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Title:

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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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.

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: 68 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: 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. GEE 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 rotators 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.

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, whilst 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 symptoms 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 components 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 wellbeing (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: 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 rotators 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 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. Patient undergoing ALND (after suffered more frequently a lymphedema which required treatment than those in the SLNB group at 5 years after surgery (33.3% vs. 3.4%, $p<0.001$) as shown in 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 (Figure 1A and 1B) showed significantly lower values among ALND patients at 1 and 5 years, while the Global Summary of FACT-B+4 (Figure 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 (Figure 1D and 1E).

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 rotators 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 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 degrees 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 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, whilst 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 symptoms 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 33.3% had clinically relevant lymphedema after ALND for breast cancer. A loss of strength for shoulder external rotators, shoulder range of motion, as well as 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.

Conflict of interest

Authors declare that they have no conflict of interest.

Authors 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. This study was sponsored by the hospital where authors work and partially by a grant of Instituto de Salud Carlos III- ISCIII (PI/06/90070), there was no other external financial support.

The authors agree to allow the journal to review our data if requested.

References

1. Lu W, Cui Y, Zheng Y, et al. (2007) Impact of newly diagnosed breast cancer on HRQL among Chinese women. *Breast Cancer Res Treat* 102:201–210. doi: 10.1007/s10549-006-9318-5
2. Mols F, Vingerhoets AJM, Coebergh JW, van de Poll-Franse L V (2005) HRQL among long-term breast cancer survivors: a systematic review. *Eur J Cancer* 41:2613–2619. doi: 10.1016/j.ejca.2005.05.017
3. Koch L, Jansen L, Herrmann A, et al. (2013) HRQL in long-term breast cancer survivors - a 10-year longitudinal population-based study. *Acta Oncol* 52:1119–1128. doi: 10.3109/0284186X.2013.774461
4. Sato F, Arinaga Y, Sato N, et al. (2016) The Perioperative Educational Program for Improving Upper Arm Dysfunction in Patients with Breast Cancer at 1-Year Follow-Up: A Prospective, Controlled Trial. *Tohoku J Exp Med* 238:229–236. doi: 10.1620/tjem.238.229
5. Montazeri A, Vahdaninia M, Harirchi I, et al. (2008) HRQL in patients with breast cancer before and after diagnosis: an eighteen months follow-up study. *BMC Cancer* 8:330. doi: 1471-2407-8-330 [pii] 10.1186/1471-2407-8-330
6. Fleissig A, Fallowfield LJ, Langridge CI, et al. (2006) Post-operative arm morbidity and HRQL. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. *Breast Cancer Res Treat* 95:279–293. doi: 10.1007/s10549-005-9025-7
7. Rietman JS, Dijkstra PU, Debreczeni R, et al. (2004) Impairments, disabilities and health related HRQL after treatment for breast cancer: a follow-up study 2.7 years after surgery. *Disabil Rehabil* 26:78–84. doi: 10.1080/09638280310001629642
8. Hayes SC, Rye S, Battistutta D, et al. (2010) Upper-body morbidity following breast cancer treatment is common, may persist longer-term and adversely influences HRQL. *Heal Qual Life Outcomes* 8:92. doi: 1477-7525-8-92 [pii] 10.1186/1477-7525-8-92
9. Sagen A, Karesen R, Skaane P, Risberg MA (2009) Validity for the simplified water displacement instrument to measure arm lymphedema as a result of breast cancer surgery. *Arch Phys Med Rehabil* 90:803–809. doi: S0003-9993(09)00134-8 [pii] 10.1016/j.apmr.2008.11.016
10. DiSipio T, Rye S, Newman B, Hayes S (2013) Incidence of unilateral arm lymphoedema after breast cancer: a systematic review and meta-analysis. *Lancet Oncol* 14:500–515. doi: 10.1016/S1470-2045(13)70076-7
11. Nesvold IL, Reinertsen K V, Fosså SD, Dahl AA (2011) The relation between arm/shoulder problems and HRQL in breast cancer survivors: a cross-sectional and longitudinal study. *J Cancer Surviv* 5:62–72. doi: 10.1007/s11764-010-0156-4
12. Lee TS, Kilbreath SL, Refshauge KM, et al. (2008) HRQL of women treated with radiotherapy for breast cancer. *Support Care Cancer* 16:399–405. doi: 10.1007/s00520-007-0328-6
13. Lee TS, Kilbreath SL, Refshauge KM, et al. (2008) Prognosis of the upper limb following surgery and radiation for breast cancer. *Breast Cancer Res Treat* 110:19–37. doi: 10.1007/s10549-007-9710-9
14. Kootstra JJ, Dijkstra PU, Rietman H, et al. (2013) A longitudinal study of shoulder and arm morbidity in breast cancer survivors 7 years after sentinel lymph node biopsy or axillary lymph node dissection. *Breast Cancer Res Treat* 139:125–134. doi: 10.1007/s10549-013-2509-y

15. Helms G, Kuhn T, Moser L, et al. (2009) Shoulder-arm morbidity in patients with sentinel node biopsy and complete axillary dissection--data from a prospective randomised trial. *Eur J Surg Oncol* 35:696–701. doi: 10.1016/j.ejso.2008.06.013
16. Hidding JT, Beurskens CHG, van der Wees PJ, et al. (2014) Treatment related impairments in arm and shoulder in patients with breast cancer: a systematic review. *PLoS One* 9:e96748. doi: 10.1371/journal.pone.0096748
17. Schulze T, Mucke J, Markwardt J, et al. (2006) Long-term morbidity of patients with early breast cancer after sentinel lymph node biopsy compared to axillary lymph node dissection. *J Surg Oncol* 93:109–119. doi: 10.1002/jso.20406
18. McLaughlin SA, Wright MJ, Morris KT, et al. (2008) Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. *J Clin Oncol* 26:5213–5219. doi: JCO.2008.16.3725 [pii] 10.1200/JCO.2008.16.3725
19. Crane-Okada R, Wascher RA, Elashoff D, Giuliano AE (2008) Long-term morbidity of sentinel node biopsy versus complete axillary dissection for unilateral breast cancer. *Ann Surg Oncol* 15:1996–2005. doi: 10.1245/s10434-008-9909-y
20. Belmonte R, Garin O, Segura M, et al. (2012) Quality-of-Life Impact of Sentinel Lymph Node Biopsy Versus Axillary Lymph Node Dissection in Breast Cancer Patients. *Value Heal* 15:907–915. doi: 10.1016/j.jval.2012.06.003
21. Purushotham AD, Upponi S, Klevesath MB, et al. (2005) Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. *J Clin Oncol* 23:4312–4321. doi: 23/19/4312 [pii] 10.1200/JCO.2005.03.228
22. Rietman JS, Geertzen JHB, Hoekstra HJ, et al. (2006) Long term treatment related upper limb morbidity and HRQL after sentinel lymph node biopsy for stage I or II breast cancer. *Eur J Surg Oncol* 32:148–152. doi: 10.1016/j.ejso.2005.11.008
23. De Gournay E, Guyomard A, Coutant C, et al. (2013) Impact of sentinel node biopsy on long-term HRQL in breast cancer patients. *Br J Cancer* 109:2783–2791. doi: 10.1038/bjc.2013.658
24. Runowicz CD, Leach CR, Henry NL, et al. (2016) American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care Guideline. *J Clin Oncol* 34:611–635. doi: 10.1200/JCO.2015.64.3809
25. Kvale EA, Huang C-HS, Meneses KM, et al. (2016) Patient-centered support in the survivorship care transition: Outcomes from the Patient-Owned Survivorship Care Plan Intervention. *Cancer* 122:3232–3242. doi: 10.1002/cncr.30136
26. Gass J, Dupree B, Pruthi S, et al. (2016) Breast Cancer Survivorship: Why, What and When? *Ann Surg Oncol* 23:3162–3167. doi: 10.1245/s10434-016-5403-0
27. Khatcheressian JL, Hurley P, Bantug E, et al. (2013) Breast cancer follow-up and management after primary treatment: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol* 31:961–965. doi: 10.1200/JCO.2012.45.9859
28. Grunfeld E, Julian JA, Pond G, et al. (2011) Evaluating survivorship care plans: results of a randomized, clinical trial of patients with breast cancer. *J Clin Oncol* 29:4755–4762. doi: 10.1200/JCO.2011.36.8373
29. Khan F, Amatya B, Ng L, et al. (2012) Multidisciplinary rehabilitation for follow-up of women treated for breast cancer. *Cochrane database Syst Rev* 12:CD009553. doi:

10.1002/14651858.CD009553.pub2

30. Pusic AL, Cemal Y, Albornoz C, et al. (2013) HRQL among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. *J Cancer Surviv* 7:83–92. doi: 10.1007/s11764-012-0247-5
31. Donatelli R, Ellenbecker TS, Ekedahl SR, et al. (2000) Assessment of shoulder strength in professional baseball pitchers. *J Orthop Sports Phys Ther* 30:544–551. doi: 10.2519/jospt.2000.30.9.544
32. Rehabilitation Medicine, Chapter 4 Clinical Evaluation. De Lisa JA, Second Edition. JB Lippincott Company Philadelphia. 1993 ISBN0-397-51262-7
33. Taylor R, Jayasinghe UW, Koelmeyer L, et al. (2006) Reliability and validity of arm volume measurements for assessment of lymphedema. *Phys Ther* 86:205–214.
34. Alonso J, Regidor E, Barrio G, et al. (1998) [Population reference values of the Spanish version of the Health Questionnaire SF-36]. *Med Clin* 111:410–416.
35. Vilagut G, Valderas JM, Ferrer M, et al. (2008) [Interpretation of SF-36 and SF-12 questionnaires in Spain: physical and mental components]. *Med Clin* 130:726–735. doi: 13121076 [pii]
36. Brady MJ, Cella DF, Mo F, et al. (1997) Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *J Clin Oncol* 15:974–986.
37. Coster S, Poole K, Fallowfield LJ (2001) The validation of a HRQL scale to assess the impact of arm morbidity in breast cancer patients post-operatively. *Breast Cancer Res Treat* 68:273–282.
38. Belmonte Martinez R, Garin Boronat O, Segura Badia M, et al. [Functional Assessment of Cancer Therapy Questionnaire for Breast Cancer (FACT-B+4). Spanish version validation]. *Med Clin* 137:685–688. doi: S0025-7753(11)00095-9 [pii] 10.1016/j.medcli.2010.11.028
39. Hislop, Helen J MJ (2007) *Techniques of Manual Examination*, Daniels & Worthingan's Muscle Testing, 8th edition. SAUNDERS ELSEVIER, St. Louis , Missouri 6314 6
40. Sagen A, Kaaresen R, Sandvik L, et al. (2014) Upper limb physical function and adverse effects after breast cancer surgery: a prospective 2.5-year follow-up study and preoperative measures. *Arch Phys Med Rehabil* 95:875–881. doi: 10.1016/j.apmr.2013.12.015
41. Veronesi U, Paganelli G, Viale G, et al. (2003) A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *N Engl J Med* 349:546–553. doi: 349/6/546 [pii] 10.1056/NEJMoa012782
42. Langer I, Guller U, Berclaz G, et al. (2007) Morbidity of sentinel lymph node biopsy (SLN) alone versus SLN and completion axillary lymph node dissection after breast cancer surgery: a prospective Swiss multicenter study on 659 patients. *Ann Surg* 245:452–461. doi: 00000658-200703000-00017 [pii] 10.1097/01.sla.0000245472.47748.ec
43. Peintinger F, Reitsamer R, Stranzl H, Ralph G (2003) Comparison of HRQL and arm complaints after axillary lymph node dissection vs sentinel lymph node biopsy in breast cancer patients. *Br J Cancer* 89:648–652. doi: 6601150 [pii] 10.1038/sj.bjc.6601150
44. Mansel RE, Fallowfield L, Kissin M, et al. (2006) Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst* 98:599–609. doi: 98/9/599 [pii] 10.1093/jnci/djj158

Fig. 1. Mean QoL scores by treatment group.

*Statistically significant changes

Figure 2 supplementary. Flow Diagram

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)										
	Mean (SD)	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										
	Mean (SD)	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										

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.

SLNB group	n	Mean (SD)			p-value (ANOVA)	p-value (vs. pre-treatment) *	
		Pre-treatment	Year 1	Year 5		Year 1	Year 5
Affected side							
External Rotators strength	40	8.3 (1.7)	8.3 (2.0)	8.7 (3.3)	0.581	---	---
Internal Rotators strength	40	9.8 (2.1)	9.3 (2.1)	9.1 (2.2)	0.128	---	---
Abductors 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 Rotators strength	40	8.1 (2.3)	8.4 (2.6)	9.3 (3.4)	0.020	1.000	0.050
Internal Rotators 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 Rotators strength	39	0.17 (2.15)	-0.18 (1.86)	-0.78 (2.60)	0.092	---	---
Internal Rotators strength	39	0.19 (1.73)	0.11 (1.32)	0.10 (1.54)	0.849	---	---
Abductors 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							
ALND group	n	Mean (SD)			p-value (ANOVA)	p-value (vs. pre-treatment) *	
		Pre-treatment	Year 1	Year 5		Year 1	Year 5
Affected side							
External Rotators strength	29	9.5 (2.6)	8.1 (2.7)	9.5 (3.5)	0.006	0.002	1.000
Internal Rotators strength	29	11.1 (2.8)	8.6 (2.8)	9.6 (2.6)	< 0.001	< 0.001	0.002
Abductors 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 Rotators strength	29	8.6 (2.2)	8.2 (2.5)	9.9 (3.1)	0.011	0.936	0.024

Internal Rotators strength	29	10.2 (2.5)	9.3 (2.4)	10.0 (2.7)	0.060	---	---
Abductors 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 Rotators strength	29	0.87 (2.12)	-0.14 (2.01)	-0.37 (2.22)	0.072	---	---
Internal Rotators strength	29	0.97 (1.26)	-0.71 (1.80)	-0.42 (1.33)	0.002	< 0.001	0.001
Abductors 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 Kg, shoulder range of motion in degrees, arm volume in mL

* Post hoc tests with Bonferroni adjustment for multiple comparisons.

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

		External Rotators Strength		Internal Rotators Strength		Abductors 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 x Time													
SLNB x 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 x 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 Rotators strength	26 (34.7%)	16 (36.4%)	10 (32.3%)	0.713
Internal Rotators strength	18 (24.0%)	6 (13.6%)	12 (38.7%)	0.012
Abductors 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

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 Bonferroni adjustment for multiple comparisons.

Table 6 Supplementary. GEE models – HRQL

		FACT-B+4 Arm Scale		FACT-B+4 Trial Outcome Index		FACT-B+4 Global Summary		SF-36 Physical Component Summary	
		Beta (SE)	p-value	Beta (SE)	p-value	Beta (SE)	p-value	Beta (SE)	p-value
Intercept		18.3 (1.7)	< 0.0001	104.2 (10.3)	< 0.0001	152.0 (14.2)	< 0.0001	77.1 (6.2)	< 0.0001
T									
	IS	ref.	.	ref.	.	ref.	.	ref.	.
	T1	0.6 (0.5)	0.287	-2.3 (3.6)	0.519	-1.9 (5.0)	0.705	0.0 (2.1)	0.984
N									
	0	ref.	.	ref.	.	ref.	.	ref.	.
	1-3	0.6 (0.8)	0.450	-0.6 (5.1)	0.901	-1.8 (6.9)	0.792	0.6 (3.1)	0.852
Group									
	SLNB	ref.	.	ref.	.	ref.	.	ref.	.
	ALND	-0.5 (0.7)	0.513	3.2 (4.6)	0.488	4.9 (6.3)	0.433	0.5 (3.2)	0.863
Interaction Treatment Group x Time									
Change from baseline of the REFERENCE (Group of SLNB)									
	Baseline	ref.	.	ref.	.	ref.	.	ref.	.
	1 year	-1.4 (0.4)	0.001	-2.7 (1.6)	0.092	-1.6 (2.2)	0.464	-5.4 (1.2)	<.0001
	5 years	-1.3 (0.3)	< 0.0001	-3.7 (2.1)	0.083	-0.5 (3.0)	0.873	-6.2 (1.4)	<.0001
Difference in change from baseline of ALND group compared with REFERENCE									
	Baseline	ref.	.	ref.	.	ref.	.	ref.	.
	1 year	-2.2 (0.7)	0.003	-4.4 (2.9)	0.129	-3.6 (4.1)	0.375	-0.6 (2.2)	0.802
	5 years	-1.3 (1.0)	0.192	-1.1 (3.9)	0.774	-2.9 (5.3)	0.591	1.6 (2.5)	0.522

Adjusted by age, body mass index, radiotherapy, chemotherapy and hormonotherapy