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Original article

Impact of lymphadenectomy on axillary recurrence and morbidity of the upper limb in breast cancer patients with negative sentinel node. A prospective randomised study☆

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A B S T R A C T

Introduction: To determine the impact of axillary lymphadenectomy on regional recurrence, the overall and disease free survival, and upper limb morbidity in patients with breast cancer and negative sentinel node (SN).

Patients and methods: A total of 176 patients with breast cancer and negative SN ($pN0_{sn}$) were either randomised to lymphadenectomy (Group I) or to observation only (Group II). The triple technique was used to identify and remove the SN. Follow-up was carried out every 3 months for the first 3 years, and then every 6 months up to 5 years. Pain, numbness (paresthesia), limitations in shoulder mobility, and arm oedema were recorded.

Results: No axillary lymph node recurrence was detected in the patients of Group II after 60 months follow up. The overall and disease free survival was similar in both groups. The proportion of patients with morbidity and who had more than two complications was significantly higher in Group I.

Conclusions: Axillary lymphadenectomy may be avoided in patients with negative SN without compromising lymph node extension studies and the patient treatment results. Axillary lymphadenectomy is associated with a higher morbidity of the upper limb compared to SN biopsy.

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Impacto de la linfadenectomía sobre la recurrencia axilar y la morbilidad del miembro superior en pacientes con cáncer de mama y ganglio centinela negativo. Estudio prospectivo aleatorizado

Palabras clave:
Ganglio centinela
Cáncer de mama
Estudio prospectivo
Estadificación ganglionar
Morbilidad
Linfedema
Supervivencia

RESUMEN

Introducción: Determinar el impacto de la linfadenectomía axilar sobre la recurrencia regional, la supervivencia global y libre de enfermedad y la morbilidad del miembro superior en pacientes con cáncer de mama y ganglio centinela (GC) negativo.

Pacientes y métodos: Ciento sesenta y seis pacientes con cáncer de mama y GC negativo ($pN0_{sn}$) fueron aleatorizados a linfadenectomía (Grupo I) o solo observación (Grupo II). Se utilizó una técnica triple para identificar y extirpar el GC. El seguimiento se realizó cada 3 meses durante los 3 primeros años y, posteriormente, cada 6 meses, hasta los 5 años. Se registraron el dolor, entumecimiento (parestesias), la limitación de movilidad del hombro y el edema del brazo.

Resultados: Tras un seguimiento mínimo de 60 meses, no se detectó recurrencia ganglionar axilar en los pacientes del Grupo II. La supervivencia global y la libre de enfermedad fueron similares en ambos grupos. La proporción de pacientes con morbilidad y los que tuvieron más de dos complicaciones fue significativamente mayor en el Grupo I.

Conclusiones: Se puede evitar la linfadenectomía axilar en pacientes con GC negativo sin comprometer el estudio de extensión ganglionar o los resultados del tratamiento. La linfadenectomía axilar se asocia a una más elevada morbilidad de la extremidad superior en comparación a la biopsia del GC.

Introduction

The presence of lymph node metastases in the axilla continues to be the most important prognostic factor in breast cancer (BC).[1,2] The presence or absence of metastases in the axillary nodes is confirmed by anatomopathological analysis of the lymph nodes which have been removed by traditional axillary lymphadenectomy (AL). However, AL is a procedure which entails certain risks. The analysis of various series of BC patients reveals that, in 40%-60% of AL cases there is no evidence of metastasis and, consequently, it might perhaps be considered an unnecessary surgical procedure.[3]

The concept of the sentinel node (SN), described by Morton et al,[4] has been applied to BC patients since 1993.[2,5] Several articles have studied and validated the technical aspects, based on which the majority of investigators identify the SN in over 90% of cases, with false negative rates of about 5%.[6-9] The identification and biopsy of the SN can replace AL as a procedure for evaluating regional extension in BC, as it avoids the morbidity associated with AL and improves lymph node extension assessment.

Some BC centres have conducted clinical trials to evaluate the SN concept, in which AL has not been performed when the SN was not metastasised.[10-13] The great innovation of the SN concept has been the decrease in morbidity which is classically associated with AL, with or without adjuvant radiotherapy: lymphoedema (LO), changes in sensitivity (numbness), pain or discomfort in the arm, and reduced shoulder mobility.[14]

As BC survival rates have improved during recent decades,[15] interest in quality-of-life and morbidity assessment has increased. AL causes morbidity in 25%-40% of patients,[16,17] LO being the most worrying complication. The application of the SN concept could lower these figures.

The objectives of this study were as follows:

1) To prove that the rate of axillary recurrence in patients not undergoing AL and with a negative SN is no higher than that of patients undergoing AL and with a negative SN.
2) To prove that overall and disease-free survival rates in AL-negative SN patients are no higher than in non-AL negative SN patients.
3) To prove that morbidity in negative SN patients not undergoing AL is lower than in negative SN patients undergoing AL.

Patients and methods

Type of study and patient selection

At the *Departamento de Oncología Quirúrgica* (Surgical Oncology Department) of the Instituto Portugués de Oncología, Centro do Porto (IPO-P), a centre exclusively dedicated to cancer treatment, we conducted a controlled, prospective, single-centre, non-superiority study, which was approved by the relevant ethics committee. The admission criteria included patients from 18 to 80 years of age, diagnosed with invasive

30 mm-diameter BC or *in situ* ductal carcinoma (ISDC) measuring over 40 mm in diameter without palpable axillary nodes. Tumour size was evaluated by means of a physical examination, ultrasound scan or mammography. The exclusion criteria were: pregnancy, neoadjuvant treatment and previous axillary surgery.

The admission phase lasted from April 2001 to June 2003. All the patients signed the informed consent for the study.

Identification technique

The technique used for SN identification combines the peritumoral injection of 99mTc colloidal sulphur (37 MBq), collection of images by a fixed gamma-camera and subareolar injection of a vital dye (patent blue V, Laboratorios Guerbet, Aulnay-sous-Bois, France) into Sappey's plexus.[18] The injection of radioisotopes was preferentially performed the day before the surgical intervention or on the same morning. The vital dye was injected in the operating room after anaesthetising the patient.

The SN is identified visually (it is blue in colour) and auditorely (depending on the amount of radioactivity), with the help of a manual detection probe (Neoprobe 1000/2000, Neoprobe Corporation, Dublin, Ohio, USA).

The SN is defined as a node which is blue in colour, a node adjacent to a blue lymph vessel, a hot node (a node with greater activity and nodes which show a level of activity up to 10% of that of a hot node) and any suspicious axillary nodes (based on observation or palpation). After its removal, the SN was immediately sent to the *Departamento de Anatomía Patológica*, where it was cut into two halves, and the cytological results were analysed. If there was metastasis, the surgeon performed an AL; if there were no metastases, a computer programme randomly assigned the case to one of the following groups: AL (group 1, control group) or observation (group 2, the study group). Patients were randomised according to age (less or more than 50 years), TNM tumour stage (cT1a *vs* cT1b *vs* cT1c *vs* T2) and invasion pattern (invasive *vs in situ*).

The definitive pathological diagnosis was based on the total inclusion of the SN and multiple 2 mm haematoxylin-eosin stained slices (HE). Negative nodes were evaluated by means of a single HE-stained slice. Immunohistochemical tests were not performed.

Axillary dissection and post-operative follow-up

The AL technique used at the *Departamento de Oncología Quirúrgica* includes the resection of Berg levels I and II and only in cases of extensive nodular involvement is level III tissue removed. The surgeons dissected the main trunk of the axillary vein, the long thoracic nerve and the thoraco-dorsal neurovascular bundle. The sensitive costo-brachial nerves were not generally preserved.

After total mastectomy with/without AL, two Redon type suction drainage catheters are put in place to drain the surgical site. The drainage tubes are removed when the drainage discharge is ≤40 cc/day or on the 6th day following surgery. Physiotherapy is initiated after drainage is removed and patients are given instructions on how to maintain their daily exercise regime at home.

Follow-up and morbidity evaluation

The patients were monitored at the breast clinic every 3 months during the first 3 years and thereafter every 6 months until the 5th year. The clinical assessment was based solely on axillary palpation. An axillary ultrasound scan was requested in cases which required further clarification.

Each time the patient came for a check-up increase in arm volume (LO), deterioration in shoulder function, and pain and numbness (dysaesthesias/paresthesias) were assessed. The results at 6, 12, 24 and 48 months were used for the study. An increase in arm volume (LO) was defined as an increase of more than 2 cm, comparing the circumference of the operated upper limb (at three points: the wrist, the midpoint of the forearm and the midpoint of the upper arm) with its (unoperated) counterpart. Patients were asked to lift their operated arm (maximum possible abduction): abduction ≥90° was considered adequate; abduction <90° was considered abnormal (shoulder joint deterioration). They were asked to answer two questions: 1) Is your arm painful in a resting position? (yes or no) and 2) Does the inside of your arm feel numb? (yes or no).

Adjuvant treatment was planned at the multidisciplinary meeting for this purpose, in accordance with the criteria of our centre, irrespective of the study group to which the patient was assigned. pN0 patients did not receive axillary radiotherapy.

Statistical analysis

The statistical tests used for the study included the Mann-Whitney U test (comparison of medians), Fisher's exact test and Pearson's chi-squared test (to compare proportions). Survival probabilities were estimated using the Kaplan-Meier method and comparisons were made using the log-rank test. The statistical tests were employed to analyse the patients in Groups 1 and 2 (pN0 patients). SPSS 13.0 software was used (SPSS Inc., Chicago, Illinois, USA).

Results

General data

During the study 170 BC patients were diagnosed at our centre and 4 of them were excluded (Figure 1) so, finally, a total of 166 patients with 167 BCs were potential candidates. The median age was 54 years (range: 31-78). Diagnosis was made by needle biopsy in 83.5% of the cases. The median follow-up was 72 months (range: 62-87).

The gammagraphy (GG) test was negative (no hot spot) in 12 cases (7.2%). However, it was possible to identify a SN in 11 of them. In 50.3% of the patients in the study the GG revealed only one hot spot, and the median of hot spots was 1 (range: 0-7). The SN identification rate was 99.4%. The median number of removed SNs was 1.9 (standard deviation 1.0) for

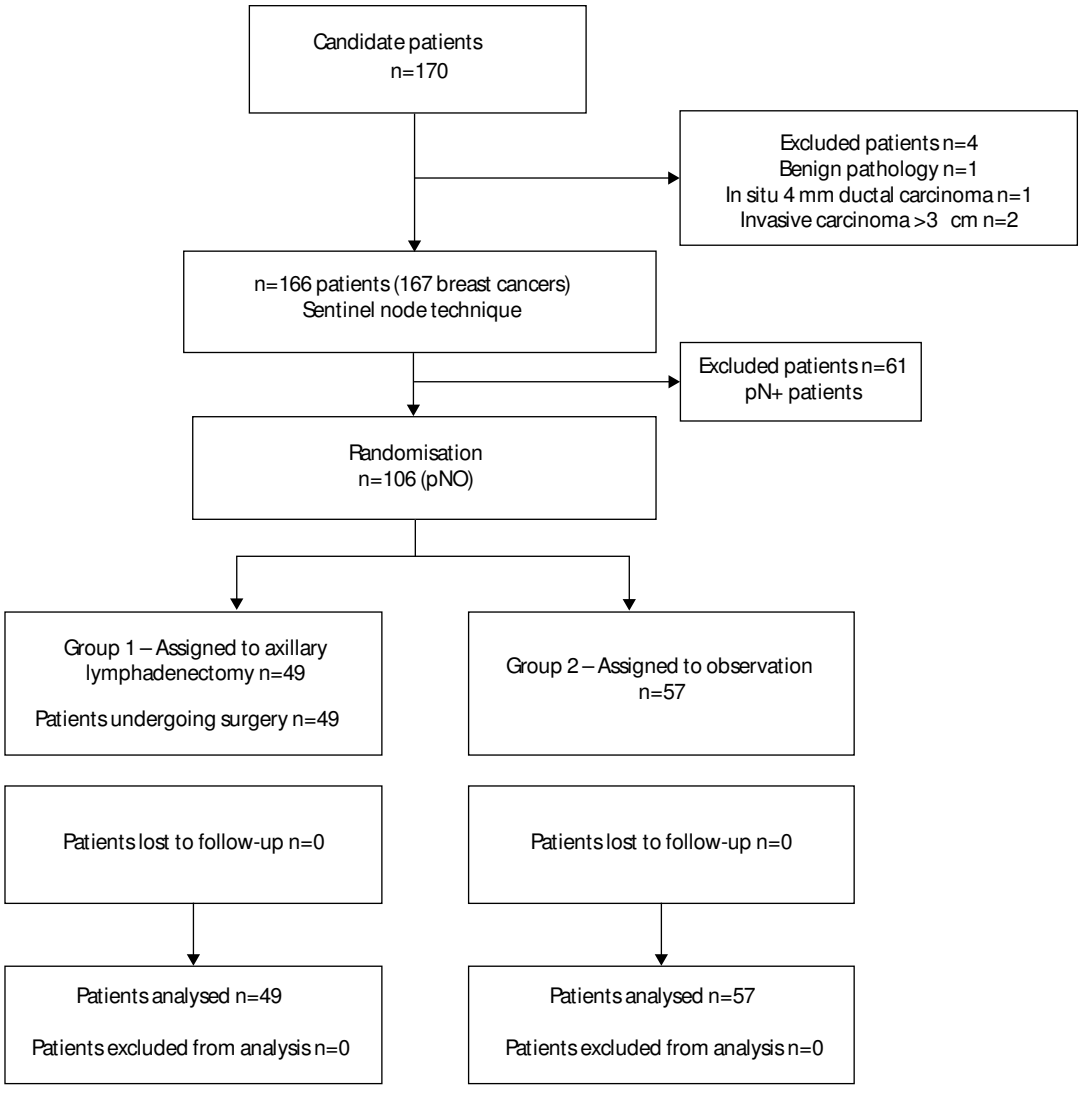


Figure 1 – Study flow chart.

group 1, 1.7 (1.1) for group 2 and 1.6 (0.9) for the positive SN group. The rate of false negatives for the technique was 6.6% (4 cases). The false negative rate for frozen samples was 15% (9 cases). We observed drainage to the internal mammary artery chain (IMA) in 22 cases (13.2%) and we removed the SN in 17 of them. One of these cases exhibited metastasis exclusively in the IMA chain.

In 61 out of the 167 (37.1%) breast cancers there was metastasis in the SN, and 49 of the remaining 106 negative SN cases were randomly assigned to group 1 and 57 to group 2 (Figure 1). Their demographic, technical and pathological characteristics and adjuvant treatments are shown in Table 1 and Table 2.

During follow-up, thirty four patients had serious problems, and 12% of them were oncological (Table 3). Axillary node recurrence was not detected during follow-up in either of the study groups. Cumulated survival after 60 months of follow-up was 94% in group 1 patients and 100% in group 2 patients. Overall survival (*P*[log-rank] =.06) (Figure 2) and disease-free survival (*P*[log-rank] =.4) were similar in both groups.

Morbidity

The proportion of patients with morbidity and those who presented more than 2 complications was significantly greater in patients in the AL group than in patients who underwent a SN biopsy without a lymphadenectomy (Figure 3).

In general, 12 months after the operation LO was present in 22.1% of the patients. This percentage stabilised at 21.4% 48 months after surgery. After 12 months, it was observed that in some AL patients there was a difference of more than 5 cm in arm circumference (2.6%, 2.1% and 4.3% of the patients after 12, 24 and 48 months of follow-up). None of the group 2 patients showed so much difference in their arm circumference measurements. LO was more common and more serious in the AL group. 59.6% of the patient total

Table 1 – General data

	Group 1 n=49	Group 2 n=57	SN + Group n=61	P
Male patients, %	2.0	0	1.6	
Black patients, %	0	0	3.3	
Age (median, range), years	56 (32-78)	53.5 (31-76)	54 (33-76)	NS[a]
Body Mass Index, median, range	26.6 (17.1-35.8)	25.8 (17.5-36.8)	26.9 (20.4-39.2)	NS[a]
Hospital stay (median, range), days	5 (3-11)	2.5 (1-10)	5 (2-21)	<0.001[a]
Preoperative assessment of tumour size (median, range), mm	17 (3-80)	15 (1-99)	22 (9-80)	NS[a]
Breast affected by tumour, %				NS[b]
Right breast	40.8	46.4	49.2	
Left breast	59.2	53.6	50.8	
Tumour localisation (%)				NS[c]
Superior-external	59.2	64.4	72.1	
Superior-internal	8.1	19.6	6.6	
Inferior-external	18.3	5.4	8.2	
Inferior-internal	8.2	3.6	3.3	
Central	6.1	7.1	9.8	
Harpoon localisation, %	22.4	23.2	4.9	NS[b]
Surgery, %				NS[b]
Total mastectomy	59.2	51.8	72.1	
Extensive excision	40.8	48.2	27.9	
Number of SNs removed (median, range)	2 (1-5)	1 (1-5)	1 (1-5)	NS[a]
Number of axillary nodes removed (median, range)	14.5 (2-29)	1 (1-5)	15 (6-30)	-

CT indicates chemotherapy; GG, mammary lymphogammagraphy; HT, hormone therapy; RT, radiotherapy; SN, sentinel node.
[a]Mann-Whitney U test.
[b]Fisher's exact test.
[c]Pearson's chi-squared test.

suffered some kind of complication during the first 12 months, this figure falling to 48.5% at 48 months. Complications were more frequent in patients undergoing AL at each follow-up appointment throughout the entire study: 2% of the AL patients presented a maximum of 13 complications within the 48-month period after surgery compared to 3.5% of patients

Table 2 – Histological characteristics and adjuvant treatments

	Group 1 n=49	Group 2 n=57	SN + Group n=61	P
Definitive tumour size (median, range), mm	17 (3-80)	15 (1-99)	22 (9-80)	NS[a]
Histological type, %				NS[b]
Invasive ductal	73.5	69.6	80.3	
Other invasive type	16.3	25.0	19.7	
In situ ductal	10.2	5.4	0	
Tumour stage, %				NS[b]
1	18.4	32.1	6.6	
2	44.9	48.2	62.3	
3	24.5	10.7	31.1	
Unknown	12.2	9.0	0	
Multifocal, %	12.2	10.7	16.4	NS[c]
Venous invasion, %	2.0	1.8	9.8	NS[c]
Lymph node invasion, %	8.2	1.8	26.2	NS[c]
Positive oestrogen receptors, %	81.6	83.9	82.0	NS[c]
Positive progesterone receptors, %	71.4	62.5	75.4	NS[c]
RT, %	53.1	62.5	76.7	NS[c]
CT, %	36.7	30.4	83.3	NS[c]
HT, %	79.6	87.5	90.0	NS[c]

CT indicates chemotherapy; GG, mammary lymphogammagraphy; HT, hormone therapy; SN RT, radiotherapy;, sentinel node.
[a]Mann-Whitney U test.
[b]Pearson's chi-squared test.
[c]Fisher's exact test.

Table 3 – Number of events in each group

Events	Group 1 n=49	Group 2 n=57	SN + Group n=61
Axillary node recurrence	0	0	0
Distant metastasis	1	1	1
Ipsilateral mammary recurrence	0	0	0
Contralateral breast cancer	1	1	1
2nd primary cancer	2	5	2
Cancer-related death	3	0	4
Death unrelated to cancer	0	2	1
Non-oncological events	4	1	4

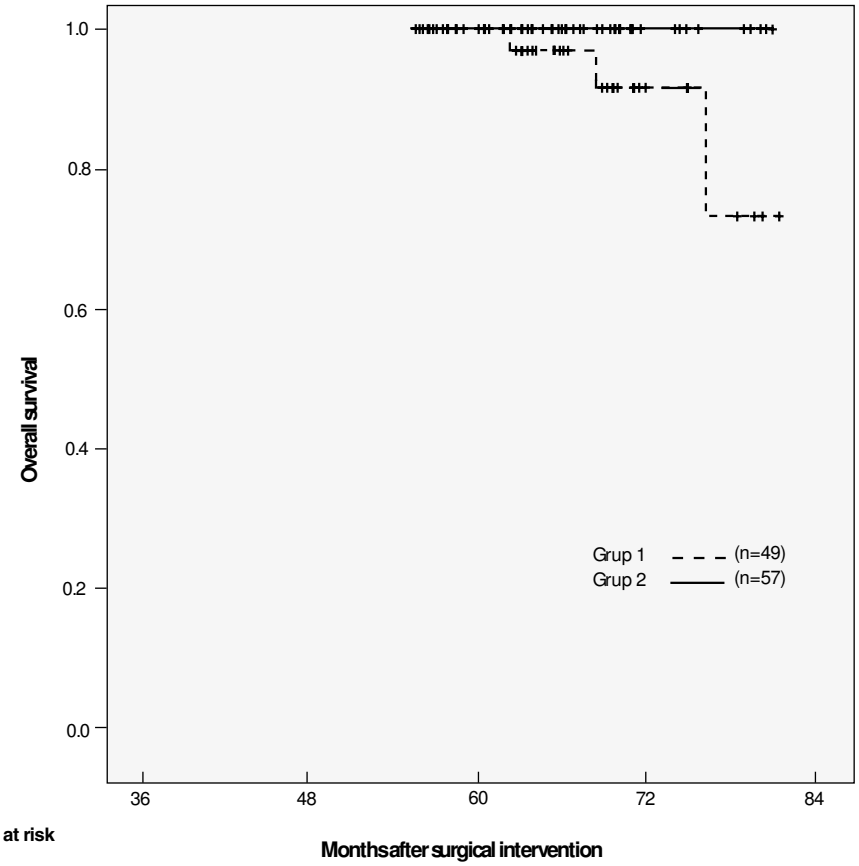
SN + Group indicates metastasised sentinel node.

not undergoing AL, who had a maximum of 6 complications. During the same period, only 8.2% of the AL patients failed to suffer any complications in comparison with 26.3% of the group which did not undergo AL.

Table 4 shows the morbidity results, considering the four complications which were evaluated (differences in arm circumference/LO, pain in the resting upper limb, arm sensitivity deterioration and shoulder joint dysfunction) at each follow-up period so that patients with and without AL can be compared.

Discussion

The aim of this study was to evaluate the consequences of not performing axillary lymphadenectomy when the SN is free of



Patients at risk

Grup 1	49	49	49	37	7
Grup 2	57	57	57	44	10

Figure 2 – Estimation of overall survival probability (Kaplan-Meier) depending on whether lymphadenectomy was performed (group 1) or not (group 2) on negative sentinel node patients (P=.0061, log-rank test).

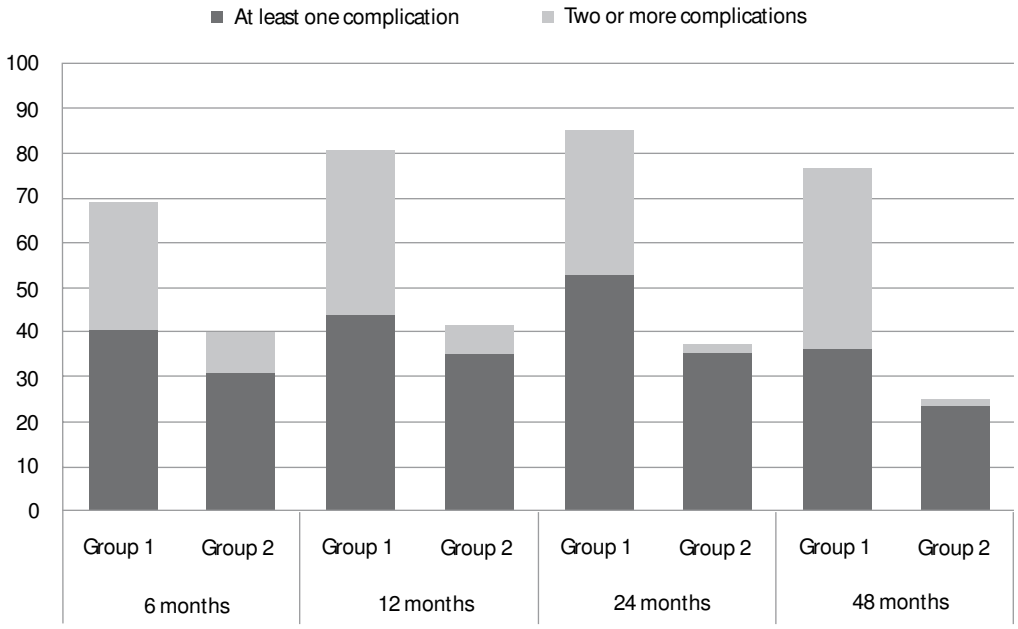


Figure 3 – Morbidity throughout follow-up.

metastasis, in terms of regional (axillary, periclavicular) node recurrence, overall and disease-free survival and upper limb morbidity.

The role of axillary SN biopsy as a predictive factor for the state of the other axillary nodes has been confirmed in a large number of clinical trials. These trials have demonstrated that the SN concept is capable of promoting and improving lymph node staging in BC patients, despite the well-known and feared rate of false negatives, which range from 5% to 10%.[19-21]

Table 4 – Morbidity in negative sentinel node patients depending on whether or not axillary dissection was performed

	Group 1 (axillary lymphadenectomy), %	Group 2 (no axillary lymphadenectomy), %	P
Follow-up at 6 months			
UL circumference >2 cm[a]	20.6	11.1	.344[c]
Pain at rest	18.9	15.9	.774[b]
Paresthesias	56.8	18.2	<.001[b]
Shoulder dysfunction	10.8	9.1	1.0[b]
Follow-up at 12 months			
UL circumference >2 cm[a]	30.8	14.9	.157[c]
Pain at rest	29.3	18.7	.318[b]
Paresthesias	58.5	10.4	<.001[b]
Shoulder dysfunction	17.1	6.2	.177[b]
Follow-up at 24 months			
UL circumference >2 cm[a]	27.6	14.3	.18[c]
Pain at rest	21.3	16.1	.612[b]
Paresthesias	70.2	8.9	<.001[b]
Shoulder dysfunction	12.8	0	.008[b]
Follow-up at 48 months			
UL circumference >2 cm[a]	38.3	7.1	.001[c]
Pain at rest	14.9	5.4	.18[b]
Paresthesias	61.7	10.7	<.001[b]
Shoulder dysfunction	23.4	3.6	.005[b]

UL indicates upper limb.
[a]Measurements of differences in circumference between the ipsilateral and contralateral UL (considering the greatest difference for the three measurement points).
[b]Fisher's exact test.
[c]Pearson's chi-squared test.

This study started in April 2001, after a validation phase which ended in February 2001, and it included 105 patients and 4 surgeons. We obtained a SN identification rate of 97% and a false negative rate of 7.1%, which has consolidated the use of the triple technique.[22] The identification and false negative rates are similar to the best published results.[23,24]

The two study groups were comparable as far as their demographics and technical results are concerned. We should emphasise the significant reduction in hospital stay for group 2 patients (Table 2). In the first randomised trial published on this area of research, Veronesi et al[25] obtained similar results. This finding is even more significant if we only compare patients who underwent surgery designed to preserve the breast and it may reduce the costs associated with the surgical treatment of breast cancer.[26]

The small number of patients in the trial, as well as the short follow-up period (five years) could diminish its clinical impact. However, the study reflects the reality of our centre and its figures show the balance achieved between the number of patients treated at the IPO-P and a reasonable admission time. We should also stress that most of the BC-related events appeared during the first 3 years of follow-up. With a similar median follow-up, Veronesi et al[25] published an 8.1% rate of oncological events, which is lower than the rate that we observed in our study.

The great advantage offered by the CG concept is better lymph node staging. During recent decades lymph nodes outside of the axilla have been ignored by surgeons, despite our extensive knowledge of the anatomy and physiology of the lymphatic drainage of the breast, and of the natural history of BC. Breast GG enables the lymphatic drainage areas of each specific tumour to be identified and the surgeon can identify and recover all the SNs, regardless of the anatomical region in which they are located. In this patient group drainage to the IMA chain was observed in 22 cases and the identification rate was 77.3%. There was only a single case where only IMA SN presented metastasis. Despite the low incidence of this event (0.6%), its occurrence had a significant impact on the evaluation of BC lymph node extension, as it modified the treatment plan, which included systemic chemotherapy and parasternal radiotherapy. Other authors found similar results in their series.[27,28]

Four false negatives were detected in group 1. Expecting to have the same number of ipsilateral axillary relapses as in group 2 patients with a median follow-up of 72 months up until June 2008, we have not had any cases of lymph node relapse. Axillary recurrence rates are generally very low.[29]

The overall survival curves and log-rank test results fail to show any advantages for one group over the other (we can even observe a small advantage for group 2, a finding which was also emphasised by Veronesi.)[25]

Arm LO is the most serious and worrying complication of BC treatment. Its prevalence varies from 0 to over 50% amongst BC patients.[17,30] An average estimation might be that one in four women will develop LO after treatment. In our study the prevalence of LO in the patients who underwent a lymphadenectomy was 38.3%.

The high prevalence of LO may be due to using a more demanding definition to establish its diagnosis and the technique used to quantify it, which makes it difficult to compare studies. Some authors use complex methods to calculate the increase in limb volume, for example the direct assessment of limb volume (water displacement) or indirect volume calculations (trunk technique).[31-33] Our intention was to use a simple immediate cheap reproducible method, such as the measurement of arm circumference in three different places: the arm, forearm and wrist. Moreover, we defined LO as a 2 cm difference in the perimeter between the treated side and the contralateral one (the point with the greatest difference).[34,35] Other authors accept a difference of only 1 cm as synonymous with LO.[32]

We believe that the time interval for the morbidity assessment in our study (4 years) is adequate. Petrek et al[36] found that nearly 80% of patients developed LO in the first 3 years following treatment and Werner[37] confirmed that 97% of patients developed LO in an interval of 4 years after treatment.

One of the well-know risk factors for the appearance of arm oedema is the association between dissection and axillary radiotherapy.[17] In our study we only compared different surgical techniques, given that none of the pN0 patients received axillary radiation. It was clear from the beginning of the study that there was a small percentage of patients with an increased arm circumference in group 2, in comparison with the AL group. This finding, which reaches statistical significance in the fourth year of follow-up, confirms the observations of other investigators: the SN concept reduces the risk of arm oedema after breast cancer treatment.[33,38-44] From the 2nd to the 4th year of follow-up, a reduction in the percentage of LO patients can be seen group 2, while in group 1 the patients show an increase in the percentage of LO.

Pain in the arm is another symptom which is closely linked to BC treatment. In our study we have confirmed a tendency towards a lower incidence of upper limb pain at rest in non-AL patients. However, this finding was not statistically significant. Other authors were also able to demonstrate this association.[35,45] Paresthesias of the inside of the arm are also a symptom which is associated with BC treatment. This is foreseeable, given that during axillary dissection the sensitive costo-brachial nerves are severed. This is why, from the outset of the study, a strong association between the absence of paresthesias and the absence of AL is to be expected and has been reported by other authors.[33,39,42,43] Shoulder dysfunction was found more often in the AL group, in particular in the long-term evaluation (two or more years of follow-up). It is a morbidity sign following BC treatment, which is often related to AL, axillary radiotherapy or both.[40] Other studies associate improvements in shoulder mobility with the absence of axillary dissection.[30,35,40,43]

In general, the group 2 patients showed lower morbidity rates and, when complications are present, the symptoms are less intense than in AL patients (group 1). One in every four patients in group 2 had no symptoms throughout the entire follow-up period, in comparison with only one in every ten patients in group 1.

However, the minimally invasive SN concept is not exempt of morbidity,[46] and in some circumstances, the morbidity rate for SN biopsy may be unacceptable.[47] Surgeons need to be

aware of the risk of pain, oedema and paresthesias affecting the inside of the arm but, on the other hand, they also need to be willing to opt for SN biopsy as a truly minimally invasive procedure. As with identification and false negative rates, the morbidity rate should be regarded as a measurement of the efficacy of the SN concept.

In short, the results of our study suggest that when the SN is not metastasised, a lymphadenectomy to assess lymph node stage is not justified in BC patients. This approach does not compromise the evaluation or treatment results for this patient group and it reduces the risk of developing upper limb complications in the long term.

Conflict of interest

The authors affirm that they have no conflict of interest.

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