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Sentinel node biopsy in breast cancer: early results in 953 patients with negative sentinel node biopsy and no axillary dissection

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Abstract

Sentinel node biopsy in patients with breast carcinoma accurately predicts the axillary nodal status. However, in some 6% of patients with negative sentinel nodes the remaining axillary nodes harbour metastases. Our purpose was to observe a large number of patients who did not undergo an axillary dissection after a negative sentinel node biopsy for the appearance of overt axillary metastases. 953 patients treated from 1996 to 2000, with negative sentinel nodes not submitted to axillary dissection, were followed-up to 7 years, with a median follow-up of 38 months. Fifty-five unfavourable events occurred among the 953 patients, 37 (4%) related to the primary breast carcinoma. Three cases of overt axillary metastases were found: they received total axillary dissection and are presently alive and well. The 5 year overall survival rate of the whole series was 98%. Patients with negative sentinel node biopsies not submitted to axillary dissection show during follow-up a rate of overt axillary metastases that is lower than that expected.

Keywords: Negative sentinel node; Follow-up; Breast cancer; Overt axillary metastases

1. Introduction

For a century, axillary dissection has been an obligatory component of the surgical treatment of breast cancer [1]. However, in the last decade, the observation that the dissection often reveals non-involved lymph nodes, due to the fact that primary breast carcinomas are treated much earlier than in the past [2], has led to the search for a preoperative test to identify patients for whom axillary dissection may be avoided [3]. While imaging procedures are, at present, not yet effective in making a preoperative diagnosis of axillary lymph node metastases, the technique of sentinel node biopsy has shown favourable results. This procedure which is being adopted on a large-scale by most centres has been recognised as effective by the members of the consensus conference of 2001 [4]. However, data on extensive clinical studies are necessary to confirm the efficacy of the sentinel node biopsy. For this purpose, we report here the findings from the clinical observations of 953 women treated with breast surgery and sentinel node biopsy, who did not undergo an axillary dissection when the sentinel node was not involved.

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2. Patients and methods

2.1. Patient characteristics

From 1996 to 2000, 2098 patients with invasive breast cancer referred to the European Institute of Oncology underwent the sentinel node biopsy procedure. The present series is composed of 953 patients who proved to have a negative sentinel node biopsy and were not submitted to axillary dissection. This group of patients is carefully studied to draw preliminary observations on breast cancer-related events after a sufficient period of follow-up. There were only a few patients in the first years of the study (1996 = 3, 1997 = 29), because in those years most patients were treated inside validation studies (which implied that the sentinel node biopsy would be immediately followed by an axillary dissection) and only following a specific request from the patient was the axillary dissection omitted when the sentinel node biopsy was negative. The number of the patients requesting this omission increased in the following years reaching a total number of 953 by the end of 2000. This was as a result of the new policy of the European Institute of Oncology which offered all patients the option of avoiding axillary dissections in cases of negative sentinel node biopsies. All patients accepting this option signed an informed consent from 198 women had already undergone an excisional breast biopsy before hospitalisation.

The characteristics of the patients are summarised in Table 1. Patients' ages ranged from 24 to 86 years (mean 55 years). The average size of the primary carcinoma was 1.2 cm, without differences in the five years of accrual. The most common histological type was invasive ductal carcinoma (711 patients, 74.6%), invasive lobular carcinomas were observed in 101 patients, (10.6%), while 141 patients (14.8%) had different types of carcinoma, mainly well-differentiated forms (cribriform, tubular, mucinous, papillary).

Table 1
Characteristics of evaluable patients ($n = 953$)

Characteristic	n	(%)
Age (years)		
$\leqslant$ 45 years	191	(20.0)
46–55	306	(32.1)
56–65	290	(30.4)
>65	166	(17.4)
Tumour size (mm)		
$\leqslant$ 5	99	(10.4)
5–10	291	(30.5)
10–15	344	(36.1)
15–20	129	(13.5)
$\geqslant$ 20	90	(9.4)
Histotype		
Invasive Ductal	711	(74.6)
Invasive Lobular	101	(10.6)
Invasive Cribriform	63	(6.6)
Invasive Tubular	21	(2.2)
Invasive Mucinous	20	(2.1)
Other	37	(3.9)
Oestrogen receptor status		
Positive	818	(85.8)
Negative	109	(11.4)
Unknown	26	(2.7)
PR		
Positive	689	(72.3)
Negative	214	(22.5)
Unknown	50	(5.2)
Proliferative rate (Ki-67)		
<20%	605	(63.5)
$\geqslant$ 20%	337	(35.4)
Unknown	11	(1.2)
Tumour grade		
I	308	(32.3)
II	422	(44.3)
III	172	(18.0)
Unknown	51	(5.4)
Peritumoral vascular invasion		
Yes	73	(7.7)
No	699	(73.3)
Unknown	181	(19.0)

PR, progesterone receptor.

2.2. The sentinel node biopsy technique

The procedure applied to all our patients was that in use at our Institute since 1996 [5]. The afternoon before surgery, 5–10 MBq of technetium-99-labelled human colloid particles (Albures, Sorin Biomedica, Italy) in 0.2 ml saline were injected in the subdermis above the tumour or in the tissue immediately surrounding it when located deeply in the breast. In cases where a previous biopsy was performed, we injected the radiotracer in the initially affected area of the breast using the diagnostic images and data from the previous surgery. Mammary and axillary planar scintigraphic scans, anterior and anterior-oblique, were taken 30 min after the injection of the radiotracer. If no nodes were visualised, a further scan was taken 3 h later. Very rarely, a second injection was needed to identify the sentinel node [6]. The skin above the first radioactive node was marked to assist the surgeon. A small incision of 1.5–2 cm was sufficient to explore the axilla with the probe which in the proximity of the sentinel node gives out a recognisable acoustic signal. The sentinel node was usually found lying deep along the lateral margin of the *pectoralis minor*. In the most recent years, removal of the sentinel node was often obtained through the same incision made in the breast for the removal of the primary carcinoma.

2.3. Treatment of the primary carcinoma

Most patients (942, 98.8%) were treated with breast conservative surgery (with wide resection or

quadrantectomy) followed by external-beam radiotherapy on the whole breast through two tangential fields (50 plus 10 Gy as a boost to the tumour bed) with a linear accelerator. No radiotherapy was delivered to the axilla and no post-operative radiotherapy was administered to the chest wall in cases treated with total mastectomy. Adjuvant treatments were applied according to the protocols in use at the European Institute of Oncology at the time of primary treatment (Table 2) [7].

2.4. Pathology

After the first 73 cases of this series, which were examined with the traditional 2–4 frozen sections during the operation leaving the remaining tissue for examination of permanent sections, all other cases were submitted to an innovative type of pathological examination [8]. The new procedure consists of the careful complete examination of the sentinel node intraoperatively, without any portion of nodal tissue left for fixative and paraffin-embedding. In other words, the frozen section examination is a complete and final one. Surgeons requested that pathologists perform this procedure when they were concerned by the need to resubmit women to a second operation (axillary dissection) in the not infrequent cases that had a negative frozen-section histology intraoperatively and a positive one at the final histology. To obtain this objective, the pathological examination consisted of some 60 sections (30 pairs), cut at 50 μm intervals. Whenever residual tissue was left, additional pairs of sections were cut at 100 μm intervals until the node was completely examined. One section of each pair was routinely stained with haematoxylin and eosin (H&E). If results were doubtful, the mirror sections were immunostained for cytokeratin, using a rapid method with mono clonal anti-cytokeratin antibody (DAKO, Copenhagen, Denmark) [5,8–10].

2.5. Follow-up

All patient were examined in the Outpatient Department of the European Institute of Oncology at 4 monthly intervals for 3 years and then at 6 monthly intervals. At every examination, special attention was paid to the axilla which were examined by a careful palpation and explored with ultrasounds whenever this was deemed necessary.

The median follow-up of the patients was 38 months. A total of 3129 person-years at risk were accumulated.

Table 2
Adjuvant treatments ($n = 953$)

Adjuvant treatment	Frequency	(%)
Chemotherapy	87	(9.1)
Hormonotherapy	637	(66.8)
Chemo + Hormonotherapy	105	(11.0)
No adjuvant treatment	124	(13.0)
Total	953	(100.0)

3. Statistics

The main study endpoint was the evaluation of the risk of developing axillary metastasis during follow-up. Time to occurrence of this unfavourable event, as well as ipsilateral or contralateral breast tumour recurrence, distant metastasis and second primary, whichever occurred first, was computed from the date of surgery. In the absence of any of the above events, observation times were censored at the date of the last follow-up assessment. Crude cumulative incidence over time of axillary metastasis and other unfavourable events was estimated within a competing-risk framework [11]. Overall survival was defined as the time elapsing from surgery to death from any cause, or the last follow-up assessment available for patients who were still alive. The survival curve for the whole series was obtained using the Kaplan–Meier method [12].

In a previous study, the rate of positive non-sentinel axillary lymph nodes among patients with negative sentinel lymph node was approximately 6% [13]. Under the assumptions that all positive nodes would become clinically-evident and would occur at a constant rate over a 15 year time interval, we computed the expected number of events taking into account person-years at risk in our series. We then compared the observed number of axillary occurrences with the expected number using a Poisson distribution. Being dependent on assumptions that cannot be tested on the available data, such an analysis is exploratory. However, we note that 15 years is a time interval over which most breast cancer recurrences are likely to occur, either at a stable rate in cases of local recurrence, or at a rate that is higher in the first years after surgery and then decreases in cases of distant metastasis [14]. It is impossible to judge which of the two situations applies to axillary metastases. Therefore, for the sake of simplicity and to simulate a "worst case" scenario, we assumed a constant rate.

4. Results

The average time for the procedure to be completed was 12 min, with a range from 6 to 32 min. The time needed to have the final answer from the pathology department, which is generally short in cases of macrometastases, ranged from 12 to 65 min (average 35 min). This time was utilised by the surgeons to complete the remodelling of the breast after the breast resection and to close the wounds.

The local morbidity following the sentinel node biopsy was very low (2%). In three cases, local haematoma of limited extent was observed, which resolved in a few weeks. Seroma occured in five cases and local infection in seven. In six cases, a limited anaesthesia was found in the inner aspect of the ipsilateral arm, in its upper portion, likely due to damage to an intercostobrachial nerve.

During the follow-up, 55 unfavourable events occurred among the 953 patients; details on the specific events are shown in Table 3, and corresponding incidence curves are plotted in Fig. 1. Three cases of overt axillary metastasis were found in 3 women 26, 37 and 29 months from the operation respectively.

The first patient had received mastectomy with sentinel node biopsy at the time of first operation. She had been affected by a 3 cm ductal invasive carcinoma Grade 1 that was oestrogen- and progesterone- positive. Two sentinel lymph nodes had been negative. The adjuvant therapy was tamoxifen. This patient developed axillary relapse 30 months after surgery.

The second patient had been initially treated in another Institution with a partial breast excision for invasive carcinoma and had subsequently received at the European Institute of Oncology an extended resection of the breast and sentinel node biopsy (one sentinel node). The final histology was a 1.3 cm ductal invasive carcinoma that was oestrogen- and progesterone- positive. The adjuvant treatment was radiotherapy to the breast. Twenty six months later, she developed axillary relapse and metastasis to one vertebra.

The last patient had received quadrantectomy with sentinel node biopsy (5 sentinel nodes) at our Institute for a 1.2 cm ductal invasive carcinoma that was oestrogen- and progesterone- positive. The adjuvant therapy was cyclophosphamide, methotrexate and 5-fluorouracil (CMF)×6 cycles, radiotherapy to the breast and tamoxifen. 38 months after surgery, she developed axillary metastases.

In these three cases, a total axillary dissection was performed with removal of all axillary lymph nodes of the three levels.

We revised the lymphoscintigrams of the 3 patients, and the sentinel nodes were correctly visualised in all cases. The second patient had received breast biopsy in another Institution before surgery at the European Institute of Oncology. During the sentinel node biopsy in the third patient, the surgeon found a widespread captation of the radiotracer in some axillary nodes: he removed five captating lymph nodes which were classified as sentinel nodes.

The estimated crude cumulative incidence of axillary metastasis (±standard error of the mean (SEM)) was very low, being equal to $0.43 \pm 0.26\%$. The observed number of events (three) was significantly smaller than the number of events expected under the assumptions described in Section 2, namely 12.9 ($P = 0.011$). The plot in Fig. 2 shows graphically the divergence between observed and predicted axillary metastases over time. It must be noted that the apparent flattening of the curve describing the expected number of events towards the fifth year of follow-up does not depend on a decreasing hazard of occurrence of axillary metastases, which was assumed to be constant in the calculation, but rather is due to the progressive reduction of patients at risk.

Table 3
Unfavourable events ($n = 953$)

Event	# Events	5-year cumulative incidence(%)	SEM
Local recurrence	12	1.57	0.46
Contralateral BC	5	0.66	0.30
Axillary metastasis	3	0.43	0.26
Distant metastasis	22	3.67	1.02
New primary	13	1.46	0.41

#, number; SEM, standard error of the mean; BC, breast cancer.

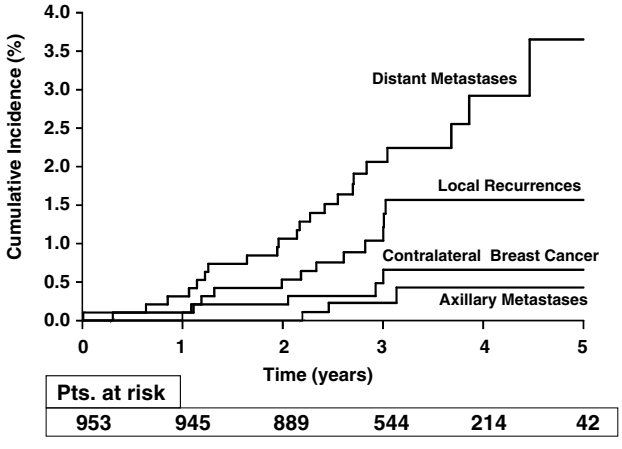

Fig. 1. Cumulative incidence of unfavourable events. Pts, patients.

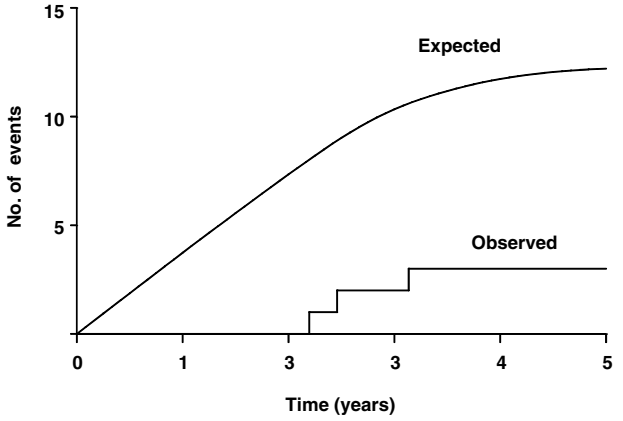

Fig. 2. Number of observed and expected axillary metastases over time.

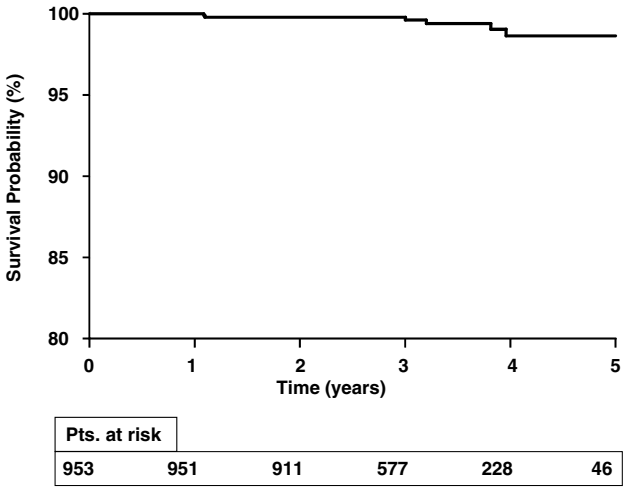

Fig. 3. Overall survival.

Considering other unfavourable events, there were 12 local recurrences in the ipsilateral breast, all of them treated by surgery, five cases of contralateral primary carcinoma and two cases of supraclavicular metastases. Twenty cases (2%) developed distant metastases, mainly osseous (seven cases) and 13 cases had new primary tumours in different organs.

The overall survival curve for the whole series is plotted in Fig. 3. There were 6 deaths, 5 due to metastatic breast carcinoma and 1 from intercurrent diseases, and the 5-year mortality estimate ($\pm$SEM) was $1.4 \pm 0.6\%$.

5. Discussion

Data from this series of 953 patients, treated with surgery and radiotherapy without axillary dissection because of sentinel node negativity, show first of all excellent results in terms of disease control and overall survival (Figs. 1 and 2). The very low rate of distant metastases (3.7%) may suggest that the maintenance of healthy immunological tissue may be beneficial [15].

The most interesting observation was the extremely low rate of overt ipsilateral axillary metastasis (three cases – 0.3%) compared with the expected one (13 cases). There may be several explanations. Post-operative radiotherapy to the breast may reach the lower part of the axilla and a few lymph nodes of the first axillary level may be irradiated and sterilised. However, the irradiation fields of our radiotherapy technique are carefully designed to avoid irradiation of the axilla and we believe that the possible effects of radiation to the axillary nodes are minimal. Our series was composed of early cases (average size 1.2 cm) with good prognoses, the occult axillary involvement is therefore likely to minimal and the development of overt metastasis may take longer than our follow-up time. Moreover, most of our cases had adjuvant treatment, mainly tamoxifen, which may delay the clinical appearance of metastasis. However, this reasoning contrasts with the appearance of distant metastases in 20 cases (22 if we consider the two cases of supraclavicular nodes metastases). Finally, it is possible that a number of occult metastases may never become clinically-evident. This hypothesis was proposed following the reporting of the 5 years results from a previous trial on 435 patients with breast carcinoma less than 1.2 cm in size that were surgically treated without axillary dissection. This study showed that the rate of axillary overt metastases was much smaller than the expected rate [16].

One of the greatest advantages of sentinel node biopsy is the nearly total absence of local post-operative complications as documented in our present report and in other studies [17]. By contrast, total axillary dissection is associated with significant post-operative pain and limitations in arm motion are common. Chronic arm lymphoedema, the most debilitating sequelae of total axillary dissection, has never been observed after sentinel node biopsy [18]. Apart from the improved quality of life, another advantage of sentinel node biopsy is its lower costs because of the reduced operative time involved and the possibility of performing the operation on an outpatient basis under local anaesthesia, without axillary drainage [19].

Data from our study give support to the development of the sentinel node procedure. This procedure which was initially successfully introduced by Donald Morton and colleagues [20] in melanoma patients, was applied first by Krag and colleagues [21] and Giuliano and colleagues [18] in breast cancer patients. The validity of the sentinel node biopsy for staging breast cancer has been subsequently confirmed by many clinical investigations, with an accuracy in predicting the involvement of the axillary nodes of 93–100% [4].

One of the problems of the sentinel node biopsy is the often unreliable results of the ordinary frozen section histology so that in 15–20% of cases [5,8] a second operation is required. To solve this problem, there are two solutions. The first is to have a complete examination of the sentinel node intraoperatively with a technique extensively in use at the European Institute of Oncology [8], consisting of a large series of sections at 50 μm intervals, so that all of the node is definitively examined without the risk that micrometastasis may escape the examination. This method is time-consuming and expensive, but the avoidance of a second operation in some 20% of the cases largely compensates for these extra costs. The second solution is to perform the sentinel node biopsy under local anaesthesia on an outpatient basis a few days before the final surgery. If the sentinel node is negative,

surgery will be limited to breast resection, again on an outpatient basis, or to mastectomy; if the sentinel node proves positive, the final surgery will include total axillary dissection [1].

Although the low rate of false-negative patients will lead to a moderate understaging of the patient, careful examination of the sentinel node leads to a considerable upstaging compared with routine axillary examination. In fact, in our seven cases undergoing sentinel node biopsy,we have a rate of positive axillas of 35% [8] compared with the usual 27% of series undergoing routine axillary histology [22].

The susbstantial increase in the number of cases with micrometastasis discovered using the newly introduced complete multi-section examination of the sentinel node results in two new problems. The first is the real need to perform a complete axillary dissection in these cases. To address this question, a randomised trial is currently in progress. The second is the need for adjuvant chemotherapy as many medical oncologists apply this therapy on the grounds that these patients automatically become stage II patients. However, there is evidence that a micrometastasis in a single axillary node is compatible with an excellent prognosis [23,24].

In conclusion, the present study dissipates fears that the axillary sentinel node biopsy policy would result in a high rate of overt axillary metastases during follow-up, with all of the associated problems. On the contrary, our study confirms the conclusions of our recently published randomised trial [25] suggesting that sentinel node biopsy should become a routine procedure in all centres dealing with breast cancer management. Certainly, a routine sentinel node programme needs a high level of competence and a sufficient training programme among members of the Surgical Department, of the Nuclear Medicine Department, and of the Pathological Department. This recommendation is in-line with the conclusions of the consensus meeting of investigators held in Philadelphia in 2001 [4], which were in favour of an extensive implementation of the sentinel node procedure worldwide.

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