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Axillary metastases in breast cancer patients with negative sentinel nodes: A follow-up of 3548 cases

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ABSTRACT

Premises: Sentinel node biopsy (SNB) in patients with breast carcinoma accurately predicts the axillary node status. However, in some 4–7% of patients with negative sentinel nodes, the remaining axillary nodes harbour cancer cells.
Objective: Our purpose was the long-term observation of a large number of patients who did not receive axillary dissection after a negative sentinel node biopsy, in order to evaluate the incidence of overt axillary metastases.
Methods: Patients (3548) treated from 1996 to 2004, with negative sentinel nodes not submitted to axillary dissection, were followed up to 11 years with a median follow-up of 48 months.
Results: Three hundred and sixteen unfavourable events occurred among the 3548 patients, 196 of which (5.5%) related to primary breast carcinoma. Thirty one cases of overt axillary metastases were found (0.9%): they received total axillary dissection and 27 of them are at present alive and well. The 5-year overall survival rate of the whole series was 98%.
Conclusions: Patients with negative sentinel node biopsy not submitted to axillary dissection show, at follow-up, a rate of overt axillary metastases lower than expected.

1. Introduction

Sentinel node biopsy (SNB) in patients with carcinoma of the breast predicts the status of axillary nodes. All the validation studies,[1–3] and the few published randomised trials,[4–7] showed favourable data as regards the improved quality of life of patients, shorter hospital stay and the overall accuracy of the patient's management. The European Institute of Oncology (EIO) randomised trial showed an 8 years survival which was somewhat better, even if statistically non-significant, of

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the group of patients submitted to sentinel node biopsy compared to the group where all patients received immediate axillary dissection.

However, it is a common observation that in a limited percentage of cases SNB fails to correctly identify the presence of axillary involvement.[3,4,8,9] In our original validation study, although the identification rate was very high (98.7%), there were 12 false negative cases which represented 6.7% of the 180 patients with axillary lymph node metastases.[9] In our randomised trial, the rate of false negative in the arm which received SNB and simultaneous total axillary dissection was of the same order (8 cases out of 91 positive axillary nodes – 8.8%).[4,8]

We can therefore realistically conclude that breast cancer patients who have a negative biopsy at the sentinel node may harbour cancer cells in the remaining axillary nodes in some 4–9% of cases. For this reason patients with negative sentinel node biopsy are generally requested to undergo a regular strict follow-up with a periodic clinical and ultrasound examination of the axilla.

The obvious risk, which was largely debated at the beginning of the sentinel node biopsy studies, is that the cancer cells which may be present in the axilla may develop into gross axillary metastases which may escape the attention of the surgeon and become difficult to treat. The second aspect of the false negative SNB is the under-staging of the patients who will be classified stage I while they are biologically stage II, therefore missing the adjuvant treatments which might be appropriate.

It is therefore imperative to ensure a careful follow-up of large series of patients whose sentinel biopsy shows absence of metastases in order to evaluate the long-term outcome.

In the present study, we report the follow-up of 3548 patients submitted to sentinel node biopsy at the EIO with negative histology and who were therefore not submitted to axillary dissection.

2. Patients and methods

2.1. Patient characteristics

From 1996 to 2004, 5622 patients with invasive breast cancer and clinically negative axilla referred to the European Institute of Oncology underwent the sentinel node biopsy after our standard lymphoscintigraphic procedure.[10] Patients (376) were treated with SNB and simultaneous axillary dissection within a validation study,[9] and 516 were treated within a randomised controlled study conducted in the years 1998 and 1999.[8] Among the remaining 4730 cases, 1182 showed a positive sentinel node and were submitted to axillary dissection, while 3548 had a negative sentinel node biopsy and no axillary dissection was performed. The latter patients are the object of the present study. The characteristics of the patients are summarised in Table 1. Patients' ages ranged from 21 to 86 years (mean 55 years). The average size of the primary carcinoma was 1.4 cm, without differences in the 8 years of accrual.

The most common histological type was ductal carcinoma (2700 patients, 76.1%). Lobular carcinomas were observed in 362 patients (10.2%), mixed ductal and lobular carcinomas in 113 patients (3.2%), while 373 patients (10.5%) had different types of carcinoma, mainly well-differentiated forms (cribriform, tubular, mucinous and papillary).

2.2. The sentinel node biopsy technique

The procedure applied to all our patients was that employed at our Institute since 1995.[3] The afternoon before surgery, 5–10 MBq of technetium-99-labelled human colloid particles (Nanocol GE Healthcare, Italy) in 0.2 ml saline was 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 above the tumour or periareolar was needed to identify the sentinel node.[11] 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 emits a recognisable acoustic signal. The sentinel node was usually found lying deep along the lateral margin of the pectoralis minor. In 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. No double tracer technique with blue dye was used since lymphoscintigraphy was able to identify the sentinel node(s) in more than 99% of our series.

The average time for the surgical procedure to be completed was 12 min, with a range from 6 to 32 min. The time needed to obtain the final report from the pathology department, ranged from 12 to 65 min (average 35 min) being short in cases of macro-metastases. This time was utilised by the surgeons either to complete the remodelling of the mammary gland after the breast resection or to deliver intraoperative radiotherapy.

In 1916 patients, one sentinel node was identified and removed, in 1039 cases two sentinel nodes and in 380 cases three nodes were removed. The remaining 213 patients had more than three sentinel nodes identified and removed.

2.3. Treatment of the primary carcinoma

Most patients (3319, 93.5%) 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 (2625 cases) or by intraoperative radiotherapy (ELIOT) with a single dose of 21 Gy (646 cases).[12] 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 1).

Table 1 – Characteristics and treatment in 3548 patients with negative sentinel node biopsy.

Characteristics	N	(%)
All patients	3548	(100)
Year of intervention		
1996	3	(0.1)
1997	21	(0.6)
1998	109	(3.1)
1999	239	(6.7)
2000	453	(12.8)
2001	517	(14.6)
2002	662	(18.7)
2003	664	(18.7)
2004	880	(24.8)
Age group		
<35	110	(3.1)
35–49	1099	(31.0)
50–59	1127	(31.8)
60–69	865	(24.4)
70+	347	(9.8)
Tumour size		
<0.5 cm	341	(9.6)
0.5–1 cm	927	(26.1)
1–1.5 cm	1119	(31.5)
1.5–2 cm	548	(15.5)
>2 cm	556	(15.7)
Not determined	57	(1.6)
pT		
pT1	2973	(83.8)
pT2	549	(15.5)
pT3/4	19	(0.5)
Unknown	7	(0.2)
Multifocal/multicentric		
No	3292	(92.8)
Yes	249	(7.0)
Unknown	7	(0.2)
Tumour grade		
G1	1024	(28.9)
G2	1567	(44.2)
G3	828	(23.3)
Unknown	129	(3.6)
Sentinel nodes removed		
1	1916	(54.0)
2	1039	(29.3)
⩾3	593	(16.7)
Histological type		
Ductal	2700	(76.1)
Lobular	362	(10.2)
Ductal + lobular	113	(3.2)
Cribriform	155	(4.4)
Tubular	52	(1.5)
Tubular + lobular	21	(0.6)
Mucinous	86	(2.4)
Other	59	(1.7)
Proliferative fraction (Ki67)		
<20%	2069	(58.3)
⩾20%	1447	(40.8)
Unknown	32	(0.9)
ER/PgR		
Both absent	488	(13.8)
ER absent/PgR present	13	(0.4)
ER present/PgR absent	472	(13.3)
Both present	2552	(71.9)
Unknown	23	(0.6)
PVI		
Absent	3198	(90.1)
Present	328	(9.2)
Unknown	22	(0.6)
Type of surgery		
Total mastectomy	229	(6.5)
Breast conserving surgery	3319	(93.5)
Radiotherapy		
None	221	(6.2)
External RT	2625	(74.0)
ELIOT	646	(18.2)
Unknown	56	(1.6)
Adjuvant systemic treatments		
None	223	(6.3)
Endocrine alone	2595	(73.1)
Chemotherapy alone	388	(10.9)
Chemotherapy + endocrine	286	(8.1)
Unknown	56	(1.6)

2.4. Pathology

The first 73 cases of this series were examined with the traditional 2–4 frozen sections during the operation leaving the remaining tissue for examination of permanent sections, and 114 patients underwent SNB under local anaesthesia in the outpatient clinic a few days before the final surgery, with the sentinel lymph node was also examined on permanent sections. The great majority of cases 3361 were submitted to an innovative type of intraoperative pathological examination.[13] The new procedure consists of the complete examination of the sentinel node intraoperatively, without any portion of nodal tissue left for fixation 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 patients that had a negative intraoperative diagnosis and a positive one at the final histological assessment. To obtain this objective, the pathological examination consists of some 60 sections (30 pairs), cut at 50 μm intervals. Whenever residual tissue is left, additional pairs of sections are cut at 100 μm intervals until the node is completely examined. One section of each pair is routinely stained with haematoxylin and eosin (H&E). If results are doubtful, the mirror sections are immunostained for cytokeratin, using a rapid method with monoclonal anti-cytokeratin antibody (DAKO, Copenhagen, Denmark).[3,13–15]

2.5. Follow-up

All patients were examined in the Outpatient Department of the European Institute of Oncology at 6-month intervals. At

every examination, special attention was paid to the axilla which was examined by careful palpation and explored with ultrasound whenever deemed necessary.

The median follow-up of the patients was 48 months. A total of 14,495 person-years at risk were accumulated.

2.6. Statistical methods

The main study end-point was the evaluation of the risk of developing axillary metastasis, as a first event, during follow-up. Cumulative incidence of axillary metastasis was calculated from the date of surgery until the date of any first event (local relapse, ipsilateral or contralateral breast tumour recurrence, distant metastases and second primary) or the date of last follow-up visit, whichever occurred first. We also evaluated overall survival (OS) calculated from the date of surgery until the date of death (from any cause) or the date of last contact. Overall survival plot was drawn using the Kaplan–Meier method,[16] while the cumulative incidence curve of axillary metastases was corrected for competing-risk.[17] Univariate and multivariate Cox proportional hazard regression analysis were used to assess the prognostic significance of various clinical and histopathological characteristics of the tumour on the development of axillary metastasis and on overall survival. Factors in multiple regression analyses included: age, tumour size, multifocality or multicentricity, tumour grade, proliferative index, hormone receptors status, PVI and treatment. In previous studies, the rate of positive non-sentinel axillary lymph nodes among patients with negative sentinel lymph node was approximately 6%.[13] Under the assumption that all non-sentinel positive nodes would become clinically evident and would occur at a constant rate over a 12-year-time interval, we computed the expected number of events taking into account person-years at risk in our series. All analyses were performed with the SAS software version 8.02 (Cary, NC). All *p*-values were two-sided.

3. Results

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

During a median follow-up of 48 months, 316 unfavourable events occurred among the 3548 patients (the 5-year cumulative incidence was 10.1% (95% confidence interval (CI) 8.9–11.3%) (Fig. 1); details on the specific events are shown in Table 2. Thirty one cases of overt axillary metastasis were found, 2–86 months from the operation (median 29 months) (Fig. 2). In all these cases, a total axillary dissection was performed with removal of all axillary lymph nodes of the three levels. The average number of removed nodes in the axilla was 25 (12–47).

The 31 cases were all carefully reviewed. The revision of the lymphoscintigrams revealed that in 15 cases only one node was visualised and removed, while in 11 cases two lymph nodes were 'hot' and equally removed. The remaining five cases had 3, 4 and 5 nodes uptaking the radiotracer and were all removed.

The 15 cases (48.4%) with one node removed had an average time interval of 38 months from primary surgery and clinical appearance of axillary metastases. The 11 cases with two nodes removed showed an average interval of 29 months, and the remaining five cases had an average interval of 15 months. As regards the number of involved axillary nodes, 18 cases had a limited axillary involvement (one to three lymph nodes with metastases) while 13 cases had four or more nodes involved.

The histology of the primary carcinoma of the 31 cases who developed axillary metastasis was ductal carcinoma in 29 patients, mixed ductal and lobular in one patient and lobular carcinoma in one patient. The average tumour size was 1.5 cm in diameter, eight cases being larger than 2 cm. Twelve cases were classified G3, 14 cases were G2 and 5 were G1. The proliferative index, measured with the Ki67 test, was lower than 20% in 7 cases, between 21% and 40% in 19 cases and more than 40% in 5 cases. Oestrogen receptors were strongly positive in 24 cases, were negative in 7 cases. In two cases there was an extensive peritumoral vascular invasion, in five cases a focal invasion and in 24 no peritumoral vascular invasion was found. After primary surgery, 19 cases had received adjuvant endocrine treatment (tamoxifen or AI with or without ovarian suppression), eight cases had received chemotherapy, two cases both chemo- and endocrine therapy while two cases had no systemic treatments.

A comparison between the characteristics of the primary carcinomas of the whole series of 3548 patients and of the series of the 31 patients who developed axillary metastases shows in univariate analysis that development of axillary metastasis was significantly associated with multi-centricity/focality, with tumour grade, proliferative fraction and peritumoural vascular invasion. In multivariate analysis adjusted

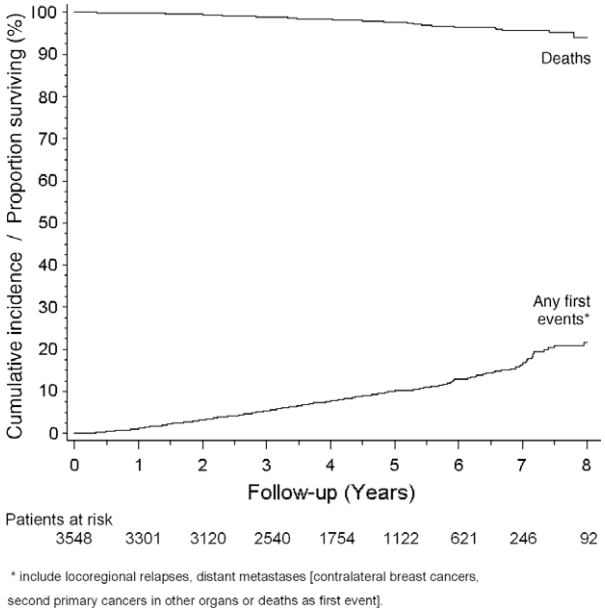

Fig. 1 – Cumulative incidence of unfavourable events and overall survival of 3548 patients with SN negative breast cancer.

Table 2 – Unfavourable events.

Events	N	Rate/1000 patient-year	Subsequent death
Any first event	316	21.8	–
Local relapse/ipsilateral breast cancer	76[a]	5.24	8 (10.5%)
Axillary metastasis	31	2.13	4 (12.9%)
Distant metastasis	91[a]	6.28	33 (36.3%)
Contralateral breast cancer	34	2.35	1 (2.9%)
Other primary cancer	66	4.55	17 (25.8%)
Death as first event	20	1.38	–
Death (overall)	82	5.15	–
Death due to breast cancer	43	2.70	–
Death due to other cancer	16	1.00	–
Death due to other cause	15	0.94	–
Death from unknown cause	8	0.50	–

a Two patients with simultaneous local relapse and distant metastasis.

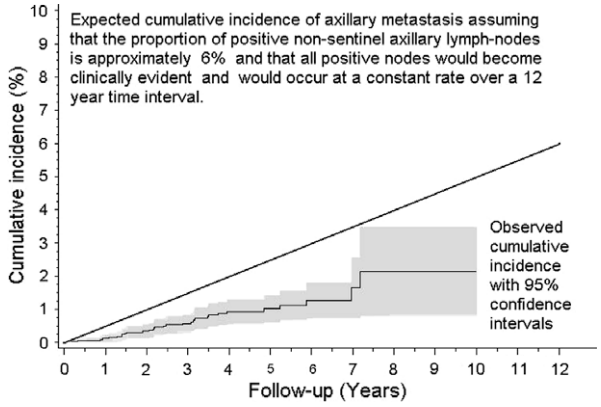

Fig. 2 – Development of axillary metastasis ($n = 31$) in 3548 women with sentinel node(s) negative breast cancer.

for all other tumour characteristics, multi-centricity/focality, proliferative fraction (Ki67) and peritumoural vascular invasion were independent predictors of axillary metastasis (Table 3).

The 31 cases were accurately followed up after the axillary dissection. Five cases developed distant metastases and four of them died one to four years after the dissection. The four patients who died had, respectively, 3, 4, 7 and 14 positive axillary nodes at the dissection. The four deaths reported among the 31 cases who developed axillary metastases represent 0.11% of the 3548 patients and only a minority of the 43 patients who died from the disease out of all series.

The cumulative incidence of axillary metastasis at 5 years was 1.0% (95% CI 0.6–1.4%), significantly lower than that expected under the assumption that approximately 6% of non-sentinel axillary lymph nodes would be positive and would become clinically evident occurring at a constant rate over a 12-year-time interval (Fig. 2). During 14,495 patient-years of follow-up, 31 women developed axillary metastasis against 72 expected ($p < 0.01$).

As regards other unfavourable events, there were 76 local recurrences or second cancers in the ipsilateral breast, all of them treated by surgery and 34 cases of contralateral primary carcinoma. Ninety one women (2.5%) developed distant metastases and 66 had new primary tumours in different organs (Table 2).

The overall survival curve for the whole series is plotted in Fig. 1. There were 82 deaths, 43 due to metastatic breast carcinoma, 16 due to cancer at other sites, 15 due to other causes, while for 8 patients the cause of death is unknown. The 5-year overall survival was 97.6% (95% CI 97.0–98.2%). In multivariate analysis, older age (70 years or more), larger tumours (>2 cm), high grade (G3) and presence of vascular invasion were associated with less good survival, while patients eligible to endocrine therapy alone had better overall survival (Table 3).

4. Discussion

Data from this series of 3548 patients, treated with surgery and radiotherapy without axillary dissection because of sentinel node negativity, show excellent results in terms of disease control and overall survival (Figs. 1 and 2). The very low rate of distant metastases (6.28/1000 patient-year) could suggest that the maintenance of healthy nodal tissue may be beneficial.[18]

A most interesting observation was the low rate of overt ipsilateral axillary metastasis (31 cases – 2.13/1000 patient-year) compared with the expected rate (72 cases – 5/1000 patient-year or 6% in a 12-year period). There may be several explanations. First as our series was composed of early cases (average size 1.4 cm), the occult axillary involvement is likely to be minimal, and the development of overt metastasis may take longer than our follow-up time. Moreover, most of our cases had adjuvant treatment, mainly endocrine, which may delay or avoid the clinical appearance of metastasis. A second explanation refers to a possible sterilisation by radiotherapy. In fact, 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. Finally, we cannot exclude that a number of occult metastases may never become clinically evident. This hypothesis was proposed following the reporting of the long-term results from a previous trial on 435 patients with breast carcinomas less than 1.2 cm in size that were surgically treated without axillary dissection. This study showed

Table 3 – Patient and tumour characteristics associated with the development of axillary metastasis and death.

Characteristics*	ALL patients	Axillary metastasis				Death			
		Events	Rate/1000 women-years	Univariate HR (95% CI)	Multivariate HR (95% CI)	Deaths	Rate/1000 women-years	Univariate HR (95% CI)	Multivariate HR (95% CI)
	3548	31	2.14			82	5.15		
Age group									
<35	110	2	4.78	1.67 (0.38–7.42)	1.11 (0.23–5.31)	7	13.97	**3.43 (1.45–8.11)**	2.05 (0.85–4.94)
35–49	1099	13	2.87	1.00	1.00	20	4.06	1.00	1.00
50–59	1127	7	1.49	0.52 (0.21–1.29)	0.61 (0.24–1.57)	16	3.10	0.75 (0.39–1.46)	0.92 (0.47–1.80)
60–69	865	7	1.95	0.68 (0.27–1.70)	0.83 (0.32–2.15)	17	4.39	1.10 (0.58–2.10)	1.54 (0.79–3.03)
70+	347	2	1.56	0.55 (0.13–2.45)	0.44 (0.09–2.29)	22	14.96	**3.72 (2.03–6.82)**	**4.19 (2.10–8.36)**
Tumour size									
<1 cm	1268	9	1.47	1.00	1.00	18	3.06	1.00	1.00
1–1.5 cm	1119	10	2.10	1.28 (0.52–3.14)	0.98 (0.39–2.49)	19	3.63	1.20 (0.63–2.29)	0.93 (0.48–1.83)
1.5–2 cm	548	4	1.85	1.13 (0.35–3.68)	0.55 (0.16–1.86)	19	7.83	**2.65 (1.39–5.05)**	1.58 (0.79–3.17)
>2 cm	556	8	4.13	2.56 (0.98–6.66)	1.31 (0.47–3.69)	25	11.58	**4.42 (2.40–8.14)**	**2.09 (1.06–4.13)**
Multifocal/multicentric									
No	3292	25	1.83	1.00	1.00	79	5.25	1.00	1.00
Yes	249	6	7.50	**4.35 (1.76–10.8)**	**4.25 (1.60–11.3)**	3	3.43	0.80 (0.25–2.56)	0.89 (0.27–2.89)
Tumour grade									
G1	1024	5	1.15	1.00	1.00	9	1.91	1.00	1.00
G2	1567	12	1.81	1.58 (0.56–4.47)	0.64 (0.19–2.12)	20	2.78	1.45 (0.66–3.18)	1.02 (0.44–2.36)
G3	828	12	3.95	**3.50 (1.23–9.93)**	0.68 (0.16–2.84)	47	13.54	**7.49 (3.67–15.3)**	**2.80 (1.05–7.48)**
Proliferative fraction Ki67									
<20%	2069	7	0.79	1.00	1.00	24	2.52	1.00	1.00
⩾20%	1447	24	4.34	**5.62 (2.42–13.1)**	**6.24 (2.12–18.4)**	57	9.11	**3.81 (2.36–6.15)**	1.28 (0.65–2.52)
ER/PgR									
Both absent	488	7	3.95	2.01 (0.85–4.72)	0.23 (0.04–1.31)	30	14.64	**4.40 (2.74–7.07)**	1.39 (0.58–3.33)
ER absent/PgR present	13	–	–	–	–	–	–	–	–
ER present/PgR absent	472	3	1.53	0.77 (0.23–2.59)	0.78 (0.21–2.83)	11	5.05	1.44 (0.74–2.80)	1.18 (0.59–2.36)
Both present	2552	21	1.99	1.00	1.00	40	3.48	1.00	1.00
PVI									
Absent	3198	24	1.83	1.00	1.00	61	4.23	1.00	1.00
Present	328	7	5.44	**3.00 (1.29–6.97)**	**2.71 (1.10–6.65)**	20	14.05	**3.42 (2.07–5.67)**	**3.26 (1.89–5.61)**
Treatment									
Total mastectomy	229	4	5.26	2.74 (0.95–7.93)	1.46 (0.45–4.68)	1	1.20	0.27 (0.04–1.96)	0.20 (0.03–1.45)
BCS without RT	62	1	4.37	2.37 (0.32–17.6)	4.18 (0.44–40.0)	5	16.61	**2.97 (1.19–7.38)**	1.37 (0.50–3.77)
BCS with external RT	2615	21	1.85	1.00	1.00	65	5.24	1.00	1.00
BCS with ELIOT	587	5	2.36	1.31 (0.53–3.23)	1.63 (0.65–4.13)	10	4.29	0.92 (0.47–1.79)	0.89 (0.44–1.79)
Adjuvant systemic treatments									
None	223	2	2.01	1.00	1.00	12	10.66	1.00	1.00
Endocrine alone	2595	19	1.77	0.89 (0.21–3.81)	0.56 (0.12–2.63)	32	2.75	**0.29 (0.15–0.56)**	**0.37 (0.17–0.83)**
Chemotherapy alone	388	8	5.49	2.78 (0.59–13.1)	2.93 (0.39–22.3)	22	13.37	1.45 (0.71–2.95)	0.60 (0.25–1.44)
Chemotherapy + endocrine	286	2	1.61	0.79 (0.11–5.61)	0.20 (0.02–1.69)	13	9.02	0.84 (0.38–1.84)	0.58 (0.23–1.51)

Hazards ratio (HR) and 95% Confidence intervals (CI) obtained from univariate and multivariate Cox proportional hazards regression models.
PVI: peritumoural vascular invasion; ER: oestrogen receptor; PgR: progesteron receptor; BCS: breast conserving surgery; ELIOT: Intraoperative electron beam radiotherapy; and RT: radiotherapy.
* Some information is missing for some patients.

at 10 years follow-up that the rate of axillary overt metastases was much lower than expected.[19]

The question we may ask ourselves is whether the appearance of axillary metastases due to the false negative axillary evaluation by the sentinel node biopsy may tarnish the value of the sentinel node concept.

Certainly the false negative sentinel node cases will lead to a moderate under-staging of the patients, but on the other hand the careful complete examination of the sentinel node by the pathologists leads to a considerable upstaging compared with routine axillary histological examination. In fact, in our cases undergoing sentinel node biopsy, we have a rate of positive axillas of 35%[13] compared with the usual 27% of series undergoing routine axillary histology.[20] The most important answer concerning the value of SNB procedure lies in the results of our randomised trial which, at ten years from its start, shows that patients who underwent a selected axillary dissection (only if the sentinel node was positive) had a higher survival than patients treated with unselected total axillary dissection.

The present study shows that the rate of axillary metastases appearing in cases with negative sentinel node biopsy is low (31/3548 cases – 2.13/1000 patient-year) and that the overall survival (97.6%) is very high. This study therefore dissipates fears that the axillary sentinel node biopsy policy would result in worsening the prognosis of breast cancer patients. Our study underlines the great advantages of sentinel node biopsy in terms of quality of life, of absence of arm lymphoedema and of reduced cost due to very short hospital stay. However, centres which practise the sentinel node biopsy must be aware that the routine sentinel node policy requires a high level of competence and a sufficient training programme among members of surgical departments, diagnostic departments, nuclear medicine departments and of the pathological departments. In addition, although axillary metastases in sentinel node negative patients are infrequent, their occurrence must be discovered as soon as possible. We recommend in the follow-up of the patients frequent clinical assessment of the axilla with an extensive use of ultrasound to detect suspicious axillary nodes. This recommendation is in keeping with the conclusions of the consensus meeting of investigators held in Philadelphia in 2001,[21] which were in favour of an extensive implementation of the sentinel node procedure worldwide.

5. Conclusions

Sentinel node biopsy was introduced in the late 1970s[22] as an intelligent solution in cases of cutaneous melanoma after an international randomised study in 1977 had shown that prophylactic node dissection was ineffective.[23] More recently the same procedure was applied to patients with carcinoma of the breast. The technique was validated by many studies which, however, showed a low rate of false negative cases.[8] Many objections were based on the assumption that in cases of false negative sentinel node biopsy, the cancer cells remaining in the axillary nodes might be the source of distant metastases and may create an axillary recurrence which might be inoperable when clinically discovered.[24] These objections lay at the basis of the low implementation of the sentinel node biopsy in many centres worldwide.

Since at the EIO we have been performing SNB in breast cancer from 1995, we reviewed all our cases which, having a negative sentinel node biopsy did not receive axillary dissection, in order to evaluate the rate of recurrence of the disease, in particular at the axilla. The present review of 3548 cases with a follow-up of 4–11 years shows that the rate of unfavourable events is low and the 5-year survival very high (97.6%), while the number of overt axillary metastases is lower than expected. We can confirm the value of sentinel node biopsy in breast carcinoma and suggest, once more, the implementation of the procedure, to all hospitals dealing with breast cancer surgery.

Conflict of interest statement

I and all authors of the manuscript entitled 'Axillary metastases in breast cancer patients with negative sentinel nodes: A follow-up of 3548 cases' have contributed significantly to and share in the responsibility for the release of any part or all of the material contained within the article noted above. All authors stipulated that the material described in this paper is new, original and has not been submitted to another publication for concurrent consideration.

We also attest that any human and/or animal studies undertaken as part of the research from which this manuscript was derived are in compliance with regulations of our institution and with generally accepted guidelines governing such work.

We further attest that we have herein disclosed any and financial or other relationships which could be construed as a conflict of interests and that all sources of financial support for this study have been disclosed and are indicated in the acknowledgement.

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