Sentinel Node Biopsy in Breast Cancer

Karl von Smitten

From the Department of Surgery, University Central Hospital, Helsinki, Finland

Correspondence to: Karl von Smitten, MD, Kirurgiska sjukhuset, PB 263, FIN-00029 Helsingfors, Finland

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The concept of breast sentinel node biopsy is based on the assumption that a breast cancer that metastasizes through the lymphatics will initially reach one or a few nodes in the corresponding lymph basin. The status of this or these sentinel node(s) will predict the status of all the other nodes in the basin. The sentinel node can be found stained blue or as being radioactive by injecting blue dye or a radioactive tracer around the tumour. Scintigraphy may further help to localize the sentinel node. The feasibility of the method has been validated by several studies comparing the status of the sentinel node with the node status of the axilla revealed by subsequent axillary clearance. Detection rates of 66–100% and false-negative rates of 17–0% have been reported. Before the method can be accepted for clinical use, a consensus concerning the accepted false-negative rate has to be reached and has to be shown in practice. From a theoretical point of view, a calculated false-negative risk rate of 2–3% can be accepted.

The surgical treatment of breast cancer involves the removal of the tumour, with clear margins as well as axillary lymph-node clearance. While local treatment of the tumour has become more conservative, only 40–50% of patients having mastectomy, total axillary clearance of levels 1 and 2 with examination of at least 10 nodes is still considered the treatment of choice (1). This radical axillary clearance causes considerable morbidity, with swelling (10–30%) (2, 3), arm weakness (16–27%) (2, 3) and numbness (75–78%) (3, 4) to such an extent that virtually all patients will still have some symptoms in the ipsilateral arm one year after surgery (3). This means that of patients with T1 tumours, only about one-quarter are node positive and will derive any potential benefit from the procedure (5, 6). Mammography, ultrasonography, and computed tomography of the axilla have so far not been sensitive enough to render axillary clearance unnecessary (7–9). Ultrasound-guided aspiration biopsy can reach a sensitivity of 80%, which is still not enough (10). Among the nuclear medicine techniques, FDG-PET could possibly be used to rule out axillary lymph-node metastasis, but at the present time the cost and logistic and technical complexity preclude routine clinical use (11). Some less-invasive methods of axillary sampling have also been discouraging (6).

A method to avoid the radical axillary clearance in breast cancer surgery would be a step forward of the same magnitude as the advent of breast-conserving surgery. Patients not subjected to axillary clearance could readily be treated by day-case surgery, even under local anaesthesia; sick leave could easily be halved from the standard practice of four weeks, and most of all, arm morbidity would be negligible.

EVOLUTION OF THE SENTINEL NODE CONCEPT

In 1977 Cabanas reported a study comprising 100 patients with penile cancer, in which he use a blue dye technique to demonstrate that the lymph from the tumour area first reached one node in the lymphatic basin (12). This innovation initiated the concept of the sentinel node, which assumes that a malignancy that metastasizes through the lymphatics will initially reach one or a few nodes in the corresponding lymph basin. This or these nodes are known as 'sentinel nodes', from the word sentinel, which is defined as a guard or one who keeps watch. Morton and his colleagues introduced this technique in the surgical treatment of melanoma, where intradermally injected blue dye will reach the sentinel node of the corresponding lymph basin (13). In 1991 Giuliano and co-workers began to study the feasibility of the method of lymphatic mapping and sentinel lymphadenectomy in breast cancer and in 1994 they published their series using lymphazurin, which reached the sentinel node from the tumour area, staining the node blue. Sentinel nodes were identified in 114 of 174 procedures (65.5%) and accurately predicted axillary node status in 109 of 114 cases (95.6%) (14). In 1993, using radioguided dissection, Krag showed in a small series of 22 patients that technetium-labelled colloid injected around the tumour reached the sentinel node in the same way as the dye, with approximately the same result (15). One of the pioneer groups in the USA, from the Moffitt Cancer Center and Research Institute, Tampa, Florida, published their results in 1996 combining the dye and the radiolabelling method. They identified the sentinel node in 57 of 62 patients (92%), the sentinel node being

positive in all 18 patients with nodal metastases (16). After these initial reports many groups from both sides of the Atlantic have reported equally good results (see Table). In these audit-type studies, including performing confirmational complete axillary dissection, the false-negative rate has varied from 0 to 17%) (see Table), and in most studies the sentinel node(s) has been identified in over 90% of the patients.

METHODS AND EQUIPMENT

There are at least four versions of the sentinel node biopsy procedure (see Table). In Europe 99mTc nanocolloid is used, either 99mTc labelled Solco Nanocoll (Sorin Radiofarmaci, Vercelli Italy) with a particle size below 80 nm, or perhaps preferably Solco Albu-Res (Amersham Sorin, Sluggia Italy) with a larger particle size of 200–1000 nm (17). In the USA Tc-9mm sulphur colloids are used, either filtered, or unfiltered with a larger particle size of average 200 nm (18).

Three different hand-held gamma-probes have been used for the radioguided sentinel node biopsies. C-Trak (Care Wise Medical Products Corporation, Morgan Hill, CA, USA) uses a scintillation crystal detector, while the two other types on the market, Neoprobe (Neoprobe Company, Columbus, OH, USA) and Navigator (Auto Suture, USA) use solid state detectors.

In Europe the blue dye Patent Blue-V (Laboratoire Guerbet, Aulney-Sous-Bois, France) is used, while in the USA isosulphan blue, lymphazurin (Zenit Parenterals, Rosemont, IL, USA) is used. Methylene blue is not a good choice because it is taken up poorly by the lymphatics and does not give good demarcation of the lymphatic area (19).

CHOICE OF METHOD

From a logistic and economic point of view, the blue-dye technique presented by Giuliano is very tempting, because there is no need for nuclear medicine logistics and an expensive gamma probe (14). This technique has of course been vigorously proposed by Giuliano, who stresses that fellows in his institute can identify the sentinel node in 75–80% of patients after as few as 10 cases. A fairly large amount of dye (5 ml) is used, the injection area is massaged, and dissection is started as early as 3 min after injection depending on injection site (20). In 1997 Giuliano reported a 93.5% success rate in 107 procedures with a 100% positive predictive value in 42 tumour-involved axillae (21). However, this technique is perceived as difficult, requiring meticulous and rather extensive dissection following the stained lymphatic vessels to the sentinel node(s). Therefore a common modification is to combine the blue-dye method and the radioguided sentinel node biopsy (22). This seems to increase the success rate, as some sentinel nodes are either only blue or only hot (16). A combination of dye and isotope tracing with scintigraphy and a hand-held gamma probe is probably the best method (23). According to this study design, a sentinel node is defined as a blue and/or hot node with a 10 : 1 ex vivo gamma probe rate of a sentinel node to a non-sentinel node (24).

Adding lymphoscintigraphy to the procedure makes the sentinel node easier to find, because a skin mark can be placed over the hot node(s) and the subsequent biopsy can be performed expeditiously through a short incision (17). A large American multicentre trial has used a similar design (25). The lymphoscintigraphy adds another new aspect: it may show drainage outside the axilla, especially to the parasternal nodes, even making it possible to harvest this sentinel node. Sentinel nodes outside the axilla may occur even in 8% of the cases (25). However, the lymphoscintigraphy adds to the cost of a commonly performed procedure, and the results of studies without scintigraphy may indicate that in the long run this procedure adds nothing but time and cost for most patients. The procedure is probably important during the learning stage.

ASPECTS OF PATHOLOGY

Sentinel node biopsy has also introduced some new aspects in the pathological handling of the nodes. Obviously, the pathologist will be able to examine the sentinel node(s) more thoroughly than if he has to examine the recommended more than 10 nodes in an axillary clearance specimen. Focusing on the sentinel node has also elicited a new interest in immunohistochemical demonstration of micrometastases in the lymph nodes. One step further is to examine part of the sentinel node by reverse transcriptase-polymerase chain reaction (26). In studies where immunohistochemistry was used, 10–14.3% of the patients turned node positive compared with the H&E study (21, 27). The intensified search for micrometastasis in the sentinel nodes may be important, as this should be taken into account when deciding on adjuvant treatment (28).

In the clinical setting of sentinel node biopsy, probably the frozen section technique will mainly be used. Of these patients up to 24% may eventually reveal metastases on paraffin-embedded sections, requiring a second operation, which is a drawback that has to be addressed (29). A fast method to demonstrate small metastatic foci in the sentinel node would therefore be very valuable, and some promising results have been published (30). However, it may be difficult to give the results sooner than after 1 h, which is a rather long time during breast cancer surgery. Intraoperative imprint cytology of sentinel lymph nodes may also be an attractive alternative (31). Pathology has to aid surgery in avoiding the need of several operations using the sentinel node biopsy procedure. Therefore one of the biggest challenges of this new concept is to develop a fast and reliable method of lymph-node analysis.

Table 1

False-negative rates in sentinel node biopsy procedures in breast cancer surgery

Author	Year	Technique	Patients	Detection (%)	False-negative (%)
Giuliano et al. (21)	1994	Blue dye	174	66	12
Flett et al. (37)	1998	Blue dye	68	82	17
Krag et al. (15)	1993	Gamma probe	22	82	0
Veronesi et al. (17)	1997	Scintigraphy + probe	163	98	5
Roumen et al. (38)	1997	Scintigraphy + probe	83	69	4
Cox et al. (24)	1998	Gamma probe + blue dye	466	94	1
Albertini et al. (16)	1996	Gamma probe + blue dye	62	92	0
Borgstein et al. (33)	1997	Scint. + gamma probe + blue dye	33	100	0

TECHNIQUES FOR INJECTING THE TRACER

Several modifications of injecting technique have to be further evaluated. The tracer is injected into (32) and around the tumour (16), as well as into the subcutaneous tissue (17) or the skin over the tumour (33). All these techniques seem to work, but more studies comparing the different techniques are needed and are probably in progress.

The volume of injected dye and radioactive tracer should also be addressed. Increasing the volume of the radioactive tracer injected can increase the rate of successful identification of the sentinel node (25).

OUTCOME VALIDATING THE SENTINEL NODE BIOPSY PROCEDURE

One of the most difficult aspects validating sentinel node biopsy is the question of false-negative rate. This should be reported as a percentage of the total number of node-positive patients in the study. The main concern is how a high rate of false-negatives can be accepted from an oncological point of view. When discussing the acceptable false-negative rate in sentinel node biopsy, we have to remember that ordinary axillary clearance is not always perfect, sometimes having a considerable false-negative rate when the operations are performed by junior staff. From a theoretical point of view a calculated risk of 2–3% false-negatives is acceptable (34, 35) and the risk of axillary recurrence following axillary clearance is dependent on the number of nodes examined, i.e. the quality of axillary surgery, so that it is about 5% when < 5 nodes are examined (36).

A consensus by a multidisciplinary approach concerning the accepted false-negative rate has to be reached before sentinel node biopsy is used in the routine clinical setting.

The false-negative rates of several sentinel node biopsy studies are presented in Table 1.

TRAINING

Courses for surgeons, nuclear medicine physicians and pathologists are held in both Europe and the US. In the US it has been suggested that approximately 20 procedures should indicate a success rate of about 90% when dye and radioactive tracer are combined in order to show that the surgeon has reached an appropriate level of training (24).

INDICATIONS

Clinically, node-negative patients with unifocal T1-2 tumours are widely accepted as candidates for this procedure. Axillary examination with ultrasound in order to perform fine-needle aspiration if the nodes are ambiguous is also recommended (22).

PRESENT STATUS

The basic concept of the validity of the sentinel node in breast cancer has been accepted by the medical community. By now on both sides of the Atlantic there still seems to be a requirement of further multicentre validation studies where false-negative rates are determined, patients who are not appropriate candidates are characterized and different technical modifications assessed in order to reach consensus on standardization of the procedure.

There are some prospective studies, at least in England and The Netherlands, where sentinel node biopsy is already used to leave those with negative nodes without axillary clearance. Thus, the procedure is still not accepted as the standard care (37, 38).

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