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Sentinel-Node Biopsy to Avoid Axillary Dissection in Breast Cancer with Clinically Negative Lymph-Nodes — Source link

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Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes

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Summary

Background Axillary lymph-node dissection is an important staging procedure in the surgical treatment of breast cancer. However, early diagnosis has led to increasing numbers of dissections in which axillary nodes are free of disease. This raises questions about the need for the procedure. We carried out a study to assess, first, whether a single axillary lymph node (sentinel node) initially receives malignant cells from a breast carcinoma and, second, whether a clear sentinel node reliably forecasts a disease-free axilla.

Methods In a consecutive series of 163 women with operable breast carcinoma, we injected microcolloidal particles of human serum albumin labelled with technetium-99m. This tracer was injected subdermally, close to the tumour site, on the day before surgery, and scintigraphic images of the axilla and breast were taken 10 min, 30 min, and 3 h later. A mark was placed on the skin over the site of the radioactive node (sentinel node). During breast surgery, a hand-held γ-ray detector probe was used to locate the sentinel node, and make possible its separate removal via a small axillary incision. Complete axillary lymphadenectomy was then done. The sentinel node was tagged separately from other nodes. Permanent sections of all removed nodes were prepared for pathological examination.

Findings From the sentinel node, we could accurately predict axillary lymph-node status in 156 (97·5%) of the 160 patients in whom a sentinel node was identified, and in all cases (45 patients) with tumours less than 1·5 cm in diameter. In 32 (38%) of the 85 cases with metastatic axillary nodes, the only positive node was the sentinel node.

Interpretation In the large majority of patients with breast cancer, lymphoscintigraphy and γ-probe-guided surgery can be used to locate the sentinel node in the axilla, and thereby provide important information about the status of axillary nodes. Patients without clinical involvement of the axilla should undergo sentinel-node biopsy routinely, and may be spared complete axillary dissection when the sentinel node is disease-free.

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Introduction

Axillary lymph nodes are the commonest site of metastasis in breast carcinoma. Metastatic involvement of the axilla is known to progress regularly, from the first, via the second, to the third axillary level; skip metastases are found in roughly 2% of cases only.[1,2]

Axillary-node status is one of the most important prognostic indicators in breast cancer, and of particular value in the choice of adjuvant therapy.[3,4] The prognostic information is gained from histological examination of all or most axillary nodes; the treatment of operable breast carcinoma almost always involves lymph-node dissection.[5] However, if a non-invasive or minimally invasive diagnostic procedure could provide accurate preoperative staging of the axilla, axillary dissection could be avoided in patients with no involved nodes. Sentinel-node biopsy has been developed for this purpose. The technique was first used by Morton and colleagues with blue dye,[6,7] and later by van der Veen and colleagues[8] with lymphoscintigraphy to select melanoma patients for regional node dissection. These researchers showed that early metastasis of melanoma almost always occurs in the first node, or sentinel node, to receive lymph from the area containing the primary tumour. In breast cancer, cells that detach from the primary tumour are likely to arrive at, and be held by, the first node to receive lymph from the involved breast area. If this sentinel node can be reliably identified, and if careful examination reveals no cancer cells, the other axillary nodes should also be clear.

In most previous investigations of the sentinel node, blue dye was injected into the peritumoral area, and the coloured node was sought through axillary incision.[9] A few studies on small series of patients used the lymphoscintigraphic technique.[10,11] The validity of the sentinel-node strategy has thus been established in breast cancer.

We designed this study to assess the value of sentinel-node biopsy in breast cancer by means of a lymphoscintigraphic technique and, in particular, a γ-ray detection probe to facilitate identification and dissection of the lymph node. We had three objectives: first, to assess the reliability of external-body lymphoscintigraphy for identification of the node that receives lymph from the region of the primary carcinoma; second, to assess the usefulness of a γ-ray detection probe in identification and removal of the sentinel node during axillary surgery; and, third, to measure, by histological analysis of all axillary nodes, the extent to which the sentinel node is a predictor of axillary-node status.

Patients and methods

Patients

We studied 163 consecutive patients with operable breast carcinoma (T1–T3) scheduled to receive axillary dissection at the European Institute of Oncology, from March to December, 1996. We excluded pregnant or lactating women, those who had

Tumour diameter	Number of patients
<1·5 cm	45
1·5 to 1·9 cm	49
≥2·0 cm	69
Type of surgery	
Mastectomy	23
Breast conversion	140
Oestrogen-receptor status	
Positive	120
Negative	43
Tumour grade*	
1	25
2	74
3	59

*Grading was not available in five patients.

Table 1: **Characteristics of 163 patients***

previously undergone biopsy or received radiotherapy to the breast. Patients with clinically extensive metastatic involvement were also excluded, as were those with tumours shown to be non-infiltrating on histological examination. Patients with carcinomas of maximum diameter less than 1 cm were rarely accrued, since most of these patients entered a randomised trial—continuing at our centre—in which axillary dissection is not carried out. The average age of the patients was 51 years (range 25–77). Tumour size, as measured on pathological sectioning, ranged from 5 to 6 cm; 140 (86%) patients underwent quadrantectomy axillary dissection and radiotherapy, and 23 (14%) received a modified radical mastectomy (table 1).

Injection of labelled colloids

The day before surgery, 5–10 (generally 7) MBq of technetium-99m-labelled human albumin colloid particles in 0·2 mL saline were administered subdermally immediately above the breast lesion, followed by 0·2 mL saline with a 25 G butterfly needle.

Before use, the colloid particles, size range 50–200 nm (Nanocoll or Albures, Sorin Biomedica, Saluggia, Italy) were checked for free technetium according to the manufacturer's instructions, and at least 95% of the radioactive technetium was bound to albumin.

Scintigraphic scans

Planar scans of the involved breast and axillary area, both anterior and oblique projections, were acquired 15 min, 30 min, and 3 h after tracer injection (acquisition time 5 min). The skin immediately above the first node that became radioactive was marked; this node was usually the only one detected by the γ camera, and had the greatest activity when more than one node was detected.

A γ-detecting probe was applied to the skin above the sentinel node to confirm the hot spot. This probe was part of a commercially available system for radioguided surgery (C-Trak System, Care-Wise, CA, USA). It consists of a 12·6×1·9 cm stainless-steel tube with angled tip to increase manoeuvrability. The probe tip contained a sodium iodide crystal for measurement of γ energies and detection of small sites of isotope concentration, such as ^{99m}Tc. Signals picked up by the probe were transduced into digital readout and acoustic signals. The intensity and frequency of the auditory signals were directly proportional to the intensity of radioactivity detected.

Intraoperative identification of sentinel nodes

Just before axillary dissection, the radio-guided probe, now in a sterile glove, was slowly passed over the marked skin area to locate the sentinel node or nodes. A 2–3 cm skin incision was made and the node or nodes excised; the acoustic signal emitted by the probe was used to guide isolation and removal of the nodes. We labelled the removed material "sentinel node", and then proceeded with axillary dissection, with the biopsy incision extended medially and laterally to give a C-shaped incision. With careful upward, medial, and lateral skin retraction, complete axillary dissection (including the third level) was not difficult.

Maximum diameter of primary tumour (cm)	Number of cases	Number with positive axillary nodes
<2·0	94	45 (48%)
≥2·0	66	40 (61%)
Oestrogen-receptor status		
Positive	117	59 (50%)
Negative	43	26 (60%)
Proliferative rate (Ki67)		
<20	97	47 (48%)
≥20	63	38 (60%)
Tumour grade*		
1	25	10 (40%)
2	72	36 (50%)
3	58	36 (62%)
Peritumoral vascular invasion		
No	92	32 (35%)
Yes	68	53 (78%)

*Not available in five patients.

Table 2: **Axillary node metastases according to pathological variables**

The mean number of nodes removed was 25 (11–47), 13 at the first level, seven at the second, and five at the third. All removed material was checked again in the operating room for radioactivity, before it was sent to the pathologist.

Pathology

The lymph nodes were isolated from axillary fat tissue without freezing or preservation, and were examined by standard techniques. Nodes of major axis greater than 0·5 cm were bisected; nodes smaller than 0·5 cm were fixed and embedded uncut. Three sections were obtained from each node at a different level (100–500 μm apart), and stained with haematoxylin-eosin. In the last 107 cases in the series, the sentinel node was sent for immediate frozen-section examination. The node was bisected, one half frozen and cut, the other half fixed and embedded in paraffin. At least three consecutive sections of the frozen node were examined. The remaining frozen tissue was thawed, fixed, and embedded to produce permanent sections.

The tumours were histologically classified according to the WHO Histological Classification of Breast Tumours,[12] as modified by Rosen and Oberman.[13] Grading of tumours was defined according to Elston and Ellis.[14] We looked for peritumoral vascular invasion according to the recommendations of Rosen and Oberman.[13] Oestrogen and progesterone receptor status and the tumour proliferative fraction were assessed by immunohistochemistry on paraffin sections, by use of an indirect avidin-biotinylated peroxidase complex staining method,[15] which followed heat-mediated antigen retrieval with citrate buffer (pH 6·0) in a microwave oven.[16] Immunoreactions were done with an automatic immunostainer (Dako-Biotech Techmate 500). Primary monoclonal antibodies to oestrogen receptors and progesterone receptors (Dako, Glostrup, Denmark) were used at 1/100 dilution, MIB-1 monoclonal antibody to the Ki-67 antigen (Immunotech, Marseille, France) was used at 1/200 dilution.

Results

The status of the axillary nodes correlated with several pathological variables (table 2). The most important predictive factor was peritumoral vascular invasion.

Sentinel lymph-node identification

Sentinel-node analysis was possible in 160 (98%) of the 163 patients. In the three missed cases, lymphoscintigraphy revealed at most very faint uptake of radioactivity; the sentinel node could not be identified with the γ probe the next day. In the remaining 160 cases, tracer uptake was sufficient for us to identify the sentinel node during surgery, though uptake varied from 10

Positive sentinel node	Number of patients
1 positive sentinel node; no other positive nodes	28
2 positive sentinel nodes; no other positive nodes	4
2–3 positive nodes*	23
4–10 positive nodes*	18
>10 positive nodes*	8
Negative sentinel node	
1 positive node†	3
2 positive nodes†	1

*Including sentinel node or nodes.
†Skip metastases.

Table 3: **Distribution of 85 cases with positive axillary nodes according to sentinel-node biopsy results**

counts per s (cps) to 2000 cps.

In 104 cases, one sentinel lymph node was detected by the probe; in 41 cases, two nodes took up radioactivity; and in 15 cases, three nodes were radioactive. All lymph nodes detected by the γ probe were removed and labelled as sentinel nodes.

Predictive value of sentinel nodes

The sentinel nodes were metastatic in 81 of the 160 patients with identifiable sentinel nodes; in 32 (40%) of them, the sentinel nodes were the only metastatic nodes, whereas in the remaining 49 (61%) patients, other axillary nodes were positive. 79 patients had negative sentinel nodes; in 75 (95%) of these, all axillary nodes were negative, whereas in four patients the sentinel node was disease free, but other nodes were positive for micrometastases. In two of these four patients, the primary carcinoma was multifocal; in the remaining two, the breast lesion was monofocal and 1·5 or 2·0 cm in size.

Therefore, overall there was concordance between sentinel-node and axillary-node status in 156 of 160 cases (97·5%). For the cases with negative sentinel nodes, there was concordance in 75 of 79 (95%).

We analysed 2117 lymph nodes from the 85 patients with axillary lymph-node metastasis (table 3); of this total, 334 (15·8%) nodes were histologically positive for metastases. In 61 cases, the site of metastases was the first axillary level only, and in the remaining 24 cases, the second or third levels were also positive.

Of the 45 patients with primary tumours of maximum diameter (less than 1·5 cm), all 22 (49%) cases with nodal involvement had a metastatic sentinel node, and all 23 cases without disease at the axilla had negative sentinel nodes.

Frozen-section examination

In the final 107 cases, sentinel nodes were sent for immediate frozen-section examination. The sentinel nodes were positive in 32 (30%) patients and negative in 75. The positive cases were all confirmed at final histological examination. Among the 75 cases with negative sentinel nodes at intraoperative examination, the final histological examination confirmed the absence of cancer cells in 57 (76%) cases, whereas in 18 (24%) cases, microfoci of metastatic cells were found. The overall concordance of sentinel-node results and final histological examination was therefore 89/107 (83·2%).

Discussion

We found radioguided resection of sentinel nodes in breast cancer simple and effective. Lymphoscintigraphy revealed the first lymph node within 30 min in most cases, and this node was the most radioactive in later scans in all cases. In 104 cases, one lymph node was identified by the probe and removed, 41 cases had two lymph nodes identified, and, 15, three nodes.

An incision of 2–3 cm was sufficient to permit removal of the sentinel node; this process was made much easier by use of the probe during dissection.

The predictive value of the sentinel node or nodes was 97·5%. This value is high enough for us to conclude that axillary dissection is probably unnecessary for patients in whom the sentinel node is negative. In patients with small tumours (less than 1·5 cm), the status of the sentinel node predicted axillary-node involvement with 100% accuracy.

We observed false-negative sentinel nodes in four cases, which represents 2·5% of all cases, and 5·4% of cases with negative axillary nodes. In two of these four patients, the primary carcinoma was multifocal. Multifocal tumours are likely to involve more than one lymphatic trunk from the mammary gland to the axillary nodes, which may give rise to skip metastases. We therefore urge that the sentinel-node method should not be used in cases of extensive multifocality—ie, in which the edge-to-edge distance between foci is 3 cm or more. The small percentage of skip metastases in this study is consistent with the findings of a previous investigation of 1446 patients with breast cancer (skip metastases in 1·3% of cases).[2]

We found that in 39·5% of cases with a positive axilla, the sentinel node was the only involved node; this finding indicates that the sentinel concept is biologically valid, and supports the argument for sentinel-node biopsy. However, there are several difficulties. The first concerns the choice of method for identification of the sentinel lymph node. In the original procedures for melanoma[6] and for breast carcinoma,[9] a vital blue dye was injected just before surgery. In the large series of Giuliano and colleagues,[9] the sentinel node was identified by this method in 65·5% of cases. Moreover, the identification rate by this method has been reported at 97% in the hands of more experienced surgeons.[17] An advantage of dye injection is that it is done a few minutes before the operation, whereas lymphoscintigraphy must be carried out at least 2 h before surgery. However, use of blue dye has an important drawback in that axillary tissue must be dissected blindly until the blue node is located. This node can be some distance from the incision. The advantage of the small hand-held probe is that it locates the node and indicates exactly where the skin incision should be made; it also guides the dissection itself, which is therefore quick and consistently successful. We were able to identify the sentinel node in 98% of cases. This advantage, we believe, is sufficient to justify the slightly greater cost of the lymphoscintigraphy method than of blue dye. Moreover, savings would be made from the reduction in elective axillary dissections, therefore the difference in cost between the two procedures becomes negligible.

The reliability of sentinel-node diagnosis on frozen sections may also be questioned. Immediate and reliable intraoperative information on the condition of the sentinel node is vital for the technique's success, since the surgeon must decide whether or not to do a total axillary dissection. We examined frozen sections of sentinel nodes in the last 107 cases. In 89 (83·2%) of these cases, the intraoperative diagnosis was confirmed by the final histological examination. However, in 18 (17%) cases, the intraoperative diagnosis was falsely negative, because micrometastatic foci were subsequently identified on permanent sections. This percentage is high enough to

cause concern, and may represent a limiting factor for the sentinel-node biopsy procedure. A patient whose sentinel node is negative in frozen section but is positive on histology will require a further operation to clear the axillary, which is likely to increase her distress. To help limit this distress, the patient should be fully informed about the problem of intraoperative false-negative results. It is important also to develop techniques to improve the frozen-section examination. Future research should concentrate on more reliable ways to identify microfoci of metastatic cells; in this respect, a rapid cytokeratin immunocytochemical assay seems promising.[18]

An expected development of sentinel-node biopsy will be its application to patients undergoing primary (neoadjuvant) chemotherapy. One of the drawbacks of neoadjuvant chemotherapy is that it can destroy small metastatic foci and down-stage the axilla before it is examined histologically after chemotherapy. Sentinel-node biopsy before chemotherapy, which reliably predicts the state of the axilla, may address this issue. On a cautionary note, however, a small number of lymph nodes identified as negative by standard histological techniques may have occult micrometastases. We believe, therefore, that patients should be followed up carefully with frequent examination of the axilla so that a possible recurrence of disease in the axilla can be swiftly detected and the axillary nodes removed. However, data from other studies[19,20] indicate a low rate of axillary metastases during follow-up of patients with clinically negative nodes which were not dissected at the time of primary surgery.

In conclusion, our results indicate that sentinel-node biopsy guided by a γ probe can identify a negative axilla with high accuracy, so that women with a negative sentinel node can be spared axillary dissection and all its risks. Since the technique is also easy to apply, we expect it to become widely adopted for most cases of breast cancer with clinically negative nodes—after further confirmatory studies and a longer follow-up. The risk of false-negative results is low, and may be further reduced if multicentric and multifocal tumours are excluded. Furthermore, since the technique's predictive value in our patients with small (<1·5 cm) carcinomas was 100%, we believe the procedure could be applied immediately in such cases as a substitute for axillary dissection. We believe that sentinel-node biopsy is an important step forward in the search for more conservative treatments for patients with breast cancer.

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