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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CHAPTER 4

Axillary and extra-axillary lymph node recurrences after a tumour-negative sentinel node biopsy for breast cancer using intra-lesional tracer administration

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Abstract

Introduction: At our institution, the tracer fluids are administered in the primary breast cancer and, in addition to the ones in the axilla, sentinel nodes outside the axilla are rigorously pursued. The objective of the present study of sentinel node-negative breast cancer patients was to determine the lymph node recurrence rates in the axilla and elsewhere, the false-negative rates, and the survival.

Methods: Between January 1999 and November 2005, 1,019 breast cancer patients underwent a sentinel node biopsy. In 748 of them, 755 sentinel node biopsies did not reveal a tumour-positive sentinel node and they did not undergo axillary node dissection. Metastases were revealed in 284 sentinel node biopsies performed in the remaining 271 patients: 247 in the axilla, twenty outside the axilla, and seventeen both in the axilla and elsewhere. The median follow-up duration was 46 months.

Results: Two of the 748 sentinel node-negative patients developed an axillary lymph node recurrence (0.25%) and two others developed a supraclavicular lymph node recurrence (0.25%). The overall lymph node recurrence rate was 0.5%. The false-negative rates were 1.4% overall, 0.8% for the axilla and 5.1% for the extra-axillary nodes. After five years, 95.9% of all sentinel node-negative patients were alive and 89.7% were alive without evidence of disease.

Conclusion: The low recurrence and false-negative rates and promising survival figures show that our lymphatic mapping method with intra-lesional tracer administration is accurate for the axilla. Outside the axilla, 5.1% of involved sentinel nodes were missed.
Introduction

Many studies have demonstrated the feasibility and accuracy of sentinel lymph node biopsy in patients with breast cancer, showing a reduction in morbidity compared to routine axillary lymph node dissection while possibly allowing for more accurate staging.1-4 As a result, the tumour-status of the sentinel lymph node has been incorporated in the staging system for breast cancer.5

A substantial number of papers have reported on recurrences in patients in whom routine axillary lymph node dissection was omitted when the sentinel node was free of disease.6 These studies concerned only axillary recurrences, not mentioning lymph node recurrences that occur outside the axilla. A review of ten large observational studies with a median follow-up duration of almost three years revealed just ten axillary recurrences in 2,664 patients (0.4%) who did not undergo axillary lymph node dissection because of a tumour-negative sentinel node biopsy.6 This overall recurrence rate is encouraging but stops short of being definitive because of the protracted nature of the disease.7

At the Netherlands Cancer Institute, we favour the intratumoural injection technique.8 In contrast to the more superficial injection techniques, this approach is known to point out sentinel nodes outside the axilla as well.9-12 Advantages and disadvantages of this approach have been described elsewhere.8,13-15 In our institute, both axillary and extra-axillary sentinel nodes are rigorously pursued. Over the years, we have encountered numerous surgeons and nuclear medicine physicians who disagreed with this approach and suggested it would cause an increase in blood-borne metastases.8 The objectives of the present study were to determine the lymph node recurrence rates in the axilla and elsewhere, the false-negative rates, the incidence of distant metastases, and the survival in sentinel node-negative breast cancer patients without a completion node dissection.

Patients and methods

Between January 1999 and November 2005, 1,019 patients underwent a sentinel node biopsy for invasive breast cancer. The median age was 57 years. Patient and tumour characteristics are described in Table 1. Histopathological proof of breast cancer was obtained preoperatively by fine-needle aspiration cytology or core biopsy. Ultrasonography of the axilla was routinely performed with fine-needle aspiration cytology in case of a suspicious node.

A two-day protocol was used for the sentinel node procedure. On the day before surgery, an intratumoural 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 performed 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. The location of a sentinel node was marked on the skin with indelible ink.

The next day, 1 ml of patent blue dye (Laboratoire Guerbet, Aulnay-Sous-Bois, France) was administered in the primary lesion immediately before the operation. The dye and a gamma ray detection probe (Neoprobe, Johnson & Johnson Medical, Hamburg, Germany) were used during the operation 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 sentinel node was defined as a lymph node upon which the primary tumour drains directly. Sentinel nodes were pursued in all regions indicated by lymphoscintigraphy. After removal of the sentinel node, the axilla was carefully palpated. Suspicious looking non-sentinel nodes were routinely removed. All sentinel 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 haematoxylin-eosin and immunohistochemical staining (CAM 5.2; Becton Dickinson, San Jose, CA, USA).

All patients were followed in the outpatient department of The Netherlands Cancer Institute. At every examination, special attention was paid to the axilla, which was examined by careful palpation and explored with ultrasound whenever the findings were uncertain. The median follow-up duration was 45.5 months with a range of 0.1 to 98.2 months.

The axillary and extra-axillary recurrence rates were calculated as a percentage of the tumour-negative sentinel node biopsies. The false-negative rate reflects the incidence of involved sentinel nodes that were missed and was calculated by dividing the number of lymph node recurrences by this same number plus all tumour-positive sentinel node biopsies. This tumour-positive sentinel node biopsy group is not described further and only included in this study for the calculation of false-negative rates. Survival curves were estimated with the Kaplan-Meier method and compared with the log-rank test. All analyses were performed in SPSS 15 (Version 15, for Windows, SPSS Inc, Chicago, IL, USA).

**Results**

A median number of 2.0 sentinel nodes were excised. A median number of 0.6 non-radioactive and unstained nodes (non-sentinel nodes) were found and excised because these felt suspicious intraoperatively. Sentinel nodes en non-sentinel nodes were free of disease in 748 patients who underwent 755 sentinel node biopsies. Completion axillary lymph node dissection was not performed in these instances.
Six of the 748 patients developed seven lymph node recurrences that could be attributed to a local recurrence or a second primary cancer in the breast. Their sentinel node biopsies were not classified as failures of the technique and were ignored. Four patients with ductal carcinoma and tumour-free sentinel nodes developed a recurrence that was classified as a failure of the technique (0.5%). Two of these patients had an axillary lymph node recurrence (0.25% of the procedures). One was a 46-year old woman with left breast cancer. Lymphoscintigraphy had shown two axillary sentinel nodes and one internal mammary chain sentinel node. All three had been harvested and were free of disease. She had received radiotherapy to the breast. Ten months later, an axillary lymph node metastasis was discovered. Axillary dissection revealed one metastatic lymph node and no further treatment was given. Forty-six months later she is alive without signs of tumour-activity. A review of the lymphoscintigrams revealed one caudal, vaguely visible lymph node on a late lateral view that had not been described originally and had not been pursued during the initial operation (figure 1).

During axillary node dissection, the metastatic lymph node was indeed found at this location. The other patient was a 65-year old woman with right breast cancer. Lymphoscintigraphy had shown one axillary sentinel node and two uninvolved axillary sentinel nodes had been removed. She had undergone radiotherapy of the breast and adjuvant hormonal treatment. Forty-four months after the operation, an involved axillary lymph node was found. Axillary node dissection yielded nine lymph nodes of which seven were tumour-positive. She received radiotherapy and chemotherapy, and is alive without signs of disease fifteen months later. Review of the lymphoscintigraphic images, the operative report and the pathology slides did not provide a clue as to the cause of the failure.
Figure 2. A 50-year old woman with right breast cancer. The anterior lymphoscintigram shows a lymphatic pathway that runs to one axillary sentinel node with subsequent nodes up to the infraclavicular fossa. There is no lymphatic drainage to the supraclavicular fossa, where the recurrence later was located.

The other two patients with a false-negative sentinel node biopsy had an extra-axillary lymph node recurrence (0.25% of the procedures). One was a 50-year old woman with right breast cancer. Lymphoscintigraphy had depicted one axillary sentinel node. This node and two axillary non-sentinel nodes had been excised. No metastases had been found. She had received radiotherapy of the breast and adjuvant chemotherapy. Eight months afterwards, an ipsilateral supraclavicular lymph node metastasis was found. Radiotherapy and chemotherapy were given. Seventeen months later, lung and brain metastases were detected to which she succumbed seven months afterwards. The original lymphoscintigraphic images were reviewed, but no lymphatic drainage to the supraclavicular fossa was seen (figure 2). No explanation for the cause of the failure was identified. The other patient was a 56-year old woman with right breast cancer. Lymphoscintigraphy had shown two axillary sentinel nodes. No metastases had been detected in the three axillary sentinel nodes and one axillary non-sentinel node that had been harvested. She had received radiotherapy to the breast and adjuvant chemotherapy. After 39 months, bone metastases were detected for which she received hormonal treatment. Thirteen months later, a metastatic supraclavicular lymph node was detected. She died nine months afterwards from her disease. No explanation for this mishap was found.

The remaining 271 patients underwent 284 sentinel node biopsies that revealed metastases. In 247 of them, the involved sentinel node was in the axilla, in twenty only outside the axilla, and in seventeen patients metastases were present both in the axilla and elsewhere. The overall false-negative rate (the fraction of existing nodal basins that were missed by lymphatic mapping) was 1.4% (4/(284+4)). This was 0.8% (2/(247+17+2)) for the axilla and 5.1% (2/(20+17+2)) for the other nodal regions.
A mean or median time to a lymph node recurrence could not be calculated by a Kaplan-Meier analysis from our data because such events were seen too infrequently. We used the incidence rate as an alternative measurement. This indicates that 0.4% of patients will have developed an axillary recurrence by five years, 0.1% an extra-axillary recurrence and 0.6% both. Distant metastases will have developed in 5.2% of all patients by five years. The overall five-year survival of all sentinel node-negative patients is 95.9% and the disease-free survival 89.7% (table 2, figure 3).

Discussion

In 1999, two comprehensive literature reviews were published concerning the learning phase performance of sentinel node biopsy followed by routine axillary lymph node dissection. Median false-negative rates were 7% and 5% (range 0-40%), which is not within the 5% range that is generally considered desirable. Serial sectioning was never performed in lymph nodes recovered from the remainder of the axilla and sensitive immunohistochemistry staining was used in only two studies, suggesting that the published false-negative rates might even be too favourable. In the current study, the false-negative rates are 0.8% for the axilla and 5.1% for the nodes elsewhere. A general goal of sentinel node biopsy is not to exceed the 1.0-2.3% axillary recurrence rate that has been reported after routine axillary clearance in node-negative patients. The present study of sentinel node-negative breast cancer patients who did not undergo
completion dissection demonstrates axillary and extra-axillary lymph node recurrence rates of 0.25% each during a median follow-up time of 46 months.

A great number of observational studies in which varying lymphatic mapping techniques were used have reported lymph node recurrence figures in patients who did not undergo axillary node dissection because their sentinel node was free of disease. A 2005 literature review showed that the recurrence rate in such patients was 0.4%, but the median duration of follow up was a mere 32 months, not enough for the results to be definitive. The same can be said for the excellent results of Naik and co-workers who published the largest series in literature up till now; 2,340 patients and only three lymph node recurrences, but with a follow-up of 31 months. We searched the literature for studies with a median follow up duration of at least four years to relate our results to. Five studies were found concerning a total of 833 patients reporting fourteen patients with an axillary recurrence, of which one developed as late as 63 months after the operation. The recurrence rate is 1.6% when these studies are combined. The false negative rate can be calculated from the data in one of the reports and is 6%. Both numbers are substantially higher than our results, but our median follow-up time is shorter.

Our 89.7% disease-free five-year survival and 95.9% overall five-year survival are comparable to numbers in previously reported studies. In the current study, 33 patients (4.4%) developed distant metastases, and calculated from these figures, 94.8% of patients (table 2) will be free of distant metastases after five years. These figures do not suggest that blood-borne metastases are frequently found in patients who underwent a sentinel node procedure with intra-lesional tracer administration. Several explanations other than improved surgical adroitness may account for the enhanced sensitivity in our hands and those of others compared with the above-mentioned learning phase studies. The radiotherapy that is part of the breast-conserving therapy and the more commonly given adjuvant systemic treatment are likely to clean up some of the involved lymph nodes that are overlooked during the operation. Preoperative ultrasound points out patients with relatively large, although still not palpable, axillary nodes that contain metastases, which results in a direct axillary dissection. If undiscovered, metastases of such size could prevent accumulation of tracer fluids, causing the node to pass unnoticed during the sentinel node procedure and leading to a recurrence later on. This phenomenon is called tumour-blockage. Moreover, several retrospective and prospective studies suggest that only about a third of the breast cancer metastases in the axilla go on to develop into clinically relevant disease. In one false-negative case in this study, the lymph node recurrence was probably caused by incorrect interpretation of the lymphoscintigram. In the other three cases no explanation was identified. Several reasons for false-negative sentinel lymph node biopsy may be contemplated. The concept of sequential dissemination may not hold up in every individual. It is conceivable that tumour cells may pass through a sentinel node and lodge in the next lymph node. The surgeon may take out the wrong node. The tumour cells in the sentinel node may go unnoticed.
because they happen not to be in the slides that the pathologist has made. It is known that metastases from lobular cancer are more difficult to detect. Tumour-blockage as an explanation for a false-negative sentinel node biopsy has been mentioned above. Tumour cells may still be in transit at the time of the sentinel node biopsy and end up in other nodes.

Our intratumoural radiopharmaceutical injection technique has a number of advantages. It facilitates identification of sentinel nodes that contain little radioactivity because the background radioactivity is removed with the segmental excision, if the order of the procedures is reversed. The sentinel node identification rate in the axilla is 97%. Probe-guided surgery of non-palpable cancer is made possible and yields better margins than wire-guided excision. It has been shown that extra-axillary sentinel nodes are more likely to be detected when an intra- or peritumoural radiopharmaceutical injection is used, compared to more superficial injection techniques. A previous report showed that such nodes are present in 27% of the patients. Lymphatic drainage to lymph node basins in other unusual locations is found in 12%. There is yet no consensus on whether extra-axillary sentinel nodes should be removed. Surgeons who pursue internal mammary chain nodes find that some 17-27% of them are involved, which improves staging and enables the treatment to be better adjusted to the needs of such a patient. Metastases are detected in 17% of the sentinel nodes that are harvested from even more exotic locations, which prompts modification of the subsequent management in 18% of such patients. The intratumoural injection technique maybe more difficult to perform than superficial injection methods, but we feel that not all, possibly metastatic, sentinel nodes on a direct pathway from the primary tumour are identified by superficial techniques. These patients may not receive suitable management, which in the end may jeopardize their survival.

It is difficult to place our extra-axillary nodal recurrence rate in perspective. Recurrence in supraclavicular nodes is rare. Recurrences in other regional nodes may not be as rare as we are often led to believe. We suspect that recurrences in internal mammary nodes, subclavicular nodes, Rotter’s (interpectoral) nodes and intramammary nodes are usually not recognized as such but are instead classified as local recurrences.

In conclusion, the 0.25% recurrence rate and the 0.8% false-negative rate show that our lymphatic mapping method with intra-lesional tracer administration is accurate for the axilla. Outside the axilla, 5.1% of involved sentinel nodes were missed. The projected 5.2% incidence of distant metastases, the 95.9% five-year survival and 89.7% disease-free survival are promising.
References


