In search of the sentinel node: validation and sophistication of lymphatic mapping and sentinel node biopsy in breast cancer and melanoma
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Breast cancer patients with extra-axillary sentinel nodes only may be spared axillary lymph node dissection

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Abstract

Introduction: In breast cancer patients with only extra-axillary sentinel nodes, surgeons typically perform axillary node dissection. The purpose of this study was to evaluate our approach to spare such patients further dissection based on the hypothesis that a sentinel node is not necessarily located in the axilla.

Methods: Between March 11, 1999 and March 5, 2008, 1,949 breast cancer patients underwent lymphatic mapping with preoperative lymphoscintigraphy and intraoperative use of a gamma-ray detection probe and patent blue dye. The tracers were injected into the tumours.

Results: Eighty-two of the 1,949 patients had only extra-axillary drainage on their lymphoscintigrams. A sentinel node was harvested from the axilla in 62 patients, but not in the remaining 20 patients. No axillary lymph nodes were removed in four of these twenty patients, suspicious palpable nodes were excised in another four patients and node sampling was done in the remaining twelve. These nodes were all free of disease. All sentinel nodes outside the axilla were removed. Two patients had a metastasis in an internal mammary chain node. No lymph node recurrences were detected in or outside the axilla in any of the twenty patients with a median follow-up time of 49 months.

Conclusion: Four percent of the patients have only extra-axillary drainage on preoperative lymphoscintigrams. It is worthwhile to explore the axilla since a sentinel node can be found in three quarters. In the remaining one percent without axillary sentinel nodes, axillary sampling seems unnecessary and the approach to refrain from axillary dissection appears valid.
Introduction

The predominant lymphatic drainage pathway from the breast is towards the axilla and axillary sentinel nodes are visualized at preoperative lymphoscintigraphy in more than 95% of breast cancer patients.\textsuperscript{1} Sentinel nodes outside the axilla are more frequently encountered with deep (intra- or peritumoural) tracer injection than with a superficial injection.\textsuperscript{2-6} These sites of extra-axillary nodes include the internal mammary chain, the infraclavicular region, the supraclavicular fossa, the breast itself, and the interpectoral (Rotter’s) space. Nodes outside the axilla are present in up to 56% of the patients.\textsuperscript{7} Without lymphoscintigraphy, such sentinel nodes would pass unnoticed.\textsuperscript{6} The intratumoural injection technique is used at the Netherlands Cancer Institute and we rigorously pursue both axillary and extra-axillary sentinel nodes. Chasing these nodes improves staging and changes the intended management in about a quarter of these patients.\textsuperscript{5,6,8}

Most patients with extra-axillary drainage on the lymphoscintigram also have a sentinel node in the axilla but some do not. In a study on the lymphatic drainage patterns of the breast after intratumoural radiocolloid injection, 4.6% of 700 patients had only drainage to lymph node regions outside the axilla.\textsuperscript{1} Exploration of the axilla with the help of blue dye and a gamma-ray detection probe will identify a sentinel node in most of these cases after all.\textsuperscript{9} If this approach fails, surgeons typically perform axillary node dissection, assuming that a sentinel node must be present and that it may not accumulate any of the tracer fluids, for instance because of massive tumour invasion. At our institute, such patients are spared axillary clearance based on the hypothesis that a sentinel node is not necessarily located in the axilla.\textsuperscript{10,11} The purpose of this study was to evaluate this approach.

Figure 1. Flowchart of the 1,949 clinically node-negative breast cancer patients.
Patients and methods

Between March 11, 1999 and March 5, 2008, 1,949 breast cancer patients underwent lymphatic mapping (figure 1). Pathological proof of breast cancer was obtained preoperatively by fine-needle aspiration cytology or core biopsy. Preoperative ultrasonography of the axilla was routinely performed with fine-needle aspiration cytology in case of a suspicious node. Axillary node dissection was done directly if fine needle aspiration established nodal involvement.

A two-day protocol was used for the sentinel node procedure. On the first day, an intratumoral injection of technetium-99m nanocolloid (Nanocoll®; GE-Healthcare, Eindhoven, the Netherlands) was given in a volume of 0.2 ml and with a radioactivity dose of 120 MBq. Static images were obtained at ten minutes, two hours and four hours after radiotracer administration. A dual-head gamma camera equipped with low-energy high-resolution collimators (Vertex®, Philips, Eindhoven, the Netherlands) was used for imaging. Both anterior and lateral images were routinely obtained and additional images if needed. A cobalt-57 flood source was placed behind the patient to outline the body contour. A sentinel node was defined as a lymph node upon which the primary tumour drains directly.12

Single photon emission computed tomography with CT scanning (SPECT/CT) was introduced in December 2006 as an additional tool and was performed when conventional imaging failed to visualize a sentinel node in the axilla.13 SPECT/CT was performed immediately after four-hour conventional imaging using a hybrid system (Symbia T, Siemens, Erlangen, Germany) without re-injection of the radiopharmaceutical. After correction for attenuation and scatter, fused SPECT/CT images were generated and displayed in both two-dimensional orthogonal multiconventional reconstruction and three-dimensional maximum intensity projection for anatomical localization of sentinel nodes. The location of a sentinel node was marked on the skin with indelible ink.

The next day, 1 ml patent blue dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) was administered in the primary lesion immediately before the operation. All procedures were performed by one of five experienced breast surgeons or under their supervision by a resident or fellow. Sentinel nodes were pursued in all regions indicated by lymphoscintigraphy. The axilla was explored looking for a blue lymph vessel. If no lymphatic vessel was found, the gamma-ray detection probe (Neoprobe, Johnson & Johnson Medical, Hamburg, Germany) was used to search for a hot node. The axilla was carefully palpated and suspicious palpable nodes were routinely removed.

All harvested lymph nodes were fixed in formalin, bisected, embedded in paraffin, and cut at a minimum of six levels at 50 to 150 μm intervals. Pathological evaluation included both haematoxylin-eosin and immunohistochemical staining (CAM 5.2; Becton Dickinson, San Jose, CA, USA).
All patients were enrolled in the follow up program of the institution. At every clinic visit, special attention was paid to the axilla, which was palpated and explored with ultrasound whenever the findings of physical examination were uncertain. Statistical analyses were performed in SPSS 15 (Version 15, for Windows, SPSS Inc, Chicago, IL, USA).

Results

Lymphoscintigraphy showed drainage only to sentinel nodes outside levels I and II of the axilla in 82 of the 1,949 patients (4.2%). The axilla was explored in all 82 patients and revealed a blue and/or hot sentinel node in 62 (76%). No sentinel node was identified in the axilla in the remaining twenty patients (24% of the patients with non-visualization, 1.0% of the whole group). Axillary dissection was not performed in these twenty patients and they are the subjects of the present study.

Eleven of the twenty patients (55%) had a tumour in the upper inner quadrant of the breast and five (25%) in the lower inner quadrant. Three patients (15%) had a centrally located tumour and one (5%) had multifocal breast cancer. The median tumour diameter was 1.2 cm (0.4 - 3.7 cm). Fourteen patients had a non-palpable tumour (70%). Three of the twenty patients (15%) had undergone a previous operation of the same breast. Two had a benign lesion removed 24 months and 28 months earlier and the third had undergone a breast conserving operation with a negative sentinel node biopsy followed by radiotherapy for cancer seven years earlier.

Not any axillary lymph nodes were removed in four of the twenty patients. In four others, a mean number of 1.3 (range 1 - 2) non-radioactive, unstained nodes were excised because these felt suspicious intra-operatively. Node sampling (mean 2.2 nodes, range 1 - 4) was done in the remaining twelve patients.

The sentinel nodes outside the axilla were removed in all twenty patients (median 1.2 nodes, range 1 – 5). Sixteen patients had internal mammary chain sentinel nodes excised and two had infraclavicular nodes excised. The remaining two patients had a sentinel node harvested from between the pectoral muscles, one in combination with an internal mammary chain sentinel node and the other in combination with an infraclavicular sentinel node.

All harvested suspicious and sampled axillary nodes were free of disease. One of the four patients in whom no axillary lymph node was removed had a micrometastasis in an internal mammary chain sentinel node and another patient had an involved non-sentinel node retrieved from the internal mammary chain.

All twenty patients underwent postoperative radiotherapy of the breast, and the two patients with an involved internal mammary chain node also received radiation on the internal mammary chain region. Another patient received adjuvant chemotherapy and three received hormonal therapy based on the primary tumour characteristics.

No lymph node recurrences were detected in or outside the axilla in any of the twenty
patients with a median follow-up time of 49 months (range twelve months to nine years and three months). The patient with the involved internal mammary non-sentinel node developed metastases in the lung after fifteen months and a local recurrence in the breast was diagnosed a month later. She passed away two years later. One patient developed a second primary cancer in the contralateral breast after one year. No other breast cancer-related events were noted in the remaining patients.

Discussion

Many people say these days that lymph fluid from the breast drains to one common node in the axilla. This perception is usually based on the work of Sappey and his publication from 1834 is frequently quoted. It is common practice to perform axillary node dissection if no sentinel node is found in the axilla based on the belief that this node is present nevertheless. Axillary node dissection will remove such node. A number of more recent, less well-known, publications have refuted Sappey’s work. It has been shown that radiopharmaceutical injection in different parts of the breast may result in visualization of different sentinel nodes. A previous study from our institute showed that breast cancer drains to the axilla in 95% of the patients, to the internal mammary chain in 22%, and exclusively to nodal areas outside the axilla in 4.6%. These observations suggest that the lymphatic drainage of the breast is more complex than Sappey perceived. A recent anatomy study by Suami and co-workers gives more insight in this complex lymphatic system. They found that almost the entire breast drained to one axillary sentinel node in some cases, but mostly there was at least one other sentinel node in or outside the axilla. They also found that separate lymphatic drainage networks exist in the ventral and in the dorsal part of the breast, which drain to the axilla and the internal mammary chain respectively and do not have apparent connections. This means that lymphatic drainage may occur exclusively to a lymph node outside the axilla and also confirms that tracer injection at the tumour site reflects its drainage pathways, which may involve both the superficial and deep lymphatic networks. Drainage from various parts of the breast to nodes in unusual locations does not follow specific patterns. The current study confirms these observations and shows the ramifications for clinical management. Of all our 1,949 patients, 4.2% percent had only drainage to nodes outside the axilla on their lymphoscintigrams. Several investigators concluded that it is worthwhile to explore the axilla in patients with persisting non-visualization of this basin, since a sentinel node can be surgically retrieved in 45-88% with the help of blue dye and a gamma-ray detection probe after all. This was also our current experience as axillary sentinel nodes were found in 76% of such situations. In one percent of all patients, an axillary sentinel node could not be identified, neither preoperatively nor intraoperatively, while extra-axillary sentinel node biopsy guided by the lymphoscintigraphy was successful. These patients were spared axillary dissection because nodal staging had been
accomplished. This appeared to be a safe policy because no lymph node recurrences were detected in the axilla during a median follow-up time of 49 months. The median time for developing such a lymph node recurrence has been described to be as long as 77 months (range 10-353 months). Therefore, our considerable period of follow-up may still not be long enough to draw definitive conclusions on the number of axillary recurrences.

One patient in the present study had an uninvolved internal mammary chain sentinel node, but an enlarged non-sentinel node nearby did reveal a metastasis. The massive tumour invasion could have prevented the accumulation of tracer fluids in this node. This case shows the value of excising suspicious-looking lymph nodes. The sampling of axillary nodes did not seem worthwhile in this study, since none of these samples revealed metastases. Axillary node sampling is an accepted practice in some institutes in the United Kingdom. The removal of at least four nodes from the lower axillary region and the axillary tail supposedly leads to an accuracy of 95% in staging the axilla. Two randomized controlled trials comparing patients who received axillary dissection or node sampling showed that node-negative patients who received node sampling had a significantly higher rate of axillary recurrence (6.8%) than the dissection patients (1.6%). This higher recurrence rate suggests that this technique is not very reliable after all.

All patients in our study underwent radiotherapy to the breast as a part of the breast-conserving therapy. Whole breast irradiation encompasses a substantial part of the axilla and may clean up a lymph node metastasis that we may have overlooked during sentinel node biopsy. The adjuvant systemic therapy that four patients received may have the same effect.

Eighty percent of the patients in the current study had a tumour in the inner quadrant of the breast, mostly in the upper inner quadrant. This is considerably more than is known to occur in unselected patients. It is known that tumours located in the inner quadrants of the breast drain more frequently to the internal mammary chain than tumours in the outer quadrants (37% versus 14.4%, p< 0.001). Two other studies found drainage to the internal mammary chain in 17 - 66% of the patients when the radiopharmaceutical was administered in the inner quadrants of the breast. The majority of our patients (70%) had a non-palpable tumour. These lesions are also known to have an increased tendency to drain to internal mammary nodes, regardless of their location.

Three patients (15%) had previously been operated on the ipsilateral breast. A sentinel node biopsy in patients with a local recurrence of breast cancer has been described to yield a sentinel node in 55% to 83% of the cases. Drainage to nodes outside of the axilla was seen in 46% of such patients in one study, and internal mammary chain sentinel nodes were seen in 30% in another study. A third paper reported that non-axillary drainage occurred significantly more often when the sentinel node procedure was done for a breast cancer recurrence (30%) compared to a primary tumour (6%). Conventional lymphoscintigraphic imaging after intratumoural injection showed lymphatic drainage in approximately 90% of breast cancer patients in the early
days of the sentinel node procedure. The visualization rate was improved to 95% with increasing experience and modifications of the technique. With the recent introduction of the hybrid SPECT/CT the visualization and intraoperative detection rates of sentinel nodes are likely to improve even further. Although these refinements in the technique of the procedure will detect additional axillary sentinel nodes, a minority of breast cancer patients with only sentinel nodes outside the axilla will remain. The current study concerns a small group of patients with a meaningful period of follow-up, whose axillae have been screened with ultrasound and in whom sentinel nodes outside the axilla were pursued. The results suggest that axillary lymph node dissection can be omitted in such patients. We also conclude that node sampling does not appear to be useful and that it is worthwhile to explore the axilla because a sentinel node can be found in 76% of the cases.

References


