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ORIGINAL ARTICLE

Prospective study of shoulder strength, shoulder range of motion, and lymphedema in breast cancer patients from pre-surgery to 5 years after ALND or SLNB

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Abstract

Objective Determine the changes in shoulder strength, shoulder range of motion, and arm volume in breast cancer patients treated with sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND)

Method Sixty-eight SLNB and 44 ALND patients were followed up from pre-surgery to 5 years after surgery. Primary outcomes were the differences between affected and non-affected sides for the following: shoulder strength measured by dynamometry, shoulder range of motion measured by goniometry, and lymphedema measured by volume. As a secondary outcome, health-related quality of life (HRQL) was assessed by the Short Form-36 Health Survey (SF-36) and the Functional Assessment of Cancer Therapy for breast cancer (FACT-B+4) questionnaires. Changes over time were tested for SLNB and ALND using univariate repeated measures analysis of variance. Generalized estimating equation models were constructed to assess the effect of SLNB and ALND over time.

Results After 5 years, the ALND group had significant loss of strength for internal rotators (1.39 kg, $p = 0.001$) and significant arm volume increase (132.45 mL, $p = 0.031$). The ALND group had a greater number of patients with clinically relevant internal rotator strength loss (38.7 vs. 13.6%, $p = 0.012$) and a greater number of lymphedema requiring treatment (33.3 vs. 3.4%, $p < 0.001$) than the SLNB group. A loss of strength for shoulder external rotators, shoulder range of motion, and HRQL in physical and arm domains persisted at 5 years in both SLNB and ALND groups.

Conclusion These results could help understand and plan the prevention, needs, and long-term care of breast cancer patients.

Keywords Breast cancer · Lymphedema · Shoulder · Quality of life

Introduction

The excellent survivorship now achieved with breast cancer patients entails the challenge of addressing the long-term adverse effects of treatments being applied, including surgery, chemotherapy, radiotherapy, and hormonotherapy.

The health-related quality of life (HRQL) of women after breast cancer is considerably worse than healthy women in the physical and psychological well-being domains [1–3]. Arm dysfunction and persistent symptoms associated with arm morbidity are related to lower HRQL among breast cancer survivors [4–8]. Pain, lymphedema, restricted range of shoulder movement, and strength deficits are the most frequently reported arm morbidities after breast cancer [7–12].

Weakness in the arm has been reported by up to one in four patients after breast cancer [13]. Longitudinal studies have found a loss of shoulder strength of the affected side during follow-up. However, there are very few studies reporting results for specific muscle groups (e.g., the shoulder rotator, abductor, or serratus anterior muscles) [14, 15]. Knowing which muscles or groups of muscles are responsible of the loss of strength could help more precise identification of the cause and possibly preventing it. Moreover, this information could help develop strategies for more efficient rehabilitation treatments.

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Patients treated with axillary lymph node dissection (ALND) are more likely than sentinel lymph node biopsy (SLNB) of reduced range of motion and reduced muscle strength, pain, lymphedema, and decreased degree of activities in daily living [16–19]. Along the same lines, the HRQL of patients treated with ALND show worse outcomes than those treated with SLNB for arm function [6, 20–22]. But few prospective studies have followed patients beyond 3 years after nodal surgery for breast cancer [14]. Kootstra et al. found that 7 years after surgery, 41% of the women treated with SLNB had one or more impairments in the arm, while impairments were found in 70% of the women treated with ALND [14]. De Gournay et al. reported a better outcome in the SLNB group than in ALND group measured with the arm symptom score at 6 years after surgery [23].

Although there are some studies trying to establish the best options for long-term care of these patients [24–28], further research is still needed to understand the impact of adverse effects and to determine the long-term needs of women who have been treated for breast cancer [2, 24, 29, 30].

The objective of the present study was to determine the changes in the upper limb in breast cancer patients treated with ALND or SLNB in a prospective way from pre-surgery to 5 years. Shoulder strength, shoulder range of motion, and the arm volume were considered primary outcomes, and HRQL as a secondary outcome.

Method

This was a prospective longitudinal observational study of breast cancer patients who had undergone surgery. Consecutive patients were recruited from the breast cancer unit of a general university hospital with a community-based breast cancer screening program. The Research Ethics Committee approved the study and it was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from participants before being included.

Inclusion criteria were having an invasive carcinoma or high-grade ductal carcinoma in situ (DCIS) of the breast, and to be considered for surgery. Exclusion criteria were bilateral breast cancer, pre-existing severe disorders on the affected or unaffected upper limbs, or cognitive impairment which could interfere with collaboration.

Clinical assessment and patient self-completion of HRQL questionnaires took place in the rehabilitation setting of the breast cancer unit, at baseline (pre-surgery) and at the first and fifth year post-surgery. The tumor characteristics, the type of surgery, and treatments applied were collected from medical records.

The shoulder strength of both arms was measured in kilograms by a hand-held dynamometer assessing external rotators, internal rotators, abductors, and the serratus anterior muscles. It was an isometric test according to the protocol described by Donatelli et al. [31]. The test positions described in this protocol were chosen to obtain good test-retest reliability, avoiding pain and minimizing synergist contribution. The shoulder range of motion of both arms was measured by a goniometer in degrees (flexion, abduction, external rotation, and internal rotation) [32].

The presence of lymphedema was monitored pre-surgery and during follow-up. The physician asked the patient about pain, heaviness, tightness, hardness, or any other symptom she could have felt, as well as if she had observed any change in the upper limb volume. The physician explored the skin aspect and consistency, the presence of inflammatory signs, swelling, and pitting. The perimeters of both upper limbs were measured at seven pre-established points. The volume of each upper limb was then obtained by the truncated cone formula [33].

HRQL questionnaires were self-administered in the waiting room. The Short Form-36 Health Survey (SF-36) version 2 [34] was used, and scores for physical and mental component summaries (PCS and MCS) were calculated using the recommended standardized procedure [35].

The FACT-B+4 questionnaire [36–38] is composed of 40 items covering four generic scales of well-being (Physical, Emotional, Social, and Functional) and two side-specific scales: Breast Cancer (9 items) and Arm (5 items). The Arm-specific scale assesses arm morbidity by asking about swelling, tenderness, pain, poor range of arm movements, numbness, and stiffness. The Trial Outcome Index is the sum of Physical and Functional wellbeing plus Breast Cancer and Arm scales (range 0–108 points). The FACT-B+4 Global Summary is obtained by adding all the items of the questionnaire (range 0–160 points). Higher scores indicate better HRQL.

Analysis

Sample size was calculated originally to detect between-group differences of 1.3 points on the Arm scale of the FACT-B+4 at short term as previously published [20]. Since evaluation at long term was focused on the shoulder, we calculated the statistical power for this outcome with our sample composed of 77 women who completed the follow-up at 5 years after diagnosis. The sample size gave a statistical power of 0.8 to detect a 20% difference in the proportion of patients with clinically relevant strength impairments between SLNB and ALND using a chi-squared test with type I error of 5%.

The analysis was performed with the groups treated by SLNB and ALND pre-surgery, at 1, and at 5 years of follow-up. The primary outcomes were the difference between affected and unaffected sides for the following: shoulder strength, shoulder range of motion, and arm volume. However, for descriptive purposes, the results of affected

and unaffected arms were also calculated. Another secondary outcome was HRQL of FACT-B+4, as well as PCS and MCS of the SF-36 questionnaire.

The characteristics of patients who underwent SLNB and ALND were compared using chi-squared or unpaired *t* tests depending on the nature of the variables. Intra-group changes in strength, shoulder range of motion, volume, and HRQL were assessed for each treatment group using univariate repeated measures analysis of variance. When change was statistically significant, post hoc comparisons between the pre-treatment evaluation and each post-treatment evaluation were made using the paired *t* test with Bonferroni's method to adjust for multiple comparisons.

The differences in the proportion of patients with clinically relevant changes at 5 years when comparing the ALND and SLNB groups were explored using the chi-squared test. The loss of shoulder strength or the loss of range of motion was considered clinically relevant when it was 20% or more compared to pre-surgery. A lymphedema was considered clinically relevant when it required treatment. This concept included a difference of 2 cm or more in some arm perimeters, but also considered relevant symptoms of lymphedema on the hand or wrist even when there was not 2 cm of difference.

Figures showing the evolution of HRQL scores for each treatment group during follow-up were constructed. The differences between SLNB and ALND in HRQL mean scores at each assessment were compared using the unpaired *t* test.

Generalized estimating equation (GEE) models were constructed to assess the effect of treatment (SLNB vs. ALND) on shoulder strength, shoulder range of motion, and arm volume over time as dependent variables. In the same way, GEE models were constructed to assess the effect of treatment on HRQL over time. The dependent variables were Arm scale, TOI, the Global Summary of the FACT-B+4 questionnaires, and the PCS of the SF-36. Age, T and N cancer staging, dominant side, radiotherapy, chemotherapy, and hormonotherapy were included in the models as adjusting factors. The statistical analyses were carried out using SPSS 12.0 and SAS 9.4 software.

Results

From October 2006 to May 2009, 134 patients were examined for eligibility. Three patients declined to participate in the study, 5 patients refused to complete the HRQL questionnaire, 2 patients were excluded because of active shoulder problems, 3 patients could not complete the baseline examination, and 9 patients did not attend any follow-up. Among the 112 patients analyzed, 89 were followed up to 1 year and 77 were followed up to 5 years. The median of the time from pre-surgery to first follow-up was 1.05 years [IQ range 1.03–1.12], and from pre-surgery to last follow-up was 5.16 [IQ range 5.04–5.35]. There were no significant differences between treatment groups.

The characteristics of the patients with incomplete follow-up were similar to those with complete follow-up (Table 1). A significant difference was found by T stage in the SLNB group where patients with incomplete follow-up had greater tumor size categories than patients with complete (T2 31.8 vs. 4.3%, $p = 0.006$). In the ALND group, the patients with incomplete follow-up received less hormonotherapy than patients with complete follow-up (46.2 vs. 77.4%, $p = 0.042$).

Shoulder strength

Table 2 shows results over time for the SLNB and ALND groups. Among patients undergoing SLNB, the unaffected side showed after 1 year significant loss of serratus anterior muscle strength from pre-surgery and an almost significant increase in external rotators strength after 5 years. The ALND group showed losses in the strength of the affected side for external rotators 1 year after surgery and for internal rotators at 1 and 5 years after surgery. The unaffected side of the ALND group showed an increase of external rotator strength from pre-surgery to 5 years after. The differences between affected and unaffected sides in ALND group showed a significant loss of strength for internal rotators after 1 (1.68 kg, $p < 0.001$) and 5 years (1.39 kg, $p = 0.001$). The mean change of differences between affected and unaffected sides at 5 years showed a significantly greater loss for internal rotator strength in the ALND group than the SLNB group (mean difference − 1.15 kg, 95% CI − 2.15 to − 0.14) (data not shown).

The GEE models (Table 3) showed differences at baseline when the dominant side was affected: beta coefficients indicated 0.3 kg more for abductors strength and 89.6 mL more in arm volume compared to the reference. The interactions between treatment groups and time indicated a significant loss of strength for external rotators (− 0.94 kg, $p = 0.016$). The ALND group only differed from SLNB for internal rotators' strength 1 year after surgery (− 0.91 kg, $p = 0.047$).

Table 4 shows the number and percentage of women with clinically relevant impairment at 5 years. The ALND group had a significantly greater number of patients with internal rotator strength loss (38.7 vs. 13.6%, $p = 0.012$) than the SLNB group.

Shoulder range of motion

The affected side of the ALND group lost shoulder range of motion comparing pre-surgery with both 1 and 5 years after (Table 2). The interactions between treatment groups and time in the GEE models (Table 3) indicated a

Table 1 Comparison between patients with complete and incomplete follow-up

	All patients			SLNB			ALND		
	Missing follow-up ($n = 35$)	Complete follow-up ($n = 77$)	p value	Missing follow-up ($n = 22$)	Complete follow-up ($n = 46$)	p value	Missing follow-up ($n = 13$)	Complete follow-up ($n = 31$)	p value
Age (years)									
Mean (SD)	59.4 (10.8)	59.5 (8.1)	0.943	58.1 (11.1)	60.3 (7.4)	0.346	61.5 (10.3)	58.4 (9.2)	0.328
Missing	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Body mass index (kg/m^2)	29.2 (5.0)	28.6 (4.7)	0.607	28.3 (5.0)	27.5 (3.9)	0.480	31.3 (4.8)	31.0 (5.5)	0.854
Missing	4 (11.4%)	10 (13.0%)		0 (0.0%)	1 (2.2%)		4 (30.8%)	9 (29.0%)	
Affected side									
Left	17 (48.6%)	34 (44.2%)	0.664	9 (40.9%)	22 (47.8%)	0.592	8 (61.5%)	12 (38.7%)	0.165
Right	18 (51.4%)	43 (55.8%)		13 (59.1%)	24 (52.2%)		5 (38.5%)	19 (61.3%)	
Missing	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Dominant side									
Non-affected	16 (48.5%)	32 (43.8%)	0.656	9 (42.9%)	21 (46.7%)	0.772	7 (58.3%)	11 (39.3%)	0.267
Affected	17 (51.5%)	41 (56.2%)		12 (57.1%)	24 (53.3%)		5 (41.7%)	17 (60.7%)	
Missing	2 (5.7%)	4 (5.2%)		1 (4.5%)	1 (2.2%)		1 (7.7%)	3 (9.7%)	
Surgery technique									
Breast conserving	32 (91.4%)	71 (92.2%)	0.888	22 (100.0%)	46 (100.0%)	–	10 (76.9%)	25 (80.6%)	0.780
Mastectomy	3 (8.6%)	6 (7.8%)		0 (0.0%)	0 (0.0%)		3 (23.1%)	6 (19.4%)	
Missing	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Nodes excised	6.6 (6.8)	7.0 (7.5)	0.793	1.7 (0.7)	1.7 (1.0)	0.976	14.6 (3.9)	14.4 (6.0)	0.915
Missing	1 (2.9%)	3 (3.9%)		1 (4.5%)	3 (6.5%)		0 (0.0%)	0 (0.0%)	
T (size category)									
IS	2 (5.7%)	9 (11.7%)	0.497	2 (9.1%)	9 (19.6%)	0.006	0 (0.0%)	0 (0.0%)	0.896
1	19 (54.3%)	48 (62.3%)		13 (59.1%)	35 (76.1%)		6 (46.2%)	13 (41.9%)	
2	11 (31.4%)	14 (18.2%)		7 (31.8%)	2 (4.3%)		4 (30.8%)	12 (38.7%)	
3	2 (5.7%)	5 (6.5%)		0 (0.0%)	0 (0.0%)		2 (15.4%)	5 (16.1%)	
4	1 (2.9%)	1 (1.3%)		0 (0.0%)	0 (0.0%)		1 (7.7%)	1 (3.2%)	
Missing	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Histology									
Ductal carcinoma	32 (91.4%)	69 (89.6%)	0.764	21 (95.5%)	42 (91.3%)	0.540	11 (84.6%)	27 (87.1%)	0.827
Lobular carcinoma	3 (8.6%)	8 (10.4%)		1 (4.5%)	4 (8.7%)		2 (15.4%)	4 (12.9%)	
Missing	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Radiotherapy	32 (91.4%)	70 (90.9%)	0.929	20 (90.9%)	41 (89.1%)	0.821	12 (92.3%)	29 (93.5%)	0.882
Missing	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Chemotherapy	22 (62.9%)	42 (54.5%)	0.410	10 (45.5%)	13 (28.3%)	0.161	12 (92.3%)	29 (93.5%)	0.882
Missing	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Hormonotherapy	22 (62.9%)	58 (75.3%)	0.176	16 (72.7%)	34 (73.9%)	0.917	6 (46.2%)	24 (77.4%)	0.042
Missing	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	

Table 2 Repeated measures analysis of variance (ANOVA) of shoulder strength, motion, and arm volume

	n	Mean (SD)			*p* value (ANOVA)	*p* value (vs. pre-treatment)*	
		Pre-treatment	Year 1	Year 5		Year 1	Year 5
SLNB group							
Affected side							
External rotator strength	40	8.3 (1.7)	8.3 (2.0)	8.7 (3.3)	0.581	–	–
Internal rotator strength	40	9.8 (2.1)	9.3 (2.1)	9.1 (2.2)	0.128	–	–
Abductor strength	40	5.4 (1.4)	5.2 (1.4)	5.1 (1.6)	0.369	–	–
Serratus anterior strength	39	12.9 (4.3)	11.4 (3.6)	12.5 (4.0)	0.211	–	–
Shoulder range of motion	41	524.6 (19.6)	514.6 (28.6)	523.5 (19.7)	0.066	–	–
Arm volume	41	2028.4 (289.9)	2062.5 (295.2)	2069.5 (283.9)	0.313	–	–
Unaffected side							
External rotator strength	40	8.1 (2.3)	8.4 (2.6)	9.3 (3.4)	0.020	1.000	0.050
Internal rotator strength	40	9.6 (2.3)	9.2 (2.1)	8.9 (2.4)	0.200	–	–
Abductor strength	40	5.6 (1.6)	5.3 (1.6)	5.0 (1.8)	0.068	–	–
Serratus anterior strength	40	13.4 (5.3)	11.3 (3.6)	12.1 (4.0)	0.038	0.029	0.525
Shoulder range of motion	41	522.2 (27.5)	521.2 (23.0)	527.3 (15.6)	0.271	–	–
Arm volume	41	2036.4 (304.0)	2059.4 (286.3)	2089.1 (305.8)	0.263	–	–
Difference between affected and unaffected side							
External rotator strength	39	0.17 (2.15)	− 0.18 (1.86)	− 0.78 (2.60)	0.092	–	–
Internal rotator strength	39	0.19 (1.73)	0.11 (1.32)	0.10 (1.54)	0.849	–	–
Abductor strength	39	− 0.24 (1.08)	− 0.07 (1.05)	0.09 (1.29)	0.370	–	–
Serratus anterior strength	38	− 0.38 (3.22)	0.05 (2.00)	0.22 (1.95)	0.460	–	–
Shoulder range of motion	41	2.44 (21.22)	− 6.59 (23.70)	− 3.78 (13.68)	0.178	–	–
Arm volume	41	− 7.96 (125.86)	3.08 (103.72)	− 19.65 (111.81)	0.419	–	–
ALND group							
Affected side							
External rotator strength	29	9.5 (2.6)	8.1 (2.7)	9.5 (3.5)	0.006	0.002	1.000
Internal rotator strength	29	11.1 (2.8)	8.6 (2.8)	9.6 (2.6)	< 0.001	< 0.001	0.002
Abductor strength	29	5.7 (1.5)	5.2 (1.6)	5.3 (1.6)	0.138	–	–
Serratus anterior strength	29	14.7 (4.2)	12.0 (4.9)	13.3 (4.4)	0.051	–	–
Shoulder range of motion	28	525.0 (18.8)	508.9 (24.1)	516.1 (23.6)	0.011	0.006	0.030
Arm volume	30	2267.8 (525.1)	2370.9 (647.3)	2472.5 (763.0)	0.020	0.128	0.068
Unaffected side							
External rotator strength	29	8.6 (2.2)	8.2 (2.5)	9.9 (3.1)	0.011	0.936	0.024
Internal rotator strength	29	10.2 (2.5)	9.3 (2.4)	10.0 (2.7)	0.060	–	–
Abductor strength	29	5.7 (1.7)	5.3 (1.4)	5.5 (1.7)	0.208	–	–
Serratus anterior strength	29	14.7 (4.5)	12.6 (4.6)	13.2 (4.3)	0.130	–	–
Shoulder range of motion	28	523.6 (22.6)	518.4 (25.0)	515.0 (42.1)	0.533	–	–
Arm volume	30	2227.5 (491.0)	2254.1 (530.4)	2299.8 (583.6)	0.493	–	–
Difference between affected and unaffected side							
External rotator strength	29	0.87 (2.12)	− 0.14 (2.01)	− 0.37 (2.22)	0.072	–	–
Internal rotator strength	29	0.97 (1.26)	− 0.71 (1.80)	− 0.42 (1.33)	0.002	< 0.001	0.001
Abductor strength	29	0.00 (0.89)	− 0.08 (0.89)	− 0.13 (0.82)	0.668	–	–
Serratus anterior strength	29	− 0.02 (2.53)	− 0.63 (2.51)	0.08 (2.51)	0.393	–	–
Shoulder range of motion	28	1.43 (17.58)	− 9.46 (21.53)	1.07 (43.81)	0.329	–	–
Arm volume	30	40.24 (141.53)	116.87 (292.12)	172.69 (316.95)	0.046	0.272	0.031

Strength is expressed in kilograms, shoulder range of motion in degrees, and arm volume in milliliters

*Post hoc tests with the Bonferroni adjustment for multiple comparisons

Table 3 GEE models for shoulder strength, shoulder range of motion, and arm volume

	External rotator strength		Internal rotator strength		Abductor strength		Serratus anterior strength		Shoulder range of motion		Arm volume	
	Beta (SE)	*p* value	Beta (SE)	*p* value	Beta (SE)	*p* value	Beta (SE)	*p* value	Beta (SE)	*p* value	Beta (SE)	*p* value
Intercept	0.04 (1.01)	0.965	− 0.17 (0.94)	0.858	0.04 (0.46)	0.936	− 0.41 (1.30)	0.753	8.64 (12.23)	0.480	− 59.61 (93.27)	0.523
T												
IS–T1	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–
T2–T4	0.10 (0.40)	0.810	− 0.04 (0.28)	0.884	0.00 (0.17)	0.986	0.97 (0.52)	0.061	− 4.10 (4.31)	0.342	21.36 (49.32)	0.665
N												
0	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–
1–3	0.08 (0.75)	0.916	0.33 (0.49)	0.495	0.47 (0.29)	0.109	− 0.48 (0.79)	0.544	− 0.47 (4.89)	0.924	64.80 (75.46)	0.391
Group												
SLNB	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–
ALND	0.48 (0.82)	0.562	0.58 (0.59)	0.329	− 0.40 (0.31)	0.189	1.21 (0.96)	0.207	− 2.36 (5.33)	0.658	− 58.74 (65.64)	0.371
Dominant side												
Non-affected	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–
Affected	− 0.14 (0.34)	0.681	0.20 (0.23)	0.378	0.32 (0.16)	0.040	− 0.07 (0.38)	0.847	− 2.00 (2.95)	0.497	89.60 (27.53)	0.001
Missing	0.00 (0.56)	0.999	0.49 (0.59)	0.399	0.11 (0.29)	0.708	− 1.26 (0.51)	0.014	0.28 (4.87)	0.955	86.11 (81.03)	0.288
Interaction group × time												
SLNB × time (SLNB change from baseline)												
Baseline	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–
1 year	− 0.40 (0.31)	0.202	− 0.44 (0.31)	0.165	− 0.14 (0.20)	0.488	0.09 (0.46)	0.845	− 11.05 (5.43)	0.042	− 8.36 (15.67)	0.594
5 years	− 0.94 (0.39)	0.016	− 0.31 (0.30)	0.314	0.08 (0.15)	0.584	0.63 (0.39)	0.108	− 7.76 (3.15)	0.014	− 34.43 (20.74)	0.097
ALND × time (difference between ALND and SLNB on change)												
Baseline	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–	Ref.	–
1 year	− 0.34 (0.53)	0.523	− 0.91 (0.46)	0.047	0.14 (0.28)	0.617	− 0.44 (0.77)	0.569	− 4.61 (8.54)	0.589	76.56 (53.35)	0.151
5 years	0.18 (0.69)	0.794	− 0.92 (0.51)	0.072	− 0.10 (0.26)	0.694	− 0.61 (1.01)	0.545	4.39 (6.60)	0.506	178.10 (64.05)	0.005

Adjusted by age, radiotherapy, chemotherapy, and hormonotherapy

Table 4 Number and percentage of women with clinically relevant impairments at 5 years after surgery

	All patients	SLNB	ALND	*p* value
External rotator strength	26 (34.7%)	16 (36.4%)	10 (32.3%)	0.713
Internal rotator strength	18 (24.0%)	6 (13.6%)	12 (38.7%)	0.012
Abductor strength	12 (16.0%)	5 (11.4%)	7 (22.6%)	0.192
Serratus anterior strength	15 (20.0%)	7 (15.9%)	8 (25.8%)	0.291
Shoulder range of motion	17 (22.1%)	9 (19.6%)	8 (25.8%)	0.517
Lymphedema treated	15 (15.5%)	2 (3.4%)	13 (33.3%)	< 0.001

significant reduction in the range of motion (− 7.76, $p = 0.014$) at 5 years post-surgery in the SLNB group (reference). The ALND group did not present any statistically significant differences from SLNB.

Arm volume

Table 2 shows no statistically significant changes in the SLNB group. The ALND group, however, increased arm volume of the affected side almost significantly 5 years after surgery. The differences between the affected and unaffected sides in the ALND group showed a significant increase after 5 years (132.45 mL, $p = 0.031$).

The increase in the arm volume was significantly greater for the ALND group than for the SLNB (mean difference 151.5 mL, 95% CI 45.8 to 257.3) (data not shown).

The GEE model (Table 3) showed a significant increase of arm volume at 5 years for the ALND group. Patients undergoing ALND suffered more frequently a lymphedema which required treatment than those in the SLNB group at 5 years after surgery (33.3% vs. 3.4%, $p < 0.001$) (Table 4).

Health-related quality of life

Table 5 shows the mean HRQL score along time testing differences from pre-surgery to 1 and 5 years after, separately for SLNB and ALND. Both surgery groups showed some worsening in Physical and Arm dimensions of FACT-B+4, but some improvement in the Emotional dimension. The PCS of the SF-36 showed statistical significant deterioration from pre-surgery to 1 and 5 years after only for the SLNB group.

Figure 1 shows the HRQL comparison between ALND and SLNB groups at each point of follow-up. The Arm and TOI components of FACT-B+4 (Fig. 1a, b) showed significantly lower values among ALND patients at 1 and 5 years, while the Global Summary of FACT-B+4 (Fig. 1c) only showed significant differences at 5 years. The PCS and MCS of the SF-36 questionnaire did not show any significant differences between groups (Fig. 1d, e).

In the FACT-B+4 Arm GEE model (Table 6, supplementary), patients undergoing SLNB (reference group) showed a statistically significant deterioration throughout follow-up compared to baseline. Beta coefficients estimated a change of − 1.3 and − 1.4 points at 1 and 5 years after surgery. The ALND group added to this deterioration − 2.2 points at year 1. The SF-36 Physical Component Summary model showed a deterioration of − 5.4 points at year 1 and − 6.2 points 5 years after surgery. The ALND group did not differ from SLNB in this model.

Discussion

From pre-surgery to 5 years of follow-up, there was a persistent loss of shoulder strength of the affected side for the internal rotators in the ALND group, which also presented more cases of upper limb lymphedema than the SLNB group. From pre-surgery to 5 years of follow-up, both SLNB and ALND groups showed impairment in the Physical and Arm components of HRQL scales, while Emotional components improved.

There was a continued loss of strength for the shoulder internal rotators of the ALND group during follow-up. The ALND group had a greater loss of shoulder internal rotator strength than SLNB. The difference between ALND and SLNB persisted when the loss of strength was dichotomized according to the clinical relevance, where the percentage of patients with loss of internal rotator strength at 5 years was significantly higher in the ALND group. The GEE model showed the same trend in the loss of internal rotator strength but did not achieve significance at 5 years.

There are few studies with a long-term follow-up of shoulder strength, and with pre-surgical information in breast cancer patients. Among them, Kootstra et al. [14] found that at 7 years after surgery, shoulder abduction strength difference between affected-unaffected sides had decreased significantly, although there were no significant differences when comparing SLNB to ALND. In the same study, the authors did not find any significant differences when comparing elbow or grip strength of the affected side. These authors classified the shoulder loss of strength considering a loss of 20% or more as clinically relevant

Table 5 Repeated measures analysis of variance (ANOVA) of quality-of-life measures

	n	Mean (SD)			*p* value (ANOVA)	*p* value (vs. pre-treatment)*	
		Pre-treatment	Year 1	Year 5		Year 1	Year 5
SLNB group							
FACT-B+4							
Physical	40	25.3 (2.9)	23.4 (4.2)	22.8 (4.4)	0.012	0.004	0.008
Social	38	23.3 (4.0)	21.3 (4.7)	22.3 (4.3)	0.087	–	–
Emotional	39	13.7 (4.7)	16.6 (4.4)	17.6 (3.7)	< 0.001	< 0.001	< 0.001
Functional	41	19.2 (4.9)	18.4 (5.5)	18.4 (4.7)	0.457	–	–
Breast	39	21.5 (5.2)	22.5 (5.1)	21.2 (5.2)	0.281	–	–
Arm	38	19.1 (2.2)	17.9 (2.8)	17.8 (2.4)	0.045	0.096	0.011
TOI	36	85.5 (11.2)	81.8 (13.6)	81.1 (13.3)	0.125	–	–
FACT-B+4 Global Summary	35	122.1 (15.8)	119.7 (20.7)	120.7 (17.3)	0.591	–	–
SF-36							
PCS	39	50.7 (8.4)	46.0 (8.2)	43.9 (9.4)	0.002	0.005	0.001
MCS	39	47.1 (13.1)	48.8 (12.1)	47.2 (11.4)	0.540	–	–
ALND group							
FACT-B+4							
Physical	30	22.9 (5.7)	20.1 (5.9)	21.9 (4.7)	0.027	0.006	0.793
Social	29	23.3 (4.7)	22.1 (4.2)	21.6 (4.8)	0.280	–	–
Emotional	29	14.3 (5.5)	16.1 (4.2)	16.5 (4.0)	0.011	0.047	0.069
Functional	27	18.0 (5.4)	17.6 (6.3)	17.6 (6.2)	0.754	–	–
Breast	27	20.2 (6.1)	20.2 (6.9)	20.2 (7.0)	0.957	–	–
Arm	25	19.1 (2.0)	15.0 (3.8)	15.6 (4.3)	0.001	< 0.001	0.004
TOI	23	78.5 (13.1)	71.7 (16.1)	74.3 (18.0)	0.096	–	–
FACT-B+4 Global Summary	23	115.1 (17.8)	109.3 (19.7)	111.7 (22.5)	0.275	–	–
SF-36							
PCS	26	45.2 (12.7)	42.0 (11.5)	43.8 (10.6)	0.249	–	–
MCS	26	44.3 (13.2)	43.0 (12.7)	42.5 (12.9)	0.637	–	–

*Post hoc tests with the Bonferroni adjustment for multiple comparisons

and they did not find any significant differences between ALND and SLNB groups at 7 years. On the contrary, and applying the same classification, this study showed a significant difference in the loss of shoulder internal rotator strength, which was greater for the ALND group.

The most important shoulder internal rotator muscles are subscapularis, pectoralis major, teres major, and latissimus dorsi [39], and these muscles are part of the anatomy of the axillary fossa. Both ALND and radiotherapy affect the axillary fossa and pectoral area and may cause damage to its structures. This could explain the internal rotator loss of strength observed in the present study. Shoulder abduction and scaption mainly depends on the deltoid and supraspinatus, muscles that are not part of the axillary fossa. As we see it, exploring the shoulder abductors is not enough to detect all deficits in shoulder strength after breast cancer surgery, and neither is the measure of elbow or grip strength.

The shoulder range of motion difference between affected and unaffected sides achieved significance in the GEE model, with a loss of 7.76° at 5 years. There were no significant differences between the SLNB and ALND groups. These results differ from some other studies where the ALND group showed significant loss of shoulder range of motion compared to SLNB at 2–3 years of follow-up [14, 22, 40–42]. In the present study, the cohort of patients was followed up in a prospective way, within a rehabilitation setting. When the physiatrist observed a loss in range of motion, the patient was sent to rehabilitation for treatment. This could explain why the patients in the present sample had very small loss of shoulder range of motion at 5 years.

The ALND group showed a significant increase in the difference between affected-unaffected arm volume at 5 years. Furthermore, this increase was significantly greater for the ALND than for SLNB patients. However, the ALND group had 33.3% of lymphedema requiring treatment while the SLNB group only had 3.4%. Most studies reporting more lymphedema after ALND than SLNB had follow up to 3 years [20–22, 40]. There are

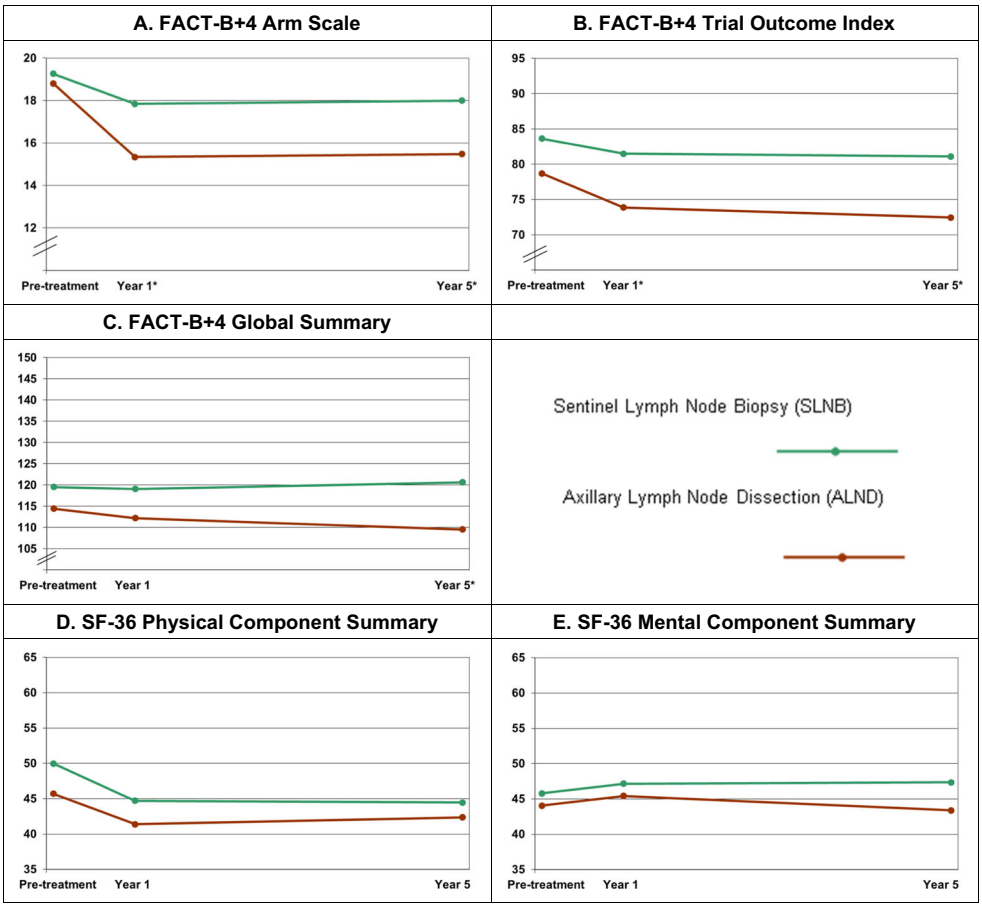

Fig. 1 Mean QoL scores by treatment group. *Statistically significant changes

two prospective studies with longer follow-ups reporting on lymphedema related to nodal surgery. De Gournay et al. [23] at 6 years of follow-up reported there was no case of lymphedema in the SLNB vs. 10% in the ALND group. Kootstra et al. [14] reported an increase in arm volume in the ALND over 7 years of follow-up, while the SLNB group remained stable. They also reported that the ALND group developed more clinically relevant impairments in arm volume than the SLNB group defining clinically relevant as a volume excess over 200 mL. Despite the difference of criteria applied about clinical relevancy in lymphedema, the results of the present study agree with those of Kootstra et al. [14]

Both SLNB and ALND groups showed impairment in the Physical and Arm components of HRQL scales, while emotional components improved over time from pre-surgery to 5 years of follow-up. At 5 years, the improvement in the Emotional component was only significant for the SLNB group. As other authors pointed out, at baseline, there were emotional problems probably related to the psychological distress of cancer diagnosis which decreases over time [22, 43].

The Physical scores of FACT-B+4 and SF-36 only worsened at 5 years for the SLNB group. These results agree with those reported by Sagen et al., where the Physical Functioning of the QLQ C-30 questionnaire did not change at 5 years of follow-up in patients treated with ALND [9]. Further studies would be necessary to confirm and interpret the present's study results.

The worsening in the Arm component of FACT-B+4 was significant for both groups at 5 years, where SLNB lost an average of 1.3 points and ALND lost an average of 3.5 points. Our results were in line with those reported by De Gournay et al. [23] who found a deterioration on the arm symptom scores of the EORTC-QLQ-C30 and the EORTC-QLQ-BR23 questionnaires over 6 years of follow-up, and also that the SLNB had significant lower deterioration than ALND. Other studies with follow-up between 1 and 3 years reported worsening in the arm component after surgery for both SLNB and ALND groups, with more deterioration of the ALND group [6, 20, 22, 44].

In the present study, the Trial Outcome Index and the Global Summary of FACT-B+4 decreased over time, but the worsening was not significant in either group, SLNB or ALND. However, De Gournay et al. [23] found that the Global Health Status scores of the EORTC-QLQ-30 decreased after surgery, increased 1 year later, and decreased again 6 years later.

When comparing both groups, we found that ALND had significant worse HRQL scores than SLNB at 1 and 5 years in the FACT-B+4 Arm scale and in the Trial Outcome Index. The difference in the FACT-B+4 Global Summary was significant only at 5 years. When adjusted by the GEE model, the deterioration of HRQL was confirmed in the Arm and in the Physical Component Summary at 5 years, but there were no differences between the SLNB and ALND groups. On the contrary, De Gournay et al. [23] found that there was no impact of SLNB and ALND procedures on the Global Health Status of the EORTC-QLQ-30 over time.

This study had some limitations. The number of patients lost during follow-up is close to one third in each group. Even though the characteristics of patients with complete and incomplete follow-up were very similar, it is uncertain how this could have affected the results. Furthermore, the present study was carried out in a rehabilitation setting where the shoulder range of motion was systematically included in the prevention protocol and treated when necessary, and this must have interfered by improving the results for this variable, although, on the other hand, some range of motion must be preserved to correctly measure strength and then this variable should have been taken into account.

This is one of the few longitudinal studies available with an evaluation pre-surgery and a long-term follow-up in breast cancer patients [9, 14, 23, 40]. The results confirm some already published findings [16–19] showing more adverse effects in patients treated with ALND than in patients treated with SLNB. As far as the authors are concerned, the most remarkable of our results is the loss of strength specifically for the shoulder internal rotators, which seems consistent with the anatomy of the area affected by surgery and radiotherapy.

In conclusion, patients showed a significant loss of strength for shoulder internal rotators and a 33.3% had clinically relevant lymphedema after ALND for breast cancer. A loss of strength for shoulder external rotators, shoulder range of motion, and HRQL in Physical and Arm domains persisted at 5 years in both SLNB and ALND groups. If these results were confirmed, they could help understand the impact of adverse events of treatments and plan the prevention, the needs, and the long-term care of breast cancer patients. More research is warranted to know which shoulder muscles lose strength in these patients.

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Compliance with ethical standards

The Research Ethics Committee approved the study and it was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from participants before being included.

Conflict of interest The authors declare that they have no conflict of interest.

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