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Patient-Reported Outcomes

Quality-of-Life Impact of Sentinel Lymph Node Biopsy Versus Axillary Lymph Node Dissection in Breast Cancer Patients

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ABSTRACT

Objectives: Controversy about quality-of-life (QOL) benefits of sentinel lymph node biopsy (SLNB) versus axillary lymph node dissection (ALND) in patients with breast cancer remains. Our aim was to compare the impact of SLNB and ALND on QOL and arm symptoms of patients with early breast cancer, using generic (short form 36 health survey) and tumor site–specific (FACT-B+4) instruments. **Methods:** This was a prospective longitudinal observational study of 93 patients (64 SLNB, 29 ALND). Patients were evaluated presurgery and 1, 6, and 12 months postsurgery. Generalized estimation equation models were constructed to assess the effect of treatment on QOL. The relative risks of edema, dysesthesia, and heaviness were calculated comparing ALND to SLND. **Results:** Most patients presented T1 (67.7%) and underwent breast-conserving surgery (92.5%). At 12 months, the SLNB group presented deterioration on the FACT-B+4 Arm Scale (beta coefficient estimated a change of −1.6 score points; $P < 0.01$) while, compared with SLNB, the deterioration in the ALND group was almost 2 additional score points higher ($P = 0.009$). FACT-B+4 global summary and short form 36 health survey did not show statistically significant differences between groups. Relative risk of dysesthesia and subjective edema was higher for the ALND group than for the SLNB group (1.97 and 2.11 at month 12; $P < 0.01$). **Conclusion:** These results confirm the benefit of SLNB due to its lower arm morbidity impact on QOL, compared with ALND. There are clinically relevant between-treatment differences in the Arm Scale of FACT-B+4, while there were no relevant differences in general well-being, measured with the disease-specific FACT-B+4 and the generic short form 36 health survey.

Keywords: breast cancer, health-related quality of life.

Introduction

Breast cancer is the most prevalent cancer among women in developed countries. In Spain, the incidence is 81.1 new cases a year per 100,000 women, the 5-year survival is 82%, and consequently the prevalence of women who have undergone breast cancer is very high [1,2]. This means that minimizing the morbidity associated with breast cancer treatments and maintaining quality of life (QOL) are priority goals.

The clinical stage plays a central role in the breast cancer surgical approach. Breast-conserving surgery is considered the standard option in early stages [3], and full dose of radiotherapy must be delivered usually after. Breast-conserving surgery provides a better body image than mastectomy initially after surgery [4]. The mastectomy approach must be chosen when there is a high risk of local recurrence. Large tumors in a small breast, persistent positive margins after resection, diffuse calcifications, predictable poor cosmetic outcome, and contraindications to radiation therapy are breast-conserving contraindications. Finally, women with early stage breast cancer may opt for mastectomy because of personal preference.

Lymph node spread is an important prognostic factor in breast cancer. In early stage tumors, with clinically and ultrasound negative involvement of the axilla, node spread can be determined by the technique of selective sentinel lymph node biopsy (SLNB). The American Society of Clinical Oncology in 2005 [5], and more recently the British Association of Surgical Oncology [6], endorsed SLNB as the recommended method of staging early breast cancer in clinically node negative patients because of its benefits compared with axillary dissection on arm morbidity. When sentinel nodes are tumor free, axillary lymph node dissection (ALND) is considered unnecessary [7], and so SLNB enables a large number of patients to save their axillary nodes and, consequently, avoid the potential side effects of axillary clearance [8–12]. Despite the extension of this conservative method, ALND remains a necessary technique in node-pos-

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Table 1 – Patient characteristics.

	All (n = 93)	SLNB (n = 64)	ALND (n = 29)	P
Age (y), mean ± SD	59.2 ± 8.6	59.8 ± 8.8	57.9 ± 8.0	0.320
Body mass index (kg/m^2)	32.1 (24.6)	32.7 (29.6)	30.7 (5.3)	0.711
Affected side				
Dominant	51 (58.0%)	34 (56.7%)	17 (60.7%)	0.720
Nondominant	37 (42.0%)	26 (43.3%)	11 (39.3%)	
Surgery technique				
Breast conserving	86 (92.5%)	64 (100.0%)	22 (75.9%)	<0.001
Mastectomy	7 (7.5%)	0 (0.0%)	7 (24.1%)	
T (tumor size category)				
IS	9 (9.7%)	9 (14.1%)	0 (0.0%)	<0.001
1	63 (67.7%)	48 (75.0%)	15 (51.7%)	
2	20 (21.5%)	7 (10.9%)	13 (44.8%)	
3	1 (1.1%)	0 (0.0%)	1 (3.4%)	
N (node involvement)				
0	68 (73.1%)	64 (100.0%)	4 (13.8%)	<0.001
1	22 (23.7%)	0 (0.0%)	22 (75.9%)	
2–3	3 (2.2%)	0 (0.0%)	3 (10.3%)	
Tumor size (mm)	13.9 (7.4)	12.6 (6.1)	18.1 (9.4)	0.009
Number of lymph nodes removed, mean ± SD	6.1 ± 7.4	1.6 ± 0.8	16.0 ± 5.1	<0.001
Histology				
Ductal carcinoma	82 (88.2%)	58 (90.6%)	24 (82.8%)	0.277
Lobular carcinoma	11 (11.8%)	6 (9.4%)	5 (17.2%)	
Multiple primary neoplasm				
No	81 (87.1%)	58 (90.6%)	23 (79.3%)	0.132
Yes	12 (12.9%)	6 (9.4%)	6 (20.7%)	
Differentiation				
I	27 (32.9%)	23 (39.7%)	4 (16.7%)	0.128
II	32 (39.0%)	20 (34.5%)	12 (50.0%)	
III	23 (28.0%)	15 (25.9%)	8 (33.3%)	
Radiotherapy	84 (90.3%)	58 (90.6%)	26 (89.7%)	0.883
Chemotherapy	47 (50.5%)	21 (32.8%)	26 (89.7%)	<0.001
Hormonotherapy	70 (75.3%)	48 (75.0%)	22 (75.9%)	0.929
Education				
Primary	61 (69.3%)	42 (71.2%)	19 (65.5%)	0.588
Secondary and university	27 (30.7%)	17 (28.8%)	10 (34.5%)	
Work				
Employed	34 (38.6%)	25 (42.4%)	9 (31.0%)	0.689
Unemployed	4 (4.5%)	3 (5.1%)	1 (3.4%)	
Housewife	31 (35.2%)	18 (30.5%)	13 (44.8%)	
Permanently incapacitated	2 (2.3%)	1 (1.7%)	1 (3.4%)	
Retired	17 (19.3%)	12 (20.3%)	5 (17.2%)	

ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy.

itive cases or is still applied as the first option in a significant number of patients.

Several studies comparing both surgical procedures, SLNB and ALND, showed that SLNB is associated with shorter hospital stay, earlier return to normal activity, and lower rates of short- and long-term morbidities, such as infection, seroma, shoulder movement impairment [11–15], neuropathy, and upper limb lymphedema [16–18].

However, QOL benefits of SLNB are not as clearly demonstrated. Most studies presented some methodological problems, such as the absence of pretreatment assessment and reliable and validated QOL instruments. Kootstra et al. [19], focusing on published well-designed prospective studies (observational or randomized clinical trials), pointed out that there were no differences in QOL between women treated with SLNB or ALND. The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial was the only exception to this pattern, showing better QOL among women of the SNLB group [20]. This striking discrepancy has been explained by suggesting certain limitations in the questionnaires to cover all relevant aspects in this area [21,22]. All the above studies used generic QOL instruments such as short form 36 health survey (SF-36) or European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30), whereas the ALMANAC trial was the only one using the FACT-B+4, a tumor site–specific instrument.

The main objective of this study was to compare the impact of SLNB and ALND on the QOL of patients with early breast cancer during the first year after surgery using both generic (SF-36) and tumor site–specific (FACT-B+4) instruments that assess upper limb impairment.

Methods

This was a prospective longitudinal observational study of incident breast cancer patients with surgery as first treatment. Authorization was obtained from the Ethics Committee on Medical Research, and all participants gave their written informed consent.

Consecutive patients of all ages were recruited from the surgery department of a general university hospital with a commu-

Table 2 – Repeated-measures analysis of variance of quality-of-life measures.

	n	Mean ± SD				P (ANOVA)	P (vs. pretreatment)*		
		Pretreatment	Month 1	Month 6	Month 12		Month 1	Month 6	Month 12
SLNB group	51								
FACT-B+4									
Physical	50	25.03 ± 3.13	23.09 ± 5.84	22.06 ± 4.53	23.27 ± 4.43	0.002	0.102	<0.001	0.092
Social	48	22.76 ± 4.31	23.14 ± 3.69	21.63 ± 4.78	21.47 ± 4.35	0.070	–	–	–
Emotional	49	14.29 ± 4.47	15.69 ± 4.37	15.69 ± 4.23	16.81 ± 4.13	<0.001	0.098	0.109	0.002
Functional	49	18.84 ± 4.72	17.94 ± 5.27	17.38 ± 4.69	18.21 ± 5.14	0.226	–	–	–
Breast	49	22.21 ± 5.22	20.57 ± 4.69	21.45 ± 5.37	22.27 ± 5.19	0.108	–	–	–
Arm	49	19.27 ± 1.93	17.96 ± 2.86	17.31 ± 4.38	17.66 ± 3.33	0.003	0.027	0.032	0.027
TOI	48	85.20 ± 11.02	79.73 ± 13.12	77.84 ± 15.74	80.89 ± 14.32	0.023	0.023	0.007	0.216
FACT-B+4 global summary	47	122.25 ± 15.78	118.62 ± 16.77	115.10 ± 21.75	119.05 ± 19.47	0.085	–	–	–
SF-36									
PCS	48	50.83 ± 8.79	42.68 ± 8.79	42.76 ± 9.46	44.65 ± 9.22	<0.001	<0.001	<0.001	<0.001
MCS	48	46.65 ± 13.09	47.41 ± 12.01	46.75 ± 11.61	47.52 ± 12.43	0.941	–	–	–
ALND Group	21								
FACT-B+4									
Physical	20	25.12 ± 2.90	21.94 ± 4.42	22.00 ± 4.50	21.70 ± 3.74	0.062	–	–	–
Social	20	23.71 ± 3.72	24.53 ± 3.42	22.62 ± 5.14	22.08 ± 4.42	0.119	–	–	–
Emotional	20	12.67 ± 5.28	14.99 ± 4.81	14.92 ± 4.96	15.70 ± 4.19	0.004	0.204	0.071	0.012
Functional	19	18.47 ± 4.67	17.72 ± 5.79	18.16 ± 6.47	18.37 ± 5.59	0.691	–	–	–
Breast	18	19.90 ± 5.02	20.57 ± 4.40	20.95 ± 5.20	20.25 ± 5.08	0.559	–	–	–
Arm	19	19.32 ± 1.86	14.89 ± 4.20	16.37 ± 2.59	15.16 ± 2.93	<0.001	0.003	0.002	<0.001
TOI	17	81.96 ± 10.72	75.10 ± 12.25	76.95 ± 14.92	75.15 ± 11.59	0.118	–	–	–
FACT-B+4 global summary	17	117.79 ± 17.58	113.91 ± 17.28	113.63 ± 22.15	111.89 ± 15.88	0.415	–	–	–
SF-36									
PCS	18	51.36 ± 8.05	42.99 ± 8.69	44.32 ± 8.48	43.49 ± 9.24	0.023	0.045	0.036	0.007
MCS	18	43.50 ± 12.20	45.35 ± 9.79	46.00 ± 13.73	46.15 ± 11.68	0.606	–	–	–

ALND, axillary lymph node dissection; ANOVA, analysis of variance; MCS, Mental Component Scale; PCS, Physical Component Scale; SF-36, short form 36 health survey; SLNB, sentinel lymph node biopsy; TOI, Trial Outcome Index.
* Bonferroni adjustment for multiple comparisons.

nity-based screening program for breast cancer. Inclusion criteria were having an invasive carcinoma or high-grade ductal carcinoma "in-situ" of the breast, and to be considered for surgery as the first choice treatment. Exclusion criteria were preexisting severe disorders on the upper limb of the side involved (i.e., nerve damage, amputations. . .), or cognitive impairment, which could make collaboration difficult.

Treatment

The patients underwent breast-conserving surgery or mastectomy with SLNB when sentinel node was negative or with level II ALND when the presurgical, perioperative, or definitive sentinel node study was metastatic. SLNB was conducted as described elsewhere [23]. SLNB indications, adjuvant systemic chemotherapy, hormonal treatment, and/or locoregional radiotherapy were applied according to the national oncological guidelines and the most recent national and international consensus [5,24,25].

Data collection and follow-up

Sociodemographic information was self-reported at baseline, and the tumor clinical characteristics were collected from medical records (type, grade and stage of tumor, surgical and adjuvant treatments applied, and number of lymph nodes removed).

Clinical assessment took place in the rehabilitation setting of the breast cancer unit, before surgery and at months 1, 6, and 12 postsurgery. Self-reported symptoms included the presence or absence of paresthesia, heaviness, and edema. The clinical examination included the detection of neurological disorders, winged scapula, the shoulder range of motion (flexion, abduction, external rotation, and internal rotation) as measured by a goniometer in degrees, and the volume of both upper limbs obtained by measuring six circumferences and applying the truncated cone formula [26]. The affected arm volume change over time was calculated by subtracting the volume at baseline from the volume at follow-up. Furthermore, the affected arm volume change was corrected by subtracting the unaffected arm volume changes. This correction allows controlling the possible variation caused by body composition changes (e.g., gains or losses in weight).

Quality-of-life questionnaires

QOL was assessed before surgery and at months 1, 6, and 12 postsurgery. Generic and breast cancer–specific questionnaires were self-administered at the waiting room before the clinical assessment. The SF-36 version 2 [27] was used. Scores for the two summary components (Physical Component Scale [PCS] and Mental Component Scale [MCS]) were calculated by using the recommended standardized procedure where scores higher or lower than 50 indicate better or worse QOL, respectively, than the general US population [28,29].

The FACT-B+4 is a QOL questionnaire [30,31] composed of 40 items covering four generic scales of well-being (Physical, Emotional, Social, and Functional) and two side-specific scales: Breast Cancer (nine items) and Arm (five items). The FACT-B+4 Spanish

Table 3 – Clinical findings and shoulder movement reductions in the SLNB and ALND groups during the 12 mo after surgery.

	SLNB	ALND	P*	RR (95% CI)†
Experienced symptoms during year				
Presence of subjective edema				
1 mo	7.9%	24.1%	0.032	1.74 (0.88–3.45)
6 mo	7.1%	31.0%	0.004	2.35 (1.03–5.37)
12 mo	11.8%	35.5%	0.002	2.11 (1.09–4.06)
Dysesthesia				
1 mo	31.7%	75.9%	<0.001	1.81 (1.29–2.53)
6 mo	42.9%	65.5%	0.048	1.37 (1.00–1.87)
12 mo	25.5%	69.2%	<0.001	1.97 (1.28–3.04)
Heaviness				
1 mo	4.8%	17.2%	0.048	1.91 (0.77–4.71)
6 mo	8.9%	24.1%	0.056	1.68 (0.84–3.33)
12 mo	9.8%	15.4%	0.471	1.22 (0.66–2.23)
	SLNB Mean (SE)	ALND Mean (SE)	P‡	Mean difference (95% CI)
Arm volume change corrected for contralateral change (mL)§				
1 mo	11.2 (19,3)	−33.3 (22.8)	0.183	44.5 (−21.4 to 110.3)
6 mo	−25.4 (16.2)	109.5 (34.7)	<0.001	−134.9 (−212.5 to −57.4)
12 mo	−6.8 (14.5)	96.7 (51.1)	0.062	−103.5 (−212.5 to 5.5)
Reductions in range of shoulder movement (in degrees) at 12 mo§				
Flexion	2.5 (1.3)	5.7 (1.5)	0.170	−3.1 (−7.5 to 1.4)
Abduction	6.6 (2.3)	7.4 (2.6)	0.830	−0.8 (−8.4 to 6.8)
Internal rotation	1.3 (1.1)	3.5 (1.3)	0.229	−2.2 (−5.8 to 1.4)
External rotation	1.8 (1.4)	6.3 (1.9)	0.071	−4.5 (−9.5 to 4.0)

ALND, axillary lymph node dissection; CI, confidence interval; SE, standard error; SLNB, sentinel lymph node biopsy.
* Chi-square tests.
† Relative risk (RR) was calculated considering the SLNB group as reference (RR = 1).
‡ Unpaired *t* test.
§ Compared with preoperative values.

version administered showed adequate psychometric properties comparable to those of the original version [32]. Patients indicated to what degree each item statement has applied over the past 7 days in a Likert five-point response option scale ranging from 0 (not at all) to 4 (very much). Two summary scores were obtained: the Trial Outcome Index (TOI) and the FACT-B+4. TOI is obtained by the sum of Physical and Functional well-being scores plus the Breast Cancer and Arm scales scores (range 0–108 points), and The FACT-B+4 is obtained by adding the scores of all the 40 items of the questionnaire (range 0–160). The TOI has been recommended [30] for clinical trials as a precise summary measure because it showed a high reliability and sensitivity. Using TOI allows enhancing measurement sensitivity and reduces outputs, summarizing physical and functional outcomes. TOI is considered an established targeted index [20,33]. Eton et al. [34] estimated the minimal important difference of TOI as 5 to 6 points. Higher scores indicate better QOL.

Analysis

A total of 110 patients (one third with ALND) were considered necessary to detect a difference between SLNB and ALND groups of 1.3 points (SD = 2) in the Arm Scale of FACT-B+4 [20] with a statistical power of at least 80% at a significance level of 5%, with an expected loss to follow-up of 20%, which corresponds to 88 patients at month 12.

Patient characteristics and clinical outcomes of the study groups (SLNB and ALND) were compared by using χ^2 or unpaired *t* tests depending on the nature of the variables. Intragroup changes in QOL were assessed by using univariate repeated-measures analysis of variance. When change was statistically significant, pairwise comparisons between the pretreatment evaluation and each posttreatment evaluation were made by using the paired *t* test with Bonferroni's method to adjust for multiple comparisons.

The objective assessment of arm swelling was expressed as changes in affected arm volume over time corrected for changes in the unaffected arm, for each patient at each time point. The 95% confidence interval of the mean difference between SLNB and ALND groups was calculated for the arm volume change and for the reductions in shoulder movement. The relative risk for the presence of subjective edema and clinical findings (dysesthesia, heaviness, winged scapula) was calculated considering the SLNB group as reference (relative risk = 1).

Figures showing the evolution of QOL scores during follow-up were constructed for each treatment group. To examine the effect of education, figures showing the evolution of QOL scores according to the level of education were also constructed. The differences in QOL mean scores at each assessment were compared between study groups by using the unpaired *t* test. Generalized estimating equation models were constructed with the Arm Scale, the TOI, and the FACT-B+4 global summary as dependent variables to assess the effect of treatment (SLNB vs. ALND) on QOL over time, while accounting for correlation among repeated measures. Age, body mass index, T and N cancer staging, radiotherapy, chemotherapy, and hormonotherapy were included in the models as adjusting factors. Time was included in the model as a categorical variable with four categories—pretreatment (reference) and months 1, 6, and 12—to prevent assum-

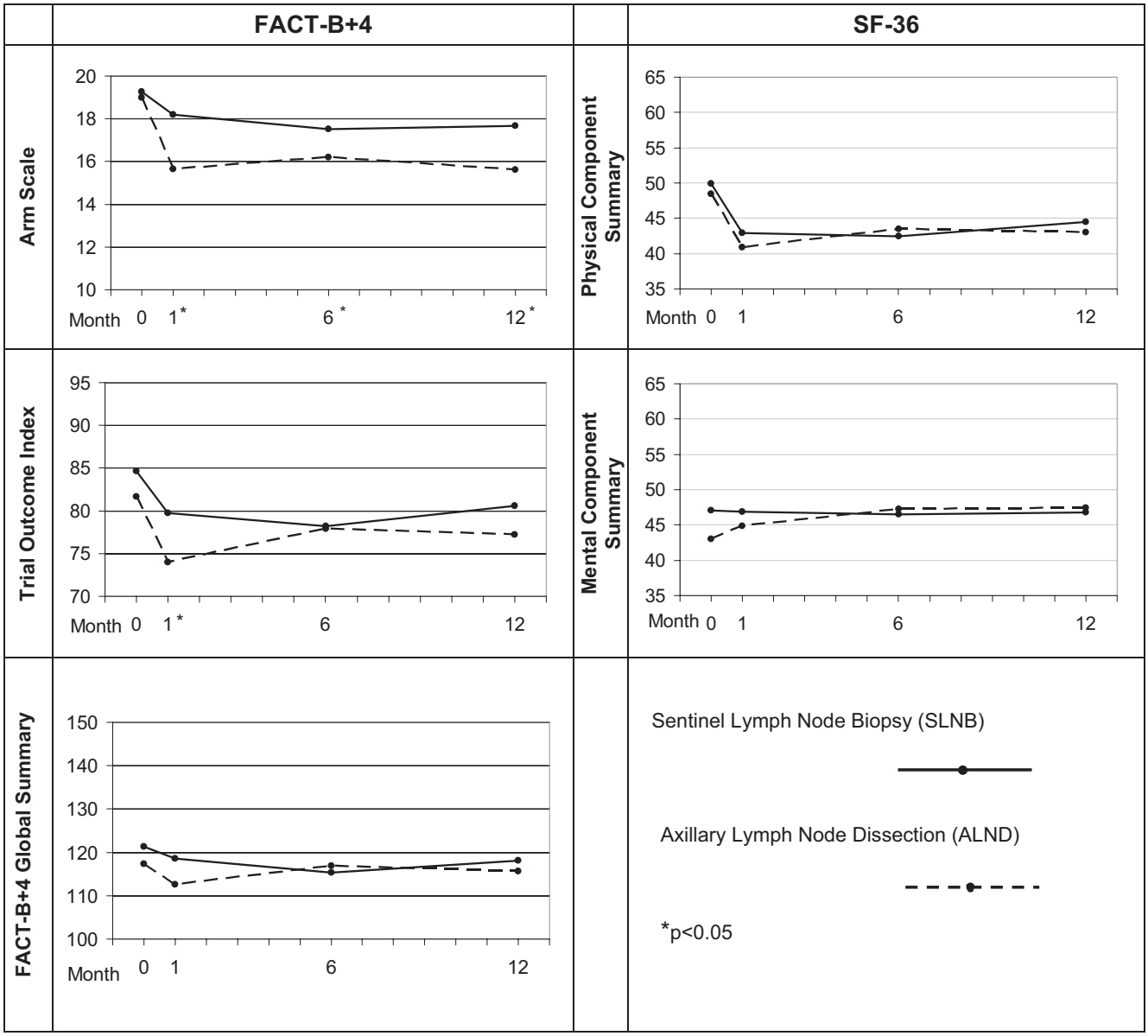

Fig. 1 – Mean QOL scores by treatment group. QOL, quality of life.

ing a linear association. SLNB was used as the reference group in the models, and interactions between treatment and time were also included. The statistical analyses were carried out by using SPSS 12.0 and SAS 9.1 software.

Results

From October 2006 to February 2009, a total of 121 patients agreed to participate. Twelve patients were excluded because of previous neoadjuvant chemotherapy, two patients because of severe shoulder pain and limitation before surgery, and one because of skin squamous cell carcinoma. Five participants refused to complete the QOL questionnaires at baseline, and another eight refused to continue in the study after baseline evaluation (five SLNB and three ALND). From 93 patients included in the study, 64 underwent SLNB, 9 SLNB followed by ALND, and 20 ALND as the first procedure. Therefore, the ALND group comprised 29 patients, 31.2% of the sample. QOL questionnaire completion rates at follow-up were 95.7% (n = 89), 90.3% (n = 84), and 86.0% (n = 80) at 1, 6, and 12 months after surgery, respectively.

Table 1 shows the patients' clinical and demographic characteristics. There were significant differences between SLNB and ALND in surgery technique: all patients in the SLNB group underwent tumorectomy while seven patients in the ALND group (24.1%) underwent mastectomy. Differences in tumor size category, node involvement, metastasis (TNM) cancer staging were also statistically significant: the SLNB group was mostly composed of patients in T1 or carcinoma in situ (89.1%) and N0, while almost half the patients presented T2 and 72.4% N ≥ 1 in the ALND group. The mean number of lymph nodes removed in the ALND group was 15.9 ± 5.4. Most patients (90.3%) received radiotherapy and 75.3% hormonotherapy without differences between SLNB and ALND groups, while chemotherapy was more frequent in the ALND group (89.7% vs. 32.8%; $P < 0.001$). The education level and the work status did not show significant differences between groups.

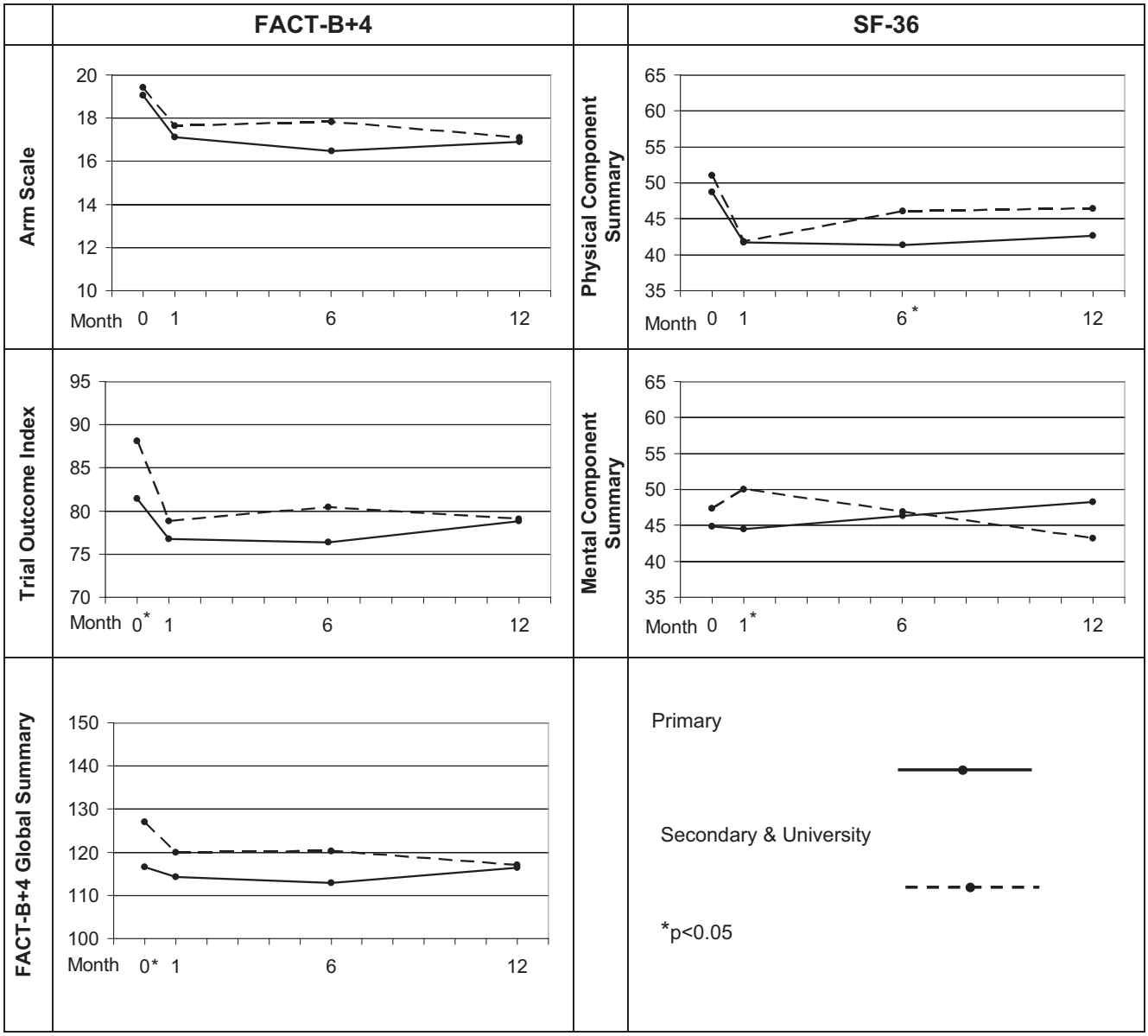

Fig. 2 – Mean QOL scores by level of education. QOL, quality of life.

Table 2 shows the pre- and posttreatment QOL scores for the SLNB and ALND groups. Among patients who underwent SLNB, deterioration after surgery was observed on the FACT Physical and Arm scales and FACT TOI summary. No statistically significant changes over time were observed for Social, Functional, and Breast scales of FACT-B+4. Compared with the pretreatment evaluation, the FACT Emotional Scale was significantly higher (better) at 12 months (means of 16.8 vs. 14.3; $P = 0.001$). This general pattern was similar for patients who underwent ALND, except for the FACT Physical Scale and FACT TOI, which presented no statistically significant differences among evaluations in this group. Both groups, SLNB and ALND, showed a significant decline in SF-36 PCS score after surgery, which persisted at 12 months of follow-up.

Table 3 shows clinical findings in the SLNB and ALND groups during the 12 months after surgery. Subjective edema was more common among patients treated with ALND than with SLNB at 1, 6, and 12 months of follow-up, with relative risk of 1.74, 2.35, and 2.11, respectively. Dysesthesia was significantly more frequent for ALND than for SLNB patients at each follow-up. Measured volume of affected upper limb increased around 100 mL more for the ALND group than for the SLNB group at 6 and 12 months. Small negative values observed at some follow-ups could be explained in part by physiological differences between both arms, as well as the associated error of measurement. However, other factors could not be excluded. There was one case of winged scapula belonging to the ALND group. The results for shoulder mobility were expressed as average reductions in the range of movements 1 year after surgery compared with preoperative values. Reduction in mobility was always higher on average in the ALND group, but differences between groups were not statistically significant.

Figure 1 shows the evolution of QOL during follow-up for each treatment group. The impact of surgery on the Arm Scale was higher among patients who underwent ALND, with the mean scores presenting statistically significant differences between groups at 1, 6, and 12 months after surgery. Surgery impact on TOI was higher in the short term, especially for the ALND group. Both groups showed a similar pattern of initial deterioration and subsequent recovery on FACT-B+4. No differences were found be-

Table 4 – GEE models constructed to assess the effect of SLNB and ALND on quality of life (adjusted by age, body mass index, radiotherapy, chemotherapy, and hormonotherapy).

	FACT-B+4 Arm Scale β (SE)	P	FACT-B+4 Trial Outcome Index β (SE)	P	FACT-B+4 global summary β (SE)	P	SF-36 Physical Component Summary β (SE)	P
Intercept	16.20 (1.94)	<0.001	85.18 (11.38)	<0.001	123.60 (14.79)	<0.001	55.74 (6.40)	<0.001
T								
IS	Ref.		Ref.		Ref.		Ref.	
T0	−0.27 (0.76)	0.721	−3.28 (4.43)	0.459	−1.84 (5.83)	0.752	−2.87 (2.59)	0.268
T2–T3	0.06 (0.92)	0.950	−3.05 (5.22)	0.559	−2.50 (7.09)	0.725	−1.12 (3.04)	0.712
N								
0	Ref.		Ref.		Ref.		Ref.	
1–3	−0.46 (0.95)	0.625	−3.10 (4.83)	0.522	−2.94 (6.51)	0.651	3.87 (2.91)	0.184
Group								
SLNB	Ref.		Ref.		Ref.		Ref.	
ALND	0.41 (0.88)	0.639	5.89 (5.22)	0.259	8.70 (7.25)	0.230	−1.89 (3.31)	0.568
Interaction Group × Time								
SLNB × Time (SLNB change from baseline)								
Basal	Ref.		Ref.		Ref.		Ref.	
1 mo	−1.15 (0.41)	0.005	−5.37 (1.69)	0.001	−2.97 (2.12)	0.161	−7.91 (1.41)	<0.001
6 mo	−1.87 (0.64)	0.004	−7.62 (2.05)	0.000	−7.88 (2.66)	0.003	−8.14 (1.58)	<0.001
12 mo	−1.58 (0.50)	0.001	−4.47 (1.87)	0.017	−3.54 (2.47)	0.152	−5.56 (1.29)	<0.001
ALND × Time (difference between ALND and SLNB on change)								
Basal	Ref.		Ref.		Ref.		Ref.	
1 mo	−2.97 (0.99)	0.003	−2.68 (3.43)	0.435	−2.28 (4.47)	0.609	−0.02 (2.86)	0.993
6 mo	−1.12 (0.92)	0.226	2.70 (3.67)	0.461	5.19 (4.93)	0.292	2.10 (2.47)	0.395
12 mo	−1.96 (0.75)	0.009	−1.76 (2.97)	0.554	−1.34 (4.12)	0.746	−1.25 (2.22)	0.572

ALND axillary lymph node dissection; GEE, generalized estimation equation; SE, standard error; SF-36, short form 36 health survey; SLNB sentinel lymph node biopsy; T, tumor size category; N, node involvement.

tween treatment groups for the physical and mental component summaries of SF-36.

Figure 2 shows the QOL evolution according to education level. Patients with primary studies showed poorer values in the TOI and the FACT-B+4 Global Summary at baseline, but these differences disappeared after surgery. SF-36 showed significant differences by education level only at 6 months in PCS and at 1 month in MCS.

Table 4 shows the results of the generalized estimation equation models constructed to assess QOL at different follow-up evaluations. In the FACT Arm model, patients in the SLNB group showed a statistically significant deterioration throughout follow-up compared with baseline. Beta coefficients estimated a change of −1.15, −1.87, and −1.58 in score points at 1, 6, and 12 months ($P < 0.01$). This deterioration was significantly higher for the ALND group, which presented −1.96 additional points of change on FACT Arm score at month 12 ($P = 0.009$) compared with the SLNB group. The model with the TOI showed that patients in the SLNB group presented a statistically significant deterioration throughout follow-up compared with baseline (beta coefficients indicated −5.37, −7.62, and −4.47 points of change at 1, 6, and 12 months, respectively; $P < 0.05$). The deterioration observed for the ALND group was not significantly different from that observed for the SLNB group. Similarly, the PCS of SF-36 showed statistically significant deterioration throughout follow-up compared with baseline. Beta coefficients estimated a change of −7.91, −8.14, and −5.56 points of PCS score at 1, 6, and 12 months without group differences. Finally, impairment measured with the FACT-B+4 Global summary was statistically significant only at month 6 (−7.88 score points; $P = 0.003$).

Discussion

In summary, this observational study of patients with breast cancer has shown that relevant differences persisted between SLNB and ALND groups for arm morbidity and its impact on functioning and QOL throughout 1 year after treatment. However, differences between groups detected by generic measures of QOL were negligible.

Deterioration of arm functioning after surgery measured with FACT-B+4 remained in both SLNB and ALND groups throughout the whole year of follow-up, but the deterioration was greater for the ALND group. The magnitude or clinical importance of the differences between SLNB and ALND groups was interpreted by using the standard categorization of effect size (ES) [35], and so 0.2, 0.5, and 0.8 of the SD represent small, moderate, and large differences, respectively. At the end of follow-up, patients in the ALND group scored almost 2 points lower in Arm score than did patients in the SLNB group (beta regression coefficient = −1.96; $P = 0.009$); given an SD of 2.0 on the Arm score at baseline, the ES was large (ES = 0.98), indicating a relevant difference between SLNB and ALND. Our findings were almost identical to those of the ALMANAC clinical trial, which included the development of the new Arm subscale to improve the breast cancer site-specific module, resulting in the FACT-B+4 questionnaire [20,31]. Peintinger et al. [22] also reported similar findings with the Arm subscale of the EORTC QLQ-BR23: patients treated with ALND showed a statistically higher deterioration (mean of change = 12.9; 95% CI 6.2 to 19.6) than did patients treated with SLNB (mean of change = −5.5; 95% CI −14.1 to 3.1).

Arm functioning was a measure of the impact of arm morbidity on the women's QOL. In this sense, differences in the Arm functioning scale observed between treatment groups reflected the

larger volume change and the higher rate of self-reported symptoms (e.g., 35.5% vs. 11.8% subjective edema at 12 months; $P = 0.002$) among patients who underwent ALND compared with patients who underwent SLNB. Our findings agree with those reported by Purushotham et al. [36] who observed that the SLNB group was less likely to have subjective edema (70%–80% reduction in overall odds ratios), a lower increase in measured volume, and less reduction of some shoulder movements.

FACT-B+4 summaries showed a decline (QOL deterioration) 1 month after surgery with a subsequent partial recovery. There were no significant differences in the TOI and global summary scores of FACT-B+4 (beta coefficients = −1.76 and −1.34, respectively, at month 12) when comparing the SLNB group with the ALND group. Reported differences between SLNB and ALND groups in the ALMANAC trial [20] were similar, around 2 points on TOI and FACT-B+4 global summaries at month 12, but statistically significant ($P = 0.011$ and $P = 0.024$, respectively). Beyond statistical significance, the clinical relevance of these differences is arguable. These 2-point differences detected in the ALMANAC trial are far from the minimal important difference of 5 points previously defined for the TOI and the FACT-B+4 summaries, and they reflect only a small ES (<0.2). This clinical relevance–based interpretation of the differences make ALMANAC findings totally consistent with ours, and also with results from previous studies using the EORTC QLQ-C30 [19,22].

Regarding the results of the generic SF-36, compared with Spanish SF-36 reference norms [29], patients presented a slight deterioration in their MCS scores (mean = 45.8; SD = 12.7) but a similar PCS score (mean = 49.5; SD = 9.4) before surgery. The median of the SF-36 MCS and PCS scores are 50.1 and 47.5 in 55- to 64-year-old Spanish women [27]. The mental component was quite stable during follow-up. The physical component deteriorated after surgery and remained quite stable throughout the whole year of follow-up, without differences between SLNB and ALND groups. In previous studies by Purushotham et al. [36] and Del Bianco et al. 37], no significant differences between these treatments were found either.

Previous studies showed QOL differences depending on education level [38,39]. In our study, women with primary school presented lower (worse) QOL scores than did those with secondary or university studies at baseline. This difference between education level groups, however, disappeared after surgery and thereafter. This finding could reflect the universal coverage of the Spanish National Health Service, which facilitates access to preventive and treatment services independently of socioeconomic status.

In summary, our findings support that general well-being scales do not reflect the impact of upper limb morbidity on QOL of patients with breast cancer. To assess the effect of SLNB versus ALND in QOL, proper questionnaires also covering the treatment impact on the arm are needed. On the other hand, it is not surprising that scales such as physical functioning do not cover this aspect because their focus is on limitations of lower limb mobility (whatever the questionnaire used). However, this is not the case for social or emotional scales whose content is not directly related to physical limitation but rather to the impact on mental health and participation in society. Therefore, these negative results might be suggesting that upper arm morbidity has no real impact on emotional and social well-being.

Some limitations of this study should be taken into account. First, this is an observational study and participants were not randomly assigned to treatment groups. ALND was applied to all patients with positive nodes, and the clinical stage itself could be a great impact in the prognosis and QOL for a patient with breast cancer. However, currently, the indication of the SLNB technique is well demonstrated and a clinical trial would not be justified in this case. To take possible effects of clinical differences into account, T and N were included in the generalized estimation equation models, which were also adjusted by other relevant variables. Second, the sample was smaller than forecasted due to 13 patients who refused to continue in the study before surgery, which led to a final sample of 93. It was, however, partly compensated by loss of follow-up, which was lower than 20% assumed in the sample size calculation (14%). Furthermore, the reasons why patients dropped out during follow-up (nine SLNB and four ALND) were not disease-related, according to the review of medical records. On the other hand, we consider that the strengths of our study were the longitudinal prospective design, which included preoperative baseline assessment, and that we used validated generic and disease-specific QOL questionnaires, the SF-36 and the FACT-B+4, thus allowing comparison with relevant previous studies to clarify the subsequent reasons for controversy.

Conclusion

In conclusion these results confirm that SLNB is associated with better patient well-being in comparison to ALND. Disagreement between previous QOL studies comparing SLNB and ALND is explained by differences in the instruments used to measure QOL. Our findings confirm that there are clinically relevant between-treatment differences in Arm functioning and upper limb morbidity, while there are no relevant differences in general well-being at this time frame, measured with disease-specific questionnaires such as the FACT-B+4 or generic questionnaires such as the SF-36.

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