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

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Citation for published version (APA):

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CHAPTER 5

EXCISIONAL BIOPSY OF BREAST LESIONS
CHANGES THE DRAINAGE PATTERN:
A REPRODUCIBILITY STUDY OF LYMPHOSCINTIGRAPHY

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Preliminary data
INTRODUCTION

Lymphoscintigraphy in breast cancer patients can visualize the lymphatic drainage pattern and position of the sentinel node. Patients with a tumor-free sentinel node can be spared an axillary node dissection. Metastasis in the sentinel node suggests further treatment, e.g. lymph node dissection, radiotherapy or adjuvant systemic therapy. Unfortunately, there is a lack of consensus on the type of patients in whom lymphatic mapping can be performed reliably. For instance, are the identification rate and false negative rate affected by prior excisional biopsy? The studies that suggest that lymphatic mapping can or cannot be done accurately after excisional biopsy either looked at confirmatory axillary node dissection instead of the more accurate recurrence rate or lacked long-term follow-up. The issue can only be resolved definitively through analysis of identification rate and axillary recurrence rate in patients with prior excisional biopsy, but this approach would require a carefully selected control group and a follow-up of many years or a randomized study. Since the issue at hand is a pressing one and concerns substantial numbers of patients, we devised another method to gather circumstantial evidence of the safety of this approach. The lymphoscintigraphy images before and after excisional biopsy of a breast lesion were compared to establish whether the drainage pattern was disturbed by the surgical procedure.

MATERIALS AND METHODS

Twenty consecutive patients who received an excisional biopsy of a breast lesion and without need of axillary treatment were investigated. Informed consent was obtained from all patients. The exclusion criteria were pregnancy and multiple breast lesions.

The first lymphoscintigraphy was performed the day before surgery. The standard imaging technique was used. Technetium-99m nanocolloid (\textsuperscript{99m}Tc-nanocolloid, Nanocol, Amersham Cygne, Eindhoven, the Netherlands) with a particle size less than 80 nm was used in a dose of about 120 MBq (3.2 mCi) and an average volume of 0.20 ml. The tracer was injected into the lesion. Images were produced using a dual head gamma camera (ADAC Vertex, Milpitas, California, United States of America) with a medium-energy, general-purpose collimator. The same investigator performed the intratumoral injection of the \textsuperscript{99m}Tc-nanocolloid and the ensuing lymphoscintigraphy. After injection, anterior and lateral static views with an acquisition time of five minutes were obtained using a flood source to facilitate orientation. The static images were repeated after two and four hours. Oblique views were obtained when there was a possibility that the node(s) might have been obscured by radiation from the injection site. Additional anterior images were performed after attaching a cobalt marker on the sternal notch in order to verify the distance between the sentinel nodes and the marker.

At least two weeks after the operation and within the following six months, the above-described procedure was repeated in an identical fashion by the same investigator. This second time, a pericavitary injection technique was used. Four depots in a total volume of 0.8 ml and an average dose of 120 MBq were administered.

The two sets of images were evaluated by a panel of two experienced observers (S.H.E. and R.A.V.O.) with regard to similarity of the following parameters: lymphatic flow pattern, draining lymph node basin, location and number of sentinel nodes. Second-echelon nodes were often visualized on the images but were not evaluated in this study. The two observers performed their evaluation independently.

The 95% confidence interval (CI) of the calculated reproducibility was determined by using the binomial distribution.
If invasive breast cancer was diagnosed, these patients were eligible for sentinel node biopsy in case of identical lymphoscintigraphic scans.

**RESULTS**

Preoperative lymphoscintigraphy visualized at least one sentinel node in all twenty patients. Discrepancy in the drainage patterns was seen in a total of fourteen out of twenty patients (70%). Therefore, the reproducibility of the overall lymphoscintigraphic results was 30% (CI: 14 - 53%). Patient characteristics and the number of visualized sentinel nodes are presented in Table 1. A mean radioactive dose of 133 MBq was administered (range: 119 - 149 MBq). The median time interval between the two sets of lymphoscintigraphic scans was 15 days (range: 11 - 132 days).

A change in drainage to the axilla after excisional biopsy of the breast lesion was seen in nine patients: an original sentinel node could not be visualized in six patients whereas one or more additional hot spots were visualized in the other three (Figures 1 and 2). The reproducibility of axillary drainage was 55% (CI: 32 - 77%).

Drainage to the internal mammary chain was preoperatively seen in ten of the twenty patients. After excisional biopsy, only two of these ten patients had the same drainage pathways. The location of a hot spot changed to another intercostal space in three patients (Figure 3). Less sentinel nodes were visualized in two patients (Figure 4), whereas in three patients no hotspot was visualized in the internal mammary chain the second time around (Figure 5). The reproducibility of drainage to the internal mammary chain was 20% (CI: 4 - 56%).

Pathological evaluation of the excisional biopsy tissue revealed invasive breast carcinoma in six patients. Four of these patients had identical drainage patterns and were therefore eligible for sentinel node biopsy. All these sentinel nodes were tumor-negative. The two other patients underwent an axillary lymph node dissection of which one contained tumor-positive nodes.

**Figure 1.** Lymphoscintigrams of patient number 5. 1= injection site, A=before excisional biopsy; the arrow points out the two axillary sentinel nodes, B=after excisional biopsy; no axillary nodes are visualized.
Figure 2. Lymphoscintigrams of patient number 7. I=Injection site, A=before excisional biopsy; no axillary nodes are visualized, B=after excisional biopsy; the arrow points out the axillary 'sentinel node'.

Figure 3. Lymphoscintigrams of patient number 1. I=Injection site. A=before excisional biopsy; the arrow points out the internal mammary chain sentinel node located in the first intercostal space. B=after excisional biopsy; the arrow points out the internal mammary chain 'sentinel node' located in the fourth intercostal space.
Figure 4. Lymphoscintigrams of patient number 10. I= injection site, A= before excisional biopsy; the arrows point out the internal mammary chain sentinel nodes located in the second and fourth intercostal space, B= after excisional biopsy; the arrow points out the only internal mammary chain sentinel node located in the second intercostal space.

Figure 5. Lymphoscintigrams of patient number 17. I= injection site, A= before excisional biopsy; the arrow points out the internal mammary chain sentinel node located in the second intercostal space, B= after excisional biopsy; no internal mammary chain sentinel nodes are visualized. It is noteworthy to draw the attention to two additional ‘sentinel nodes’ in the axilla after excisional biopsy (arrow).
<table>
<thead>
<tr>
<th>Patient nr</th>
<th>Age</th>
<th>Primary lesion</th>
<th>Preoperative</th>
<th>Postoperative</th>
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<td>NP</td>
<td>1 / IC3</td>
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UOQ=Upper outer quadrant, UIQ=Upper inner quadrant, LOQ=Lower outer quadrant, LIQ=Lower inner quadrant, P=Palpable, NP=Non-palpable.
SNs=Sentinel nodes, IMC=Internal mammary chain, IC=Intercostal space.
REPRODUCIBILITY OF LYMPHOSCINTIGRAPHY

DISCUSSION

In a study by Tanis et al., the 100% reproducibility of preoperative lymphoscintigraphy using intralesional tracer injection has been proven in patients with their primary breast cancer still present. The current study shows a reproducibility of a mere 30% if post-excisional lymphoscintigraphy is compared to the preoperative drainage from the actual breast lesion (difference between the study by Tanis et al. and the current study: Fisher exact test: \( P < 0.001 \)).

In some institutes, breast cancer patients with prior excisional biopsy have already been included in the routine sentinel node protocol. Surgeons in other institutes are reluctant to do so because the ensuing disruption of breast lymphatics might theoretically modify the drainage pathways. At The Netherlands Cancer Institute, breast cancer patients with prior excisional biopsy have thus far been excluded from the sentinel node procedure pending evidence of its safety. We first wanted to study the possible effect of excisional biopsy before implementing lymphatic mapping in this patient group. One way to study this is through analysis of such patients and comparing them with patients in whom the primary lesion is still present. Using this approach, Haigh et al. conclude 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 after excisional biopsy of the primary tumor either.

Different types of injection methods have been described. At The Netherlands Cancer Institute, the intratumoral injection technique is used. Most of our colleagues in other institutions prefer a pericavitary technique in case of prior excisional biopsy. The technique of pericavitary injection is based on the finding that, when administered into the cavity itself, the tracer agent tends to just sit there rather than disperse into the lymphatics. Based on this experience, we used the pericavitary technique after the excisional biopsy.

We realize there are some weak points in this study. Preoperative lymphoscintigraphy and the combined intraoperative detection technique with blue dye and a gamma ray detection probe are recommended for lymphatic mapping in breast cancer. The current study involved only preoperative lymphoscintigraphy and, therefore, does not provide conclusive evidence that lymphatic mapping is unsafe after excisional biopsy of the primary tumor. Perhaps blue dye would have pointed out sentinel nodes in our patients in whom less were depicted on the second set of scintigrams. But on the other hand, the discrepancy might even be bigger if the blue dye would have shown even more nodes in the situation that more nodes were visualized. The observation that more, less or other nodes were shown does not necessarily mean that these would have been tumor-positive. Even if this were to be the case, it could be debated whether it would have impact on survival and regional control. So, analysis of identification rate and axillary recurrence rate in patients with prior excisional biopsy would be preferred to resolve this issue definitively.

The finding of a high percentage (50%) of extra-axillary sentinel nodes in our series is not surprising. Most of the breast lesions were non-palpable. In a previous study we showed that these lesions have a tendency to drain more often to the internal mammary chain when compared to palpable lesions. Non-palpable lesions might be non-palpable because of their deeper location within the breast. Therefore, the intratumoral injection will be deeper as well and the radioactivity will drain to the internal mammary chain via the retromammarian lymphatics.

Even though the sample size is small, two important conclusions can be made from this study. First, excisional biopsy of the breast causes non-visualization of axillary sentinel nodes in more...
than one third of the cases. Secondly, the locations of the internal mammary chain sentinel nodes visualized after excisional biopsy should not be trusted. The current study makes us question the accuracy of sentinel node biopsy after excisional biopsy. Every effort should be made to obtain a preoperative pathological diagnosis through needle aspiration cytology or true cut biopsy so that the need for axillary staging after diagnostic excision can be avoided. If that situation does come up, we resort to axillary node dissection in lieu of sentinel node biopsy. Several studies have suggested the existence of lymphatic watersheds in the breast.\textsuperscript{11,12} Based on the outcome of the current study, one may also wonder about the accuracy of peritumoral injection, or injections even further away from the primary lesion.

In conclusion, this study implies that sentinel node biopsy should be performed prior to excisional biopsy to ensure optimal sensitivity.

REFERENCES