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Shoulder Strength Changes One Year after Axillary Lymph Node Dissection or Sentinel Lymph Node Biopsy in Breast Cancer Patients

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TITLE PAGE**Running head**

Shoulder strength after breast cancer

Title

SHOULDER STRENGTH CHANGES ONE YEAR AFTER AXILLARY LYMPH NODE DISSECTION
OR SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER PATIENTS

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Conflicts of interest

We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated.

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SHOULDER STRENGTH CHANGES ONE YEAR AFTER AXILLARY LYMPH NODE DISSECTION OR SENTINEL LYMPH NODE BIOPSY IN BREAST CANCER PATIENTS

Objective: To assess the changes in shoulder strength of breast cancer patients during the first year after surgery; and to compare the effect of sentinel lymph node biopsy (SLNB) and axillary lymph node dissection (ALND) on shoulder strength.

Design: Prospective longitudinal observational study from pre-surgery to one year after.

Setting: Tertiary hospital.

Participants: Of 129 consecutive patients examined for eligibility, a sample of 112 women with breast cancer were included (44 underwent ALND and 68 SLNB).

Main outcomes measures: Difference between the affected and the unaffected arm in strength of shoulder external rotators, internal rotators, abductors and serratus anterior, measured by dynamometry. Evaluations were performed prior to surgery and at 1, 6 and 12 months after surgery.

Results: After breast cancer ALND surgery, strength decreased significantly at the first month for internal rotators, without having recovered pre-surgery values after one year of follow-up with a mean difference of 2.26 Kg ($p=0.011$). There was no significant loss of strength for patients treated with SLNB. The loss of shoulder range of motion was only significant the first month for the ALND group. The factors identified as associated with strength loss in the General Estimating Equation Models were the ALND surgery and having received physical/occupational therapy during follow-up.

Conclusions: One year after breast cancer surgery, patients treated with ALND had not recovered their previous shoulder internal rotators strength, while those who underwent SLNB presented no significant loss of strength. This provides important information for designing rehabilitation programs targeted specifically at the affected muscle group after nodal surgical approach.

Keywords: Breast neoplasm, lymph node excision, shoulder muscle strength, shoulder mobility.

List of abbreviations

ALND axillary lymph node dissection

POT physical/occupational therapy

SLNB sentinel lymph node biopsy

Introduction.

Over the last few decades, parallel to the improvement in breast cancer survival rates, the morbidity and persistent impairments caused by treatments have been recognized as an important aspect to consider. Several studies demonstrated that one year after breast cancer surgery patients still suffer from upper limb impairment that negatively influences their health related quality of life. Among the most persistent upper limb impairments are pain, numbness, lymphedema and the loss of shoulder function [1-10].

There is a growing body of evidence suggesting that exercise decreases the risk of many cancers[11,12], and data supporting the premise that exercise may extend life expectancy for breast and colon cancer survivors[13-16]. Exercise training is safe during and after cancer treatments and results in improvements in aerobic fitness, muscular strength, health related quality of life, and fatigue in breast, prostate, and hematologic cancer survivors[17]. However, a panel of experts has identified the need to tailor exercise prescription according to the specific cancer and treatment. They recommend the evaluation for arm/shoulder morbidity before planning upper body exercise for breast cancer patients, in order to prevent specific risk of injuries[17].

Some authors have reported a loss of shoulder strength of the affected side compared to the unaffected side after surgery in breast cancer patients[4-18]. In addition, longitudinal studies have found a loss of shoulder strength of the affected side during follow-up[19,20]. In general, sentinel lymph node biopsy (SLNB) generates less morbidity than axillary lymph node dissection (ALND) [21]. Some studies have shown differences in how the surgical node approach affects shoulder

strength, the magnitude of the changes and their impact on health related quality of life[5,9,19,22]. However, there are very few studies reporting results for specific muscle groups such as shoulder rotators, abductors and serratus anterior.

The objective of this study was to assess the changes in shoulder strength of internal rotators, external rotators, abductors and serratus anterior of breast cancer patients during the first year after surgery; as well as to compare the effect of SLNB and ALND on shoulder strength of these muscle groups.

Methods

This study was approved by the Hospital del Mar Clinical Research Ethics Committee and was conducted in accordance with the Declaration of the World Medical Association. A written informed consent was obtained from all participants prior to inclusion.

This was a prospective longitudinal observational study of surgically treated breast cancer patients. From October 2006 to May 2009 consecutive patients of all ages were recruited from the breast cancer unit of the Hospital del Mar, Barcelona, a general university hospital with a community-based screening program for breast cancer. Inclusion criteria were having a recently diagnosed breast cancer, and to be considered for surgery. Exclusion criteria were pre-existing severe disorders of the upper limb of the involved side (e.g. nerve damage or amputation), active shoulder pain disorders such as subacromial impingement, or cognitive impairment, which could interfere with collaboration.

The patients underwent breast conserving surgery or mastectomy with sentinel lymph node biopsy or axillary lymph node dissection. Surgery, neoadjuvant systemic chemotherapy, adjuvant systemic chemotherapy, hormonal treatment and radiotherapy were applied according to the national oncological guidelines which follow international consensus[23,24]. Information on biopsy results and treatments applied were obtained from medical records. Patients self-reported socio-demographic information (education level and working status) and upper limb dominance at baseline.

According to the program of the breast cancer unit, the first week after surgery patients with ALND were instructed about performing some exercises at home to restore shoulder range of motion and to maintain the arm function. Physical or occupational therapy (POT) was only prescribed during follow-up if required for a specific problem. Patients were classified into three POT categories: No treatment; Treatment for lymphedema; and Treatment for shoulder pain, motion restriction or functional impairment.

Patients were evaluated at the rehabilitation setting of the breast cancer unit into the 3 weeks prior to surgery and at 1, 6 and 12 months after surgery. At each follow-up, patients were examined by a physician who systematically asked about symptoms. The clinical exam included weight, height, assessment of muscle strength, and the passive shoulder range of motion degrees (flexion, abduction, external rotation and internal rotation). The total degrees summary score was obtained by adding all the degrees of shoulder range motion.

The isometric muscular strength was tested on both shoulders by a hand-held dynamometer^a at each clinical exam. We followed the protocol described by

Donatelli[25]. The test positions described in this protocol were chosen to obtain good test-retest reliability, avoiding pain and minimizing synergist contribution. The examined muscle groups were shoulder external rotators, internal rotators, abductors and serratus anterior. A wedged-shaped cushion was used to obtain the positions described by Donatelli[25]. Each group of muscle strength was evaluated in three active isometric tests. The non-affected shoulder was assessed before the affected side. The subject was instructed to increase force gradually until maximum contraction was achieved. The dynamometer records the maximum force exerted on each test. The shoulder muscular strength of each group was calculated by the average of the three tests.

Analysis

The statistical analyses were carried out using SPSS 12.0 software. A total of 110 patients were estimated necessary to detect a difference between SLNB and ALND groups (half patients at each group) of 0.5 standard deviation in the abductors strength with a statistical power of at least 80% at a significance level of 5%.

Normality was checked examining the histogram of the variables and Kolmogorov-Smirnov Test. Characteristics of patients treated with SLNB and ALND were compared by un-paired t-test or chi squared test, according to the nature of the variables. The difference in shoulder measurements between affected and unaffected sides was used in the analyses. Graphs were plotted showing the evolution of this difference on shoulder muscular strength and range of during follow-up. Differences between SLNB and ALND groups were compared at each evaluation by unpaired t-test.

Intra-group changes were assessed using univariate repeated measures analysis of variance. Post hoc pairwise comparisons comparing each follow-up evaluation with pre-surgery were made using the paired t-test with Bonferroni's method to adjust for multiple comparisons.

Bivariate analysis to test differences in changes (from pre-surgery to 12 months) among groups defined by clinical and treatment variables was performed with one-way analysis of variance. Generalized estimating equation (GEE) models were constructed with the difference in strength between affected and unaffected sides as the dependent variable to assess the effect of nodal treatment (SLNB or ALND) and POT, while accounting for correlation among repeated measures. Variables with statistical association in the bivariate analysis were included in the models as adjusting factors. Time was included in the model as a categorical variable with four categories: pre-surgery and months 1, 6, and 12, to prevent assuming a linear association. Interactions of time with nodal treatment and POT were also included, and the group of SLNB without POT was used as reference.

In order to test the clinical relevance of the changes in the measurements, the patients of both ALND and SLNB groups who had loss of function equal to or greater than 20%, were compared by unpaired T test.

Results

From October 2006 to May 2009, 129 patients were examined for eligibility. Three patients declined to participate in the study, 2 patients were excluded due to active shoulder problems, 3 patients could not complete the baseline exam, and 9 patients

161 did not attend follow-up. Among the 112 analysed patients, 100 were followed-up at
162 first month, 94 were followed-up at sixth month and 89 at one year.

163 Baseline exam was done a median of 14.5 days before surgery (interquartile range
164 8.0, 22.0). After surgery first follow-up was done a median of 34.0 days (interquartile
165 range 27.0, 35.0); second follow-up was done a median of 188.0 days (interquartile
166 range 181.0, 202.0); last exam was done a median of 370.0 days (interquartile range
167 363.0, 384.0).

168 Of the 112 women included in the study (table 1); 68 (60.7%) underwent SLNB and
169 44 (39.3%) underwent ALND. The median age at cancer diagnosis was 59.5 (SD 9.0)
170 years. There were statistically significant differences in the baseline characteristics
171 between SLNB and ALND groups for body mass index (overweight 44.8 % and 29.0,
172 respectively, $p=0.006$); type of surgery (breast conserving 100% vs. 79.5%,
173 $p<0.001$); tumor size category (86.8% in situ or 1 vs. 43.2%, $p<0.001$); excised nodes
174 (1.7 vs. 14.5, $p<0.001$); and chemotherapy (33.8% vs. 93.2%, $p<0.001$). No
175 significant differences between groups were observed among POT categories (21
176 patients received treatment for shoulder problems and 5 for upper limb
177 lymphedema); nor among education level (29.5% completed secondary or university
178 studies). Neither were there any significant differences among groups for working
179 status (38.7% were employed and 30.6% were housewives).

180 Figure 1 shows that the ALND group had greater loss of function than the SLNB one,
181 with statistically significant differences in the first month for strength in internal
182 rotator, and serratus anterior, and shoulder range of motion. At this evaluation,
183 patients in the ALND group had less strength and less shoulder range of motion than
184 patients who had undergone SLNB.

Table 2 shows that patients treated with ALND presented a statistically significant reduction in internal rotator strength at each follow-up, with a mean loss of 2.26 Kg at 12 months ($p=0.011$). In addition, the mean loss of shoulder range of motion summary was 12.07 degrees at month 1 ($p=0.003$). However, there were no significant differences for any of the outcomes among women treated with SLNB. The variables significantly associated with shoulder strength reduction during follow-up in the one way analysis of variance were the affected dominant side, the nodal surgery type, the T size tumor category, the breast surgery type and POT (Table 3).

Table 4 shows the results of the GEE models constructed with the shoulder strength difference between affected and unaffected side as dependent variable. In the external rotator model, the reference group (SLNB without POT) showed no statistically significant change at any follow-up. The ALND group showed 1.3 Kg of additional loss compared to the reference group at first month ($p<0.001$), and 0.8 Kg loss at 12 months of follow-up ($p=0.046$). Patients who received POT for shoulder problems showed 1.2 Kg of additional loss at 12 months than those who did not receive treatment ($p=0.036$). Patients who received POT only for lymphedema did not show statistically significant differences. The model of the internal rotators also showed no statistically significant change at any follow-up in the reference group (SLNB without POT). This model showed a significant strength loss for ALND patients of 1.9 and 1.4 Kg at 1 and 12 months, respectively, compared to the reference group. Patients who received POT for shoulder problems showed an additional loss of 2.0 Kg at 12 months compared to those who did not receive treatment ($p=0.006$). Patients who received POT only for lymphedema showed a significant additional loss of 2.2 and 1.7 Kg at 1 and 6 months, respectively, compared to those who did not receive treatment.

No statistically significant change at any follow-up in the reference group (SLNB without POT) was observed in the abductor model. Compared to reference, ALND patients only showed a significant loss of 0.7 Kg at 1 month of follow-up. Patients who received POT for shoulder problems showed an additional loss of 0.9 Kg at 12 months compared to the reference group. Finally, the serratus anterior model showed baseline statistically significant differences among POT groups: patients receiving POT for shoulder and lymphedema problems had -2.2 and -4.0 Kg less strength than those not receiving. The reference group (SLNB without POT) presented a significant loss of strength of 2.4 Kg at 12 months ($p=0.001$); and the ALND group showed an additional loss of 2.9 Kg at 1 month of follow-up compared with reference.

Table 5 shows the number and percentage of women with a loss of shoulder function equal to or greater than 20% at 12 months respect pre-surgery. The values ranged from 11.1% to 34.3%. There was no significant difference between ALND and SLNB.

Discussion

After breast cancer ALND surgery, strength of the internal rotators decreased significantly at the first month, and it did not recover to pre-surgery values during the first year of follow-up. Furthermore, ALND patients presented a significant loss of shoulder range of motion at month 1. In contrast, patients treated with SLNB had no significant decrements in shoulder strength nor range of motion at any follow-up.

Other authors have also reported higher loss in shoulder strength for ALND than SLNB[5,19, 27]. It seems reasonable to attribute varying effects on muscle function to different surgical procedures. ALND is normally a more extensive procedure and

has a greater effect on the axilla than SLNB. The differences in surgical damage and soft tissue healing could play a role in muscle function. More research is required to answer this question. Springer et al.[26] reported that all function measurements were significantly reduced 1 month post-surgery in a sample of women treated with ALND or SLNB, but most recovered baseline levels at one year post-surgery.

Strength in this case was measured as a composite score defined as the sum of six individual shoulder strength tests. The differences in strength measurements between studies preclude a more detailed comparison of results.

In the present study the only significant loss of strength was observed for internal rotators. Kootstra et al.[9,20] reported some loss of strength for abductors but all patients recovered their preoperative strength level at 2 years of follow-up. Rietman et al.[27] found a loss of strength of shoulder abductors one year after surgery for both SLNB and ALND groups. Most studies took into account only one shoulder muscle function (usually abduction),[5,19,27] so they did not have the possibility to observe differences in internal rotators as we did; neither did the studies with strength values analysed as composite or summary scores. [26]

The reduction of range of motion in the shoulder for the ALND group was higher than the reduction in the shoulder for the SLNB group but only statistically significant one month after surgery (Fig 1). This finding is consistent with other authors who reported a greater reduction of shoulder range of motion after surgery in ALND groups [8,9].

Although the decrement in shoulder range of motion was statistically significant one month after surgery in our study, this change could be considered clinically mild.

Similarly, Springer et al.[26] used a single composite score (defined as the sum of shoulder flexion, abduction, external and internal rotation) to measure shoulder range

of motion prior and after breast cancer surgery. They reported that all measurements of function were significantly reduced 1 month post-surgery, and that most of them recovered baseline levels at 1-year post-surgery.

The factors associated with higher loss of shoulder strength in the bivariate analysis were dominant side breast cancer, nodal surgery, T size category, mastectomy, and received POT. Consistent with our findings, Hayes et al.[3] also found higher odds of decline in upper body strength among women with breast cancer of the dominant side, and Kootstra et al.[9] reported that chemotherapy did not have any significant effect on shoulder strength. Association with radiotherapy has been described previously.[21] In our sample, the majority of patients received radiotherapy (89.9% of SLND and 91.3% of ALND) and given the low number of non irradiated patients, this variable was excluded of the analysis. Shoulder range of motion was not associated with loss of strength, which could be explained by the low magnitude of the loss observed in our sample.

In the GEE constructed models, SLNB patients without POT did not present loss of strength (except for serratus anterior 12 months after surgery), while ALND patients showed loss of strength after 1 month for all muscle groups, and after 12 months for external and internal rotators. A systematic review found level 1 evidence for ALND, and level 2 evidence for SLNB, as risk factors for reduced muscle strength.[21]

Patients who received POT for lymphedema had significant additional loss of shoulder strength for internal rotators 1 and 6 months after surgery, but the difference was not significant at 12 months. However those who received POT for shoulder problems had significant loss of shoulder strength at 12 months for external rotators, internal rotators and abductors. This finding indicates that patients requiring

rehabilitation treatment for shoulder problems would present a clinically relevant decrease in strength 12 months after surgery. Therefore, we should try to specifically improve shoulder strength in patients requiring POT for shoulder problems in this period.

Regarding the relevance of the observed loss of strength, Kootstra et al.[20] addressed this aspect considering that it is clinically important when the difference between pre-surgery and after surgery was greater than 20% for the difference of subtracting the affected to the unaffected side strength. Taking into consideration this approach, we did not find significant differences between ALND and SLNB groups on the percentage of women with clinically relevant impairment. This finding is consistent with results of Kootstra et al.[20] that also showed no statistically significant differences on strength of abduction, elbow flexion and grip, neither for shoulder range of motion.

Some limitations of this study should be taken into account. Regarding internal validity, first of all, this is an observational study and participants were not randomly assigned to treatment groups. Secondly, the evaluation of the main outcome, strength in each muscle group, always presents an associated error. However, in our study it was minimized by using a validated hand-held dynamometer, applying a previously described protocol to obtain good test-retest reliability, evaluating each muscle group three times, and calculating the mean. In terms of external validity, the results are not generalizable to patients who do not meet the inclusion and exclusion criteria applied in this study.

Among the strengths of this study was the prospective design, ranging from the pre-surgical evaluation to one year post-surgery. The comparison between affected and

unaffected side shoulders for the principal outcomes (strength and range of motion) allows the neutralization of other factors that could cause generalized weakness in patients with breast cancer, such as chemotherapy, hormonotherapy or the disease itself. Thus, the differences between both sides could be related to factors that act locally such as surgery or radiotherapy.

The present study provides information on how the shoulder strength decreases after ALND. If these findings were confirmed, preventive programs for patients undergoing ALND should emphasize exercises to strengthen the shoulder internal rotator muscles. We should also establish a particular emphasis on this aspect for breast cancer patients who received rehabilitation treatment for shoulder impairments.

Conclusions

In conclusion, the strength of the shoulder internal rotators in patients treated with ALND decreased significantly the first month and the loss was maintained until a year after breast cancer surgery. Patients who underwent SLNB presented no significant loss of strength. Finally, patients who received POT for specific problems during the follow-up, such as pain or severe restriction of motion, presented a clinically relevant additional strength loss of 1-2 Kg in internal and external rotators and abductors one year after surgery.

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Figure Legends

Figure 1 – Figure 1 – Means and 95% Confidence interval of the difference between affected and unaffected sides on shoulder measurements at each evaluation by treatment group.

*Unpaired T test comparing SLNB with $p < 0.05$.

Strength in Kg. Range of motion in degrees.

ALND axillary lymph node dissection

SLNB sentinel lymph node biopsy

Suppliers

^a Nicholas Manual Muscle Tester, Lafayette Instrument Company, 3700 Sagamore Pkwy N, Lafayette, IN 47904, USA

Table 4. GEE models constructed to assess the effect of nodal surgery and physical/occupational therapy on shoulder muscle strength (adjusted by age, T size category, affected dominant side, breast conserving surgery).

		External Rotators Strength			Internal Rotators strength			Abductors Strength			Serratus Anterior Strength		
		Beta	[IC- , IC+]	p-value	Beta	[IC- , IC+]	p-value	Beta	[IC- , IC+]	p-value	Beta	[IC- , IC+]	p-value
Intercept		10.7	[8.1 , 13.4]	< 0.001	11.8	[9.1 , 14.6]	< 0.001	6.5	[4.6 , 8.5]	< 0.001	22.5	[18.7 , 26.2]	< 0.001
Age		0.0	[-0.1 , 0.0]	0.023	0.0	[-0.1 , 0.0]	0.039	0.0	[0.0 , 0.0]	0.242	-0.2	[-0.2 , -0.1]	< 0.001
T (size category)													
	In situ	(ref)			(ref)			(ref)			(ref)		
	1	0.8	[-0.2 , 1.9]	0.102	0.9	[0.0 , 1.8]	0.051	0.1	[-0.8 , 1.1]	0.766	0.7	[-1.4 , 2.7]	0.539
	2	0.7	[-0.5 , 1.8]	0.242	0.6	[-0.5 , 1.8]	0.284	0.3	[-0.7 , 1.3]	0.612	0.4	[-1.9 , 2.7]	0.741
	3	0.7	[-1.2 , 2.6]	0.455	0.6	[-1.6 , 2.7]	0.592	0.6	[-0.8 , 2.0]	0.370	2.4	[-1.0 , 5.9]	0.170
	4	-1.4	[-4.6 , 1.9]	0.418	-3.9	[-6.2 , -1.7]	0.001	-1.6	[-3.4 , 0.3]	0.092	-4.6	[-8.5 , -0.6]	0.023
Affected Dominant Side													
	No	(ref)			(ref)			(ref)			(ref)		
	Yes	-0.1	[-0.2 , 0.0]	0.108	0.0	[-0.2 , 0.2]	0.800	-0.1	[-0.2 , 0.0]	0.014	0.2	[0.0 , 0.5]	0.105
Breast Conserving Surgery													
	No	(ref)			(ref)			(ref)			(ref)		
	Yes	0.8	[-0.4 , 2.0]	0.179	0.6	[-0.9 , 2.2]	0.418	0.7	[-0.2 , 1.6]	0.117	0.1	[-2.3 , 2.5]	0.940
Physical/Occupational Therapy													
	No	(ref)			(ref)			(ref)			(ref)		
	Shoulder	-0.8	[-1.5 , 0.0]	0.054	-0.3	[-1.3 , 0.6]	0.475	0.1	[-0.6 , 0.8]	0.772	-2.2	[-4.0 , -0.5]	0.013
	Lymphedema	-1.2	[-2.5 , 0.2]	0.092	-0.2	[-1.8 , 1.5]	0.828	-0.3	[-1.5 , 0.9]	0.621	-4.0	[-6.5 , -1.5]	0.001
Nodal Surgery													
	SLNB	(ref)			(ref)			(ref)			(ref)		
	ALND	0.8	[-0.3 , 1.8]	0.166	0.9	[-0.3 , 2.0]	0.149	-0.1	[-0.7 , 0.6]	0.829	0.6	[-1.4 , 2.5]	0.555
Interaction Time & Nodal Surgery													
Change from baseline of the REFERENCE (Group of SLND without Physical/Occupational Therapy)													
	Baseline	(ref)			(ref)			(ref)			(ref)		
	1 month	0.2	[-0.2 , 0.6]	0.307	-0.2	[-0.7 , 0.3]	0.487	0.2	[-0.3 , 0.7]	0.503	0.6	[-0.6 , 1.8]	0.356
	6 months	0.0	[-0.5 , 0.6]	0.903	-0.3	[-0.8 , 0.3]	0.396	-0.1	[-0.5 , 0.2]	0.472	-1.0	[-2.2 , 0.2]	0.111
	12 months	0.0	[-0.5 , 0.5]	0.991	-0.2	[-0.7 , 0.4]	0.591	-0.2	[-0.6 , 0.1]	0.139	-2.4	[-3.8 , -1.0]	0.001
Difference in change from baseline of ALND group compared with REFERENCE													
	Baseline	(ref)			(ref)			(ref)			(ref)		
	1 month	-1.3	[-1.9 , -0.7]	< 0.001	-1.9	[-2.8 , -1.1]	< 0.001	-0.7	[-1.4 , -0.1]	0.018	-2.9	[-4.9 , -0.9]	0.005
	6 months	-0.5	[-1.4 , 0.4]	0.269	-1.0	[-2.0 , 0.0]	0.056	0.1	[-0.5 , 0.8]	0.705	-1.1	[-3.0 , 0.7]	0.234
	12 months	-0.8	[-1.6 , 0.0]	0.046	-1.4	[-2.3 , -0.4]	0.004	0.2	[-0.4 , 0.8]	0.495	-0.4	[-2.4 , 1.6]	0.710
Interaction Time & Physical/Occupational Therapy													
Difference in change from baseline of Shoulder group compared with REFERENCE													
	Baseline	(ref)			(ref)			(ref)			(ref)		
	1 month	-0.1	[-0.8 , 0.6]	0.728	-0.5	[-1.4 , 0.4]	0.261	-0.4	[-1.1 , 0.2]	0.192	0.5	[-1.4 , 2.4]	0.602
	6 months	-0.9	[-2.2 , 0.4]	0.163	-1.2	[-2.6 , 0.2]	0.104	-0.6	[-1.4 , 0.2]	0.158	-1.5	[-3.5 , 0.6]	0.162
	12 months	-1.2	[-2.3 , -0.1]	0.036	-2.0	[-3.5 , -0.6]	0.006	-0.9	[-1.6 , -0.2]	0.009	0.5	[-2.0 , 3.0]	0.704
Difference in change from baseline of Lymphedema group compared with REFERENCE													

Baseline	(ref)				(ref)			(ref)			(ref)		
1 month	0.0	[-0.9 , 0.9]	0.982	-2.2	[-3.7 , -0.7]	0.005	-0.6	[-1.7 , 0.4]	0.241	1.3	[-1.1 , 3.8]	0.288	
6 months	-0.4	[-1.0 , 0.3]	0.265	-1.7	[-3.0 , -0.4]	0.009	-0.8	[-1.7 , 0.0]	0.053	2.4	[-1.4 , 6.2]	0.216	
12 months	0.2	[-0.6 , 1.1]	0.598	-0.7	[-1.6 , 0.2]	0.112	-0.3	[-0.9 , 0.2]	0.271	2.3	[-2.2 , 6.7]	0.317	

Table 2. Intra-group analysis of variance of the difference between affected and unaffected sides on shoulder measurements for each nodal surgery.
Strength in Kg. Range of motion in degrees.
ALND axillary lymph node dissection SLNB sentinel lymph node biopsy

	n	Mean (SD)				p-value	p value (Comparison with pre-surgery)*		
		Pre-surgery	1 month	6 months	12 months	ANOVA	1 month	6 months	12 months
(a) ALND									
External Rotators Strength	31	0,52 (2,2)	-0,77 (1,7)	0,01 (1,5)	-0,45 (2,0)	0.055	---	---	---
Internal Rotators Strength	31	0,80 (1,4)	-1,53 (2,6)	-0,69 (2,2)	-1,46 (4,0)	0.001	< 0.001	0.004	0.011
Abductors Strength	30	-0,07 (0,7)	-0,60 (1,1)	-0,21 (1,0)	-0,19 (0,8)	0.101	---	---	---
Serratus Anterior Strength	30	-0,08 (2,1)	-2,15 (3,7)	-0,26 (2,6)	-0,54 (2,9)	0.070	---	---	---
Range of Motion Summary	29	-0,34 (17,2)	-50,17 (70,6)	-11,72 (43,8)	-12,41 (23,4)	0.008	0.003	0.900	0.170
(b) SLNB									
External Rotators Strength	47	0,20 (2,0)	-0,15 (1,9)	-0,10 (2,2)	-0,24 (1,9)	0.430	---	---	---
Internal Rotators Strength	47	0,34 (1,6)	-0,32 (1,7)	-0,34 (1,8)	-0,16 (1,6)	0.176	---	---	---
Abductors Strength	46	-0,05 (1,1)	-0,26 (1,2)	-0,25 (0,9)	-0,13 (1,2)	0.683	---	---	---
Serratus Anterior Strength	45	-0,36 (3,2)	-0,55 (3,1)	-0,48 (2,8)	-0,27 (2,3)	0.961	---	---	---
Range of Motion Summary	47	4,04 (21,5)	-6,91 (33,0)	-8,62 (37,4)	-7,02 (33,9)	0.192	---	---	---

*Bonferroni adjustment for multiple comparison

Table 5 – Number and percentage of women with clinically relevant shoulder impairments at-12 months after surgery

	All patients	ALND	SLNB	p-value
External Rotators	26 (29.5%)	12 (33.3%)	14 (26.9%)	0.517
Internal Rotators	27 (30.7%)	12 (33.3%)	15 (28.8%)	0.654
Abductors	14 (15.9%)	4 (11.1%)	10 (19.2%)	0.306
Serratus Anterior	16 (18.4%)	8 (22.2%)	8 (15.7%)	0.438
Range of Motion Summary	26 (29.9%)	12 (34.3%)	14 (26.9%)	0.462

Table 1. Patient characteristics

ACCEPTED MANUSCRIPT				
	All (n = 112)	SLNB (n = 68)	ALND (n = 44)	p
Age (years). Mean (SD)	59,5 (9,0)	59,6 (8,7)	59,3 (9,5)	0.888
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Body Mass Index				
Normal (18.5 – 24.9)	21 (21.4%)	18 (26.9%)	3 (9.7%)	0.006
Overweight (25 – 29.9)	39 (39.8%)	30 (44.8%)	9 (29.0%)	
Obese(≥ 30)	38 (38.8%)	19 (28.4%)	19 (61.3%)	
Missing	14 (12.5%)	1 (1.5%)	13 (29.5%)	
Affected dominant side				
No	48 (45.3%)	30 (45.5%)	18 (45.0%)	0.964
Yes	58 (54.7%)	36 (54.5%)	22 (55.0%)	
Missing	6 (5.4%)	2 (2.9%)	4 (9.1%)	
Breast Surgery				
Breast Conserving	103 (92.0%)	68 (100.0%)	35 (79.5%)	< 0.001
Mastectomy	9 (8.0%)	0 (0.0%)	9 (20.5%)	
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Nodes Excised	6.9 (7.2)	1.7 (0.9)	14.5 (5.5)	< 0.001
Missing	4 (3.6%)	4 (5.9%)	0 (0.0%)	
T (size category)				
In situ	11 (9.8%)	11 (16.2%)	0 (0.0%)	< 0.001
1	67 (59.8%)	48 (70.6%)	19 (43.2%)	
2	25 (22.3%)	9 (13.2%)	16 (36.4%)	
3	7 (6.3%)	0 (0.0%)	7 (15.9%)	
4	2 (1.8%)	0 (0.0%)	2 (4.5%)	
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Histology				
Ductal carcinoma	101 (90.2%)	63 (92.6%)	38 (86.4%)	0.120
Lobular carcinoma	9 (8.0%)	3 (4.4%)	6 (13.6%)	
Other	2 (1.8%)	2 (2.9%)	0 (0.0%)	
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Chemotherapy	64 (57.1%)	23 (33.8%)	41 (93.2%)	< 0.001
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Radiotherapy	102 (91.1%)	61 (89.7%)	41 (93.2%)	0.529
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Hormonotherapy	80 (71.4%)	50 (73.5%)	30 (68.2%)	0.541
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Physical/Occupational Therapy				
Shoulder	21 (23.1%)	13 (24.1%)	8 (21.6%)	0.183
Lymphedema	5 (5.5%)	1 (1.9%)	4 (10.8%)	
No	65 (71.4%)	40 (74.1%)	25 (67.6%)	
Missing	21 (18.8%)	14 (20.6%)	7 (15.9%)	
Education				
Primary incomplete	19 (31,1%)	7 (22,6%)	26 (28,3%)	0.346
Primary complete	24 (39,3%)	14 (45,2%)	38 (41,3%)	
Secondary	11 (18,0%)	3 (9,7%)	14 (15,2%)	
University	7 (11,5%)	7 (22,6%)	14 (15,2%)	
Missing	20 (17,9%)	7 (10,3%)	13 (29,5%)	
Work				
Employed	24 (38,7%)	11 (35,5%)	35 (37,6%)	0.926
Unemployed	4 (6,5%)	1 (3,2%)	5 (5,4%)	
Housewife	19 (30,6%)	12 (38,7%)	31 (33,3%)	
Permanently incapacitated	2 (3,2%)	1 (3,2%)	3 (3,2%)	
Retired	13 (21,0%)	6 (19,4%)	19 (20,4%)	
Missing	19 (17,0%)	6 (8,8%)	13 (29,5%)	

Table 3 – Change (from pre-surgery to 12 months) of the difference between affected and unaffected sides on shoulder measurements according to clinical and treatment characteristics.
ALND axillary lymph node dissection SLNB sentinel lymph node biopsy

		External Rotators	Internal Rotators	Abductors	Serratus Anterior
Body Mass Index (kg/m²)					
	Normal (18.5 – 24.9)	-0,28 (1,75)	-0,96 (1,63)	0,52 (2,69)	-0,14 (0,78)
	Overweight (25 – 29.9)	-0,93 (2,63)	-0,91 (2,71)	-0,05 (4,12)	-0,12 (1,27)
	Obese (≥ 30)	-0,03 (2,44)	-0,51 (1,93)	-0,49 (3,11)	0,28 (1,78)
	p-value	0,347	0,750	0,493	0,674
Affected Dominant Side					
	No	0,04 (2,75)	-0,68 (2,67)	-0,03 (3,37)	-0,09 (1,57)
	Yes	-1,08 (2,22)	-1,07 (2,12)	-0,21 (3,61)	-0,04 (1,23)
	p-value	0,043	0,450	0,884	0,816
T (size category)					
	In situ	-0,01 (1,20)	-1,26 (1,43)	-1,73 (1,65)	0,35 (0,78)
	1	-0,40 (2,60)	-0,46 (2,38)	0,28 (3,49)	-0,08 (1,48)
	2	-1,17 (2,64)	-2,10 (2,38)	-0,63 (3,95)	-0,06 (1,34)
	3	-1,21 (2,03)	-0,56 (1,11)	0,74 (1,82)	-0,21 (1,02)
	4	-0,57 (0,80)	-9,72 (12,85)	-3,80 (1,23)	-0,93 (0,09)
	p-value	0,697	< 0,000	0,805	0,235
Breast Conserving Surgery					
	Yes	-0,52 (2,51)	-0,82 (2,33)	-0,15 (3,34)	-0,08 (1,34)
	No	-1,53 (1,32)	-4,60 (6,40)	-0,55 (4,58)	0,07 (1,56)
	p-value	0,300	0,001	0,784	0,766
Nodal Surgery					
	SLNB	-0,41 (2,43)	-0,44 (2,43)	0,02 (3,65)	-0,05 (1,55)
	ALND	-0,88 (2,48)	-2,12 (3,43)	-0,46 (3,12)	-0,09 (1,01)
	p-value	0,379	0,009	0,911	0,528
Nodes Excised					
	1	-0,43 (2,05)	-0,80 (2,30)	-0,20 (3,41)	-0,11 (1,74)
	2 – 9	-0,82 (2,85)	-0,89 (4,30)	0,40 (3,94)	0,05 (1,33)
	≥10	-0,60 (2,58)	-1,71 (2,07)	-0,50 (2,94)	-0,14 (0,92)
	p-value	0,843	0,447	0,849	0,616
Chemotherapy					
	No	-0,55 (2,24)	-0,58 (2,32)	0,26 (3,86)	-0,04 (1,70)
	Yes	-0,64 (2,61)	-1,52 (3,34)	-0,50 (3,06)	-0,09 (1,04)
	p-value	0,878	0,143	0,845	0,306
Hormonotherapy					
	No	-0,72 (2,42)	-2,11 (4,46)	-0,19 (3,65)	-0,20 (1,00)
	Yes	-0,56 (2,48)	-0,81 (2,30)	-0,18 (3,38)	-0,03 (1,45)
	p-value	0,803	0,082	0,605	0,990
Physical/Occupational Therapy					
	Shoulder	-1,62 (2,66)	-3,10 (4,62)	-1,66 (4,04)	-0,52 (1,30)
	Lymphedema	-0,03 (1,32)	-1,17 (0,89)	-0,13 (2,09)	-0,33 (0,28)
	No	-0,36 (2,42)	-0,56 (2,15)	0,19 (3,25)	0,08 (1,40)
	p-value	0,126	0,004	0,218	0,129
Shoulder Range of Motion					
	≤ 115	-0,82 (1,61)	-2,00 (3,94)	-0,05 (3,30)	-0,22 (0,95)
	520 – 535	-0,20 (3,26)	-0,45 (2,95)	-0,92 (3,98)	0,13 (1,65)
	≥ 540	-0,64 (2,50)	-0,91 (2,25)	0,05 (3,29)	-0,06 (1,42)
	p-value	0,710	0,193	0,708	0,586