Sentinel node biopsy. Evolving from melanoma to breast cancer
Jansen, L.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 6

TECHNIQUE OF SENTINEL NODE BIOPSY
IN BREAST CANCER

E.J.Th. Rutgers¹, L. Jansen¹, O.E. Nieweg¹, J. de Vries², H. Schraffordt Koops², B.B.R. Kroon¹

¹Department of Surgery, The Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands
²Department of Surgical Oncology, Groningen University Hospital, the Netherlands

EUR J SURG ONCOL 1998; 24: 316-9
In patients with invasive breast cancer, lymphatic staging is of importance to estimate the prognosis and to establish the treatment policy. Regional lymph node metastasis is related to a worse prognosis, indicating the need for adjuvant regional and systemic treatments. This will lead to improved regional control and survival.\(^1\)
\(^3\)

The "golden standard" for lymphatic staging in invasive breast cancer is a complete axillary dissection and histological examination of all - preferably at least ten- lymph nodes. Unfortunately, in a large proportion of patients, this procedure with its well known side effects has been an unnecessary therapeutic effort as lymph nodes appear negative on pathological evaluation.

In a number of studies, lymphatic mapping and sentinel node (SN) biopsy, introduced in cancer staging by Morton and co-workers, has been shown an equally accurate staging procedure as axillary dissection in early stage breast cancer.\(^6\)\(^9\). Most investigators are able to identify the SN in over 90% of the patients. After performing a confirmational complete axillary dissection, the presence of metastasis in non-sentinel nodes, while the SN node is tumour negative (false negative test result), is rare: 0-6%\(^6\)\(^9\). Thus the identification and removal of the SN might replace complete axillary lymph node dissection as staging procedure.

This paper describes our technical approach, and summarises unresolved questions about the SN technique in breast cancer. It concludes with guidelines on how to implement this technique in routine clinical practice.
The two techniques for lymphatic mapping currently applied are: lymphoscintigraphy followed by intraoperative tracing of the "hot" nodes by a gamma probe\textsuperscript{8,9} and injection of a blue dye in, around or intra(sub)dermally over the tumour after which the blue stained afferent lymphatics will direct to the blue SN\textsuperscript{7}.

From our experience in melanoma\textsuperscript{10-12} and a careful anatomic study in breast cancer\textsuperscript{13} we designed the following technique. First preoperative lymphoscintigraphy is performed. The objectives are to identify the draining lymph node basin(s), to determine the presence and number of sentinel nodes, and to determine the presence or absence of second-echelon nodes. Between 4 and 36 hours (usually about 18-20 hours) preceding the operation a single dose of 60 MBq \textsuperscript{99m}Tc-nanocolloid (0.2 ml, Solco Nuclear, Birsfelden Switzerland) with a particle size less than 80 nm is administered into the primary tumour in the breast, for both lymphoscintigraphy and intraoperative lymph node detection. A fine type of needle (< 0.7 mm diameter) is used. Immediately after injection, dynamic images with the gamma camera are obtained to visualise the lymphatic drainage. Dynamic imaging is continued for a minimum of 20 minutes to a maximum of 45 minutes. Subsequently, static scintigrams are obtained, which are repeated after two hours. In absence of visualisation of SN, static images are repeated after 4 to maximally 7 hours. Anterior and lateral images are obtained, complemented by posterior and oblique images when indicated. A lateral or prone position ("hanging breast technique") may help to discriminate the injection site from the draining lymph node basin.

The position of the SN is indicated on the skin. Repeat injections of the radiopharmaceutical are not performed. The lymphoscintigrams are discussed with the operating surgeon.

The operation is performed within 24 hours following lymphoscintigraphy. After induction of anaesthesia and sterile draping, a
dose of 1.0 ml patent blue-V (2.5% in aqueous solution containing 0.6% sodium chloride and 0.05% disodium hydrogen phosphate; Laboratoire Guerbet, Aulney-Sous-Bois, France) is administered into the tumour in the breast.

Before the incision is made, the number of radioactive counts per second is measured over the site where the SN are presumed with the help of the gamma detection probe (Neoprobe® 1000/1500, Neoprobe Company, Columbus Ohio, USA). Background measurements are performed in the ipsilateral drainage basin away from tumour site.

Shortly after injection (usually about 5 minutes), an incision is placed in the axilla in such a way that it can be incorporated in the incision for the subsequent mastectomy or axillary node dissection. Usually a 2 to 3 cm incision dorsal from the lateral margin of the major pectoral muscle in the lower axilla enables the visualisation of the blue lymphatics. Gentle massage of the injection site will enhance blue lymphatic drainage and improve visualisation. Usually the blue lymphatics are found underneath Scarpa's fascia. Lymphatic vessels are carefully dissected and followed to the SN, which is identified by its blue discoloration.

The accumulated radioactivity in the SN is measured with the gamma detection probe. If no blue node or blue lymphatics can be found, the probe is used for tracing. The node(s) identified as the SN is (are) excised and the number of counts is measured ex vivo to confirm the nodal activity. The wound is explored with the probe for additional "hot" nodes that maybe first-echelon nodes. The number of remaining counts in the wound is recorded after all SN are removed.

Occasionally scintigraphy and lymphatic mapping with blue dye do not discriminate between first- and second-echelon nodes. In these instances all nodes that maybe interpreted as SN are excised. In our prospective study, after SN biopsy a confirmational complete axillary lymph node dissection is carried out in all patients.
SN(s) are embedded entirely in paraffin, nodes over 1 cm are bisected. After serial sectioning, usually 3 to 5 sections are stained with H&E, and by immunohistochemistry with cytokeratin and CAM 5.2 antibodies. From the axillary dissection specimen at least 10 lymph nodes are retrieved and embedded. One to two sections per non-sentinel node are stained routinely with H&E, cytokeratin and CAM 5.2 antibodies.

With these techniques, in a prospective trial we were able to identify the SN in 90% of the patients with palpable breast cancers (mean tumour size 2.1 cm, clinically node negative, confirmational complete axillary dissection in all patients). In this study, no false negative SN(s) were retrieved\textsuperscript{14}.

**QUESTIONS ABOUT THE TECHNIQUE**

We feel confident with the described technique, which is endorsed by our results without false negative cases. Thanks to our experience in melanoma the learning phase was short, as no difference in SN retrieval was seen in early versus recent patients. Nevertheless, the SN procedure in breast cancer is technically more demanding and requires a patient surgeon and a meticulous surgical technique. For instance, when a blue lymphatic is severed it is more difficult to follow and trace the first blue node. We find dynamic lymphoscintigraphy helpful, acting “as a roadmap in a strange city”.

Many different ways to retrieve the SN in breast cancer are described, which raises many questions about as to what constitutes the optimal technique ensuring the identification of the true SN. These questions are the following.
• Regarding the location of injection. Injection into the tumour and around the tumour has both been applied, while some authors have even advocated injection into the subcutaneous tissue or the overlying skin. Theoretical rationale for these latter two sides is based on the fact that the embryological origin of the mammary gland is an appendix of the skin.

An interesting observation in this regard is that a radiopharmaceutical injected around the tumour and blue dye injected intradermally, both drain to the same axillary nodes. The absence of parasternal drainage after intradermal injection, however queries the validity of the intradermal approach. A clear advantage of subcutaneous and dermal administration is swift drainage to the axillary nodes, which is said never to fail. We inject into the tumour as we are only interested in the lymphatic drainage of the tumour itself, not of other parts of the breast. Whether this hypothesis leads to a more selective SN identification has to be confirmed in comparative studies.

In our experience axillary drainage after intratumoural injection of \textsuperscript{99}Tc-nanocolloid failed in about 15% of the patients.

Another complicating factor is the short distance between an injection site of a tumour in the upper outer quadrant and the axilla. This may cause problems in discriminating the radioactivity of the SN from the radioactivity at the injection site. Excising the radioactive tumour area before performing SN biopsy might help to reduce overshining activity from the injection site, but such a policy may interfere with the blue dye lymphatic mapping part of the procedure. Another pitfall may be that the location of the injection of the tracer cannot always be determined as precisely as it can for melanoma, due to the deeper tumour localisation.

• Regarding the injected volume of the dye or radioactive tracer: both small volumes (up to 1ml) into the tumour (our technique) and intradermally, and large volumes (4-5 ml) around the tumour are used. Both techniques are leading to the identification of the SN in the large majority of patients.

\textbf{TECHNIQUE FOR BREAST CANCER}
• Regarding the compounds: we use $^{99m}$Tc-nanocolloid, resulting in an adequate lodging of the radioactive tracer in the SN for at least 24 hours. Larger albumen particles are used by Veronesi et al\textsuperscript{8} with good results: 96% sentinel node retrieval. In the USA the application of human albumen products is under regulatory restrictions. Therefore, mostly $^{99m}$Tc-sulfur colloids are applied. Due to large differences in particle size the number of nodes in which the tracer lodges differs: filtered sulfur colloid results in more "hot" nodes compared to non-filtered sulfur colloid\textsuperscript{17}.

In the USA, Isosulphan blue (Lymphazurin, Zenith Parenterals, Rosemont Illinois, USA) is readily available as blue dye tracer. Methylene blue is not a suitable dye, as it will not result in a adequate lymphatic drainage. Patent V blue is mostly used in European countries.

• Regarding the combination of intra-operative techniques. We feel strongly that combining both techniques, particularly in the learning phase, will lead to a more selective and reliable identification of the SN. The abandonment of the blue dye technique in breast cancer, and thus merely relying on the radioactive tracer, as advocated in one study\textsuperscript{8} has provoked criticism\textsuperscript{18}. It was stated that with radioactivity alone, SN cannot always reliably be discriminated from second-echelon nodes, resulting in the removal of too many not relevant nodes.

• Regarding the selection of patients. We only perform the SN procedure in clinically node negative women. Patients in whom the clinical palpation of axillary nodes is ambiguous will undergo ultrasound directed FNA cytology. If negative, the SN procedure will follow. Furthermore we restrict the procedure to patients with unifocal T1-2 tumours (up to 4-5 cm).

Multicentricity will lead to uncertainties about lymphatic drainage of the different tumour sites. Whether the SN procedure after initial excisional biopsy of the tumour is reliable, has to be proven yet.

The SN procedure in clinical occult breast cancer is logistically more difficult. Diagnosis of invasive cancer has to be established by core needle
biopsies. The radioactive tracer has to be injected on the radiology department under ultrasound guidance. In many institutions this will face regulatory problems. Also the patent blue dye must be administered under image guidance. Many uncertainties exist about the validity of the SN procedure after neo-adjuvant chemotherapy.

THE IMPLEMENTATION OF THE TECHNIQUE

SN biopsy in breast cancer is not a "see one, do one and teach one" procedure. It requires careful logistic and technical processing. A close co-operation between a dedicated nuclear physician with a well equipped department, a surgeon (surgical oncologist?) experienced in breast surgery and aware of the lymphatic anatomy of the breast, and an interested pathologist is mandatory. Once this co-operation is protocolised and established, and the SN research protocol is approved by the institutional review board, the technique can be mastered in patients who agreed upon a complete axillary dissection. The accuracy of the technique has to be validated in a number of patients undergoing a conformational axillary dissection after SN retrieval.

If the team shows the ability to retrieve the SN in over 85-90% of the T1-2N0 patients, with a false negative rate of less than 5% (as missing positive nodes will jeopardise regional control and possibly deprive patients from systemic therapy) one could think of using the SN procedure as a staging procedure equal to complete axillary node dissection.

How many patients this learning phase should comprise is not clear. Most groups have performed at least 100 confirmational axillary dissections before allowing themselves to use SN biopsy as staging procedure and leaving the axilla untreated if the SN is tumour-negative. However, these studies were designed to prove the validity of the SN concept in breast cancer, and not meant as only a learning experience. So,
whether such a large number of patients is always necessary, remains to be discussed. Proper training through one of the available courses, or by an experienced group is mandatory. After performing 30-50 well documented cases, an audit by an experienced group might help to decide on how to proceed with this technique in daily clinical practice.

The SN technique is one of the major improvements in breast cancer care for the coming decade, comparable to the implementation of breast conservation. If the technique is well performed, a large proportion of patients with early invasive breast cancer can be spared an unnecessary complete axillary dissection. However, we should not throw out the baby with the bath water. Before applying this technique in routine daily practice, we have to be sure for our patients and ourselves that the technique in our hands is an as accurate staging procedure as described by the experienced groups. This requires a dedicated team that works according to a well designed and approved protocol.


