invisible but for the probe. We never resect a rib if the sentinel node is inaccessible, because the additional morbidity is not justifiable for such an experimental procedure in our opinion. Increasing experience of the surgeons, an increase in radioactivity dose and in colloid particle concentration may result in more frequent identification. The morbidity is limited to an occasional injury to the internal mammary artery or pleura. A separate incision of a few centimeters may be necessary. If so, it should be made as caudal as possible to avoid scars in the neckline area. Long-term sequelae have not been encountered so far.

Preoperative lymphoscintigraphy is mandatory to detect non-axillary sentinel nodes. Intraparenchymal tracer injection is essential because intradermal or subdermal injection will rarely visualize the IMC. An advantage of our technique of intratumoral tracer administration is that it allows visualization of lymph drainage from the actual breast cancer. The small volume that was injected limits the risk of disturbing the normal physiology. Intraleral tracer administration in a small volume also facilitates sentinel node retrieval because primary tumor excision virtually eliminates the background scatter from the injection site. This approach also enables probe-guided excision of the primary breast cancer in case of non-palpable tumors.

**Drainage to the IMC**

We have described the lymphatic drainage patterns from the breast elsewhere. Observations that were made were that tumors in the medial side of the breast drain more often to the IMC ($P<0.001$) and that non-palpable tumors drain more frequently to the IMC, irrespective of the quadrant ($P=0.001$). The hypothesis on the finding of more extra-axillary drainage in non-palpable breast cancer patients has been described in a recent paper. Anatomical studies dealing with the arrangement of the breast lymphatics show that internal mammary nodes and interpectoral nodes are supplied by retromammarian lymphatics. These lymphatics arise from the breast lobules, run on the surface of the pectoral fascia and accompany penetrating
blood vessels on their way through the pectoral and intercostal muscles. The finding that a deep tracer injection in particular will visualize IMC sentinel nodes supports this observation. Deeper located tumors are less accessible to palpation. So, the depth of the tumor may be the explanation of the difference in extra-axillary drainage between palpable and non-palpable lesions and this seems to be independent of tumor size. But why do tumors with IMC drainage metastasize less frequently to lymph nodes compared to tumors draining only to the axilla (27% vs. 38%), while no significant difference was observed regarding tumor size (Table 2)? Silverstein et al. made a similar observation. They found that nodal positivity was significantly higher for palpable breast tumors compared to non-palpable breast tumors within the same T category. No definitive explanation was given, but a tendency for worse pathological markers was found in palpable lesions.

It is well known that breast cancer in a medial quadrant drains more frequently to the IMC. However, our series show that even the lower outer quadrant has a surprisingly high chance of 30% of draining to the IMC. Byrd and coworkers found that a similar 27% of tumors in the lower outer quadrant drain to the IMC. For the upper outer quadrant, the upper inner quadrant and the lower inner quadrant these percentages were 11, 17 and 25 respectively. If drainage is observed on lymphoscintigraphy, the chance of harvesting a tumor-positive IMC sentinel node seems to be similar regardless of the primary tumor location, but our small patient numbers preclude any statistical analysis between the quadrants.

**Implications**

Our series show that biopsy of an IMC sentinel node results in stage migration in 17% of the patients in whom such a node is retrieved. Other investigators have reported similar results. Is that enough benefit for the hunt for IMC sentinel nodes to begin in the absence of an established survival benefit? The old studies on survival concerned extended radical mastectomy that was performed in otherwise unselected breast cancer patients. The majority of those patients had a primary tumor in a lateral quadrant. The number of patients with drainage to the parasternal region must have been small. Probably a minority of the patients who did have drainage to the parasternal region had metastases there. As a result, patients without tumor-positive IMC nodes outnumbered those who could benefit from the procedure. To show a moderate or small survival difference in that situation requires more patients than were enrolled in the studies. The situation was more encouraging in the subgroup of patients with both a primary tumor in a medial quadrant and metastatic nodes in the axilla. Five-year survival in this subgroup was 52% after radical mastectomy but 71% after extended radical mastectomy. The primary tumor location and the tumor-status of the axilla are still rough parameters to select individuals who may benefit from treatment of the internal mammary nodes. Lymphoscintigraphy enables selection of the patients of whom the tumor actually drains to the parasternal nodes. Within this group of patients, biopsy of such a node allows the selection of the very patients who indeed have metastatic disease there. In other words, lymphatic mapping allows a much more accurate selection of patients who may benefit from treatment of the parasternal region. Surgical removal of all parasternal lymph nodes in these patients requires a disfiguring procedure and seems inappropriate in the age of breast-conserving treatment. Several studies with different results have been published regarding radiotherapy to this region. A multivariate analysis published in 1988 suggested a beneficial effect of treatment of the IMC on the risks of death and distant metastases for patients with medial tumors. However, radiotherapy has been associated with an increased risk of myocardial infarction due to associated irradiation.
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of the heart.\textsuperscript{29,31} It is understandable that many radiation oncologists are reluctant to electively treat these nodes despite the fact that radiotherapy techniques have improved.\textsuperscript{12} Marks et al presented a possible compromise by selectively irradiating only the superior IMC (intercostal spaces 1, 2 and 3) and excluding the lower spaces with shielding of the heart.\textsuperscript{13} This appears insufficient in view of our data that shows involvement of the fourth intercostal space in 13\% (Table 1). The value of radiotherapy to the internal mammary nodes is in fact the subject of ongoing randomized trials in Europe and Canada.

Whether adjuvant systemic therapy will prove to be beneficial in patients with a tumor-containing IMC sentinel node is also not known yet. Common sense suggests that the prognostic impact of a tumor-positive sentinel node is similar in the axilla and the parasternal region. In some institutes (including our own), it is felt that it is justified to give systemic therapy to patients with tumor-positive IMC sentinel nodes because of their presumed substantially worse prognosis.\textsuperscript{3,5,7,13,14}

CONCLUDING REMARKS

Twenty-two percent of our breast cancer patients have a sentinel node in the IMC. The majority (87\%) could be retrieved without appreciable morbidity and these were tumor-positive in 17\%. Upstaging was seen in 17\% of the patients and led to a better selection of patients who might benefit from postoperative radiotherapy to the IMC and from adjuvant systemic treatment. Only prospective randomized trials can determine if this will result in improved disease-free and overall survival. It is questionable whether such studies will ever be conducted. Therefore, the decision to begin the hunt for the IMC sentinel nodes should be based on the established improved staging and common sense.

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