

ORIGINAL ARTICLE

Changes in arm morbidities and health-related quality of life after breast cancer surgery – a five-year follow-up study

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Abstract

Background and purpose. Many breast cancer survivors (BCS) suffer from long-term upper limb morbidities after axillary node dissection. The purpose of this five-year follow-up study was to describe changes in long-term upper limb morbidities, physical activity level, and Health-Related Quality of Life (HRQoL) and to find factors that predict HRQoL five years after surgery. **Patients and methods.** This study included 204 women aged 55 ± 10 years who had primary breast cancer surgery with axillary node dissection. The subjects were examined for arm volumes and arm lymphedema, arm pain, sensation of heaviness, shoulder function, physical activity level, and HRQoL, prior to surgery, and six months and five years after surgery. The statistical analyses used included ANOVA for repeated measures and multivariate linear regression. **Results.** ALE (13%), pain (36%), and sensation of heaviness (21%) in the upper limbs were present five years after surgery. ALE was the only morbidity that continued to increase over time. Several dimensions of HRQoL temporarily declined after surgery, but significantly improved in the period from six months to five years after surgery. The significant predictive factors of HRQoL five years after surgery included HRQoL prior to surgery, physical activity level at leisure time (both prior to and at six months after surgery), and duration of sick leave after surgery (in weeks). **Conclusions.** The overall HRQoL improved significantly from baseline to five years, despite the chronic arm pain and increase in ALE. Three independent predictive factors of HRQoL were identified.

The majority of breast cancer survivors (BCS) have long-term upper limb and shoulder morbidities, including lymphedema, pain, and reduced shoulder function, and have a lower physical activity level compared with activity level prior to surgery [1]. Moreover, increased physical activity has been shown to reduce these morbidities, as well as the incidence of relapse for breast cancer, and to increase Health Related Quality of Life (HRQoL) [1–4]; however, long-term follow-up studies on upper limb morbidities and HRQoL in BCS after axillary node dissection (ALND) are sparse [4–7].

Arm lymphedema (ALE), is commonly associated with breast cancer surgery with ALND and is most frequently reported to be influenced by the number of nodes removed and high body mass index (BMI) [8–12]. The incidence of ALE increases over time and varies according to differences in follow-up time, definition of and methods used for measuring

ALE, and study design [13,14]. Preoperative assessments of arm volume have led to a more precise prevalence of ALE [13]; however, we only identified one study including measurement of preoperative ALE and long-term follow-up (prevalence of ALE = 16%) [9]. Other long-term arm morbidities, such as chronic arm pain, have a prevalence of 20–50% five to 12 years after surgery [15,16] and are strongly associated with HRQoL [16].

The HRQoL outcomes for patients with locally advanced breast cancer have reported to decrease temporarily during cancer treatment, but return to baseline levels after treatment [17]. The cancer treatment seems to affect several parameters included in HRQoL questionnaires [3,4]. Women diagnosed with ALE, arm pain or other arm symptoms have shown to have a lower physical and mental HRQoL compared to BCS without ALE or arm symptoms [6,18]. In addition, physical activity

level and chemotherapy are associated with changes in physical functioning [3]; however, cancer treatment does not seem to influence negatively the overall long-term HRQoL in BCS [4].

The primary aim of this prospective five-year cohort study was to describe changes in arm volume and ALE, arm and shoulder symptoms, physical activity level and HRQoL, prior to surgery and six months and five years after surgery. Our secondary aim was to identify predictive factors for the HRQoL five years after breast cancer surgery.

Material and methods

Patients

This study included 204 women with an average age of 55 ± 10 years (32 to 75 years) with early stage breast cancer (stages I and II) and who underwent mastectomy or breast-conserving surgery with ALND (levels I and II), with or without radiotherapy, chemotherapy, or hormone treatment (Table I). Patients were recruited before surgery between 1999 and 2003 at the Ullevaal and Akerhus University Hospitals in Norway. Subjects participated in a randomized controlled intervention study with two different physical therapy regimens during the first six months that showed no significant differences in outcome between the two rehabilitation groups [12]. The exclusion criteria were: patients older than 75 years of age, too fragile to participate, problems understanding Norwegian, metastasized breast cancer, other cancer diseases, and injuries that affected the functioning of the upper limbs. The participants were given physical therapy and lymphedema treatment (when needed) during the five-year follow-up period.

Measurements

The participants were assessed at baseline (prior to surgery) and prospectively at six months and five years after surgery.

Arm volume (milliliters) and difference in arm volume between the affected and control arms (Voldiff) were measured using the Simplified Water Displacement Instrument (SWDI) [19]. Definition of ALE was based on a criteria commonly used in the literature: a 10% increase in the affected arm volume compared with the control arm volume ($(\text{affected} - \text{control})/\text{control} \times 100$) [20].

Pain and sensation of heaviness in the affected limb during physical activity and at rest were evaluated using visual analogue scales (VAS) [20] and were assessed by the participants assisted by a physical therapist. Sensation of heaviness in the affected limb is part of the variety of sensations in

Table I. Demographics, preoperatively and at the five-year follow-up time point.

	Preoperatively n = 204	5 years follow-up n = 157
Age (years)	55 (10)	60 (9)
Type of work affecting upper limbs		
Heavy physical work (nursing, kindergarten, flight attendant, grocery store worker, etc)	45 (22%)	36 (23%)
Light physical work (administration, teacher, secretary, housewife, retired, etc)	159 (79%)	121 (77%)
Number of lymph nodes removed	13 (4.0)	13 (4)
Number of metastasized lymph nodes	2 (3.3)	1.6 (3)
Breast ablation	106 (52%)	77 (49%)
Breast preservation	98 (48%)	80 (51%)
Surgery at dominant side	109 (53%)	90 (57%)
Radiotherapy of supraclavicular nodes	87 (43%)	62 (40%)
Radiotherapy of breast	151 (74%)	115 (73%)
Chemotherapy	80 (39%)	58 (40%)
Hormone treatment	106 (52%)	81 (52%)
Histology grade 1	44 (22%)	37 (24%)
Histology grade 2	112 (55%)	89 (57%)
Histology grade 3	48 (24%)	30 (19%)
Arm volume (ml), affected side	2 386 (389)	2 555 (468)
Arm volume (ml), control	2 383 (486)	2 496 (465)
Voldiff (ml)	3 (127)	59 (165)
BMI	25 (3.7)	25 (3.9)
Physical activity at leisure time in min per week	126 (82)	124 (76)

Numbers and percent (%), mean and standard deviations (SD)

the post mastectomy pain syndrome [21] and has previously been used as an outcome measurement for lymphedema patients [6,7].

Shoulder function was evaluated using the “shoulder, elbow, and wrist movement impairment” score, validated and reliability tested for women with rheumatoid arthritis [22].

Height and weight were recorded to determine BMI (kg/m^2).

Physical activity during leisure times was assessed using a questionnaire that included the frequency per week of sessions of moderate to vigorous physical activity lasting at least 20 min. The questionnaire has previously been used to assess adherence to physical activity interventions [12].

The HRQoL was evaluated using The Core Quality of life Questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30, version 3.0) [23]. The raw scores were calculated into scales (0–100) using the recommended EORTC procedures. The 30 questions

were sectioned into five scales: physical functioning, functioning, symptoms, fatigue, and global health status.

Statistical analyses

The planned sample size of 204 participants was based on power calculations of the primary end point (ALE) [12]. Analysis of Variance (ANOVA) for repeated measures was used to assess the differences in arm volume, BMI, physical activity level, shoulder function, and HRQoL scales between baseline, six-month, and five-year follow-ups. Student's *t*-tests were used to assess pain and sensation of heaviness in the affected limb at six months and five years after surgery (no preoperative data for pain and sensation of heaviness were recorded). Bonferroni adjustments were made to allow paired comparisons for multiple testing. We included descriptive data, 95% confidence intervals (CI), and significance tests for hypothesized changes (the significance threshold was set at $p < 0.05$). To identify predictive factors for the HRQoL at the five-year follow-up, the following model was used: relevant predictive factors were analyzed using a univariate linear regression analysis; in cases where p was lower than 0.05 (two-tailed), the significant factors were included into a multivariate linear regression analysis with forward variable selection. Data were analyzed using the SPSS 11.0 software (SPSS Inc, Chicago, IL).

Ethics

The regional Committee for Medical Research Ethics approved the study and the patients signed a written consent form prior to participation in the study.

Results

One hundred and fifty-seven (77%) of the 204 women originally recruited, participated at the final five-year follow-up (Table I). Seven women had recurrence but participated in the follow-up at five

years, 28 (14%) died, six moved elsewhere, five were not available via telephone or at their address, and eight refused to participate in the five-year follow-up.

Arm lymphedema was found in 12 women (7%) at six months follow-up and increased to 21 women (13%) at the five-year follow-up (Table II). The change in Voldiff increased significantly from baseline to six months, but not from the six-month to the five-year follow-ups (Table III). The mean BMI increased significantly from baseline to six months, but not from baseline to five years (Table III).

During physical activity arm pain was observed in 56% of the woman at 6-months follow-up, and at rest in 60% of the women. At the five-years follow-up the number of women with pain decreased significantly to 36% and 30%, respectively (Table II). Sensation of heaviness was detected in 46% of the women during activity and in 45% during rest at six months, and decreased significantly to 21% and 20% at 5 years, respectively (Table II).

Four of the five function scores for the affected shoulder significantly decreased from baseline to six months (from 29.7 ± 0.8 points to 28.9 ± 1.9 points) ($p < 0.001$), but there were no significant changes from baseline to five years ($p = 0.171$). The control side scores did not change over time.

The mean physical activity level did not change significantly (CI, -3 to 25) ($p = 0.167$) from baseline to six months, or from baseline to five years (CI, -17 to 20) ($p = 1.000$).

The HRQoL scale for Physical Functioning did not change significantly over time (Table IV, Figure 2), but the Functioning scale decreased significantly over time from baseline to five years (Table IV, Figure 2). The Symptoms scale and the Fatigue scale significantly increased temporarily from baseline to six months, but did not change significantly from baseline to five years (Table IV, Figure 2). The Global Health scale significantly increased over time from baseline to five years (Table IV, Figure 2).

The multivariate analysis showed that the physical activity level at leisure time both at baseline and at six-month follow-up were a significant predictive

Table II. Pain and sensation of heaviness and arm lymphedema (ALE) for the affected limb.

	6 months (n = 190)		5 years (n = 157)	
	Mean (SD)	(%)	Mean (SD)	(%)
Arm pain during physical activity (mm)	12 (19)	56	10 (19)	36*
Arm pain during rest (mm)	11 (18)	60	8 (17)	30*
Sensation of heaviness during activity (mm)	9 (17)	46	7 (17)	21*
Sensation of heaviness during rest (mm)	8 (16)	45	6 (18)	20*
ALE		7		13*

*Paired *t*-tests six months to five years $p < 0.05$. Mean and standard deviations (SD), and percent (%). Arm pain and sensation of heaviness in millimeters (mm) Visual Analogue Scale.

Table III. Changes* in arm volume and BMI.

	Baseline to 6 months (n = 190)	6 months to 5 years (n = 157)	Baseline to 5 years (n = 157)
Affected (ml)			
Mean difference	113	34	148
95% CI	81–145	–17–86	92–203
p-values	<0.001	0.34	<0.001
Control (ml)			
Mean difference	63	38	102
95% CI	36–90	–9–86	54–150
P values	<0.001	0.16	<0.001
Voldiff (ml)			
Mean difference	50	6	44
95% CI	21–78	–34–23	11–77
p-values	<0.001	0.64	<0.001
BMI			
Mean difference	0.6	–0.1	0.5
95% CI	0.4–0.9	–0.5–0.3	0.1–0.9
p-values	<0.001	0.10	0.009

Changes from baseline (prior to surgery) to six months and five years. BMI and arm volumes, Voldiff (volume difference between affected and control). Mean difference, standard deviations (SD), *P* values, and 95% Confidence Intervals (CI). *Positive differences imply increase.

factor of the Physical Functioning scale at five years (Table V). The multivariate analysis revealed that the duration of sick leave at six months was the only significant predictive factor of Functioning at five years (Table V). The multivariate analysis showed that the Symptoms scale prior to surgery was the only significant predictive factor of Symptoms at five years (Table V). The multivariate analysis revealed that both the Global Health scale prior to surgery

and the duration of sick leave at six months were significant predictive factors of Global Health status at five years (Table V).

Discussion

To our knowledge, this is the first five-year follow-up study that evaluated upper limb morbidities including preoperative assessment of arm volume,

Table IV. Changes* in the HRQoL scales from baseline to 6 months and 5 years.

Subscales	Baseline to 6 months n = 204	6 months to 5 years n = 190	Baseline to 5 years n = 157
Physical Functioning			
Mean difference	–1.9	1.6	–1.1
CI	4.4–0.5	–.5–4.6	–4.2–1.9
p-values	0.12	0.31	0.45
Functioning			
Mean difference	–4.1	–5	–8.6
CI	–6.7––1.6	–7.7––2.2	–12.4––4.6
p-values	0.002	<0.001	<0.001
Symptoms			
Mean difference	5.1	–4.5	1.1
CI	3–7.2	–1.8––7.1	–1.6–3.9
p-values	<0.001	<0.001	0.42
Fatigue			
Mean difference	6.8	–5.3	1.2
CI	3.5–10	–9.5––1.2	–3.4–5.8
p-values	<0.001	0.012	0.62
Global Health Status			
Mean difference	3.5	4	7.3
CI	0.0–6.9	0.0–8.2	3.0–11.4
p-values	0.050	0.052	<0.001

Mean change, 95% Confidence Intervals (CI), and *P* values. *Positive changes imply increase.

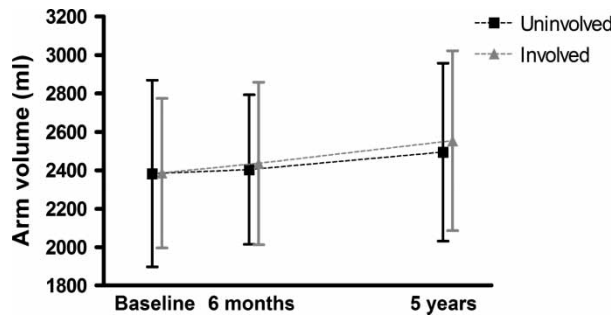


Figure 1. Arm volumes from baseline ($n=204$) (before surgery) to five years ($n=157$) after surgery.

arm and shoulder symptoms and HRQoL in breast cancer patients with ALND.

As shown in other studies, we found that the incidence of ALE increased by time after surgery [11,12]. Similarly we, as the others, found a significantly increased arm volume from baseline to six months after surgery, both in the affected and in the control arms [2,13,24]. However we did not find a significant increase in arm volume from six months to five years (Figure 2, Table III). Furthermore, BMI increased exclusively during the first six months (Table III), which is in accordance with previous reports [8,12]. Accordingly the first six months seems to be most important if one plans interventions to prevent this development.

Studies with preoperative assessments tend to report lower rates of ALE [9,11,12] than studies without preoperative data on arm volume. Furthermore, studies of self-reported data for lymphedema and arm symptoms tend to report the highest incidences [18]; Norman et al. reported a prevalence of 42% within 5 years after diagnosis [7] and Meeske et al. reported an incidence of 24% within 18 months after the diagnosis [10]. However, Ahmed et al. only disclosed lymphedema in 8% of the BCS eight years after the diagnosis by using the same self-report measure of lymphedema as Norman [6]. These huge differences in the incidence of ALE by

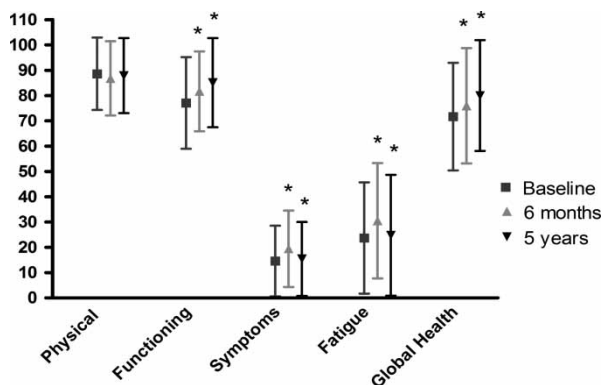


Figure 2. HRQoL scales from baseline ($n=204$) (before surgery) to five years ($n=157$) after surgery. * $p < 0.05$.

using the same instrument may indicate poor validity. Closer to our low results of ALE (13%) (Table II) was the reported incidence of 16% in a five-years follow-up by McLaughlin et al. [9] who included preoperative objective measurements.

Previous studies have found a lower incidence of ALE in patients given physical therapy treatment compared to those who did not receive such treatment [13]. The incidence of ALE increased from 7 to 13% in the period between six months to five years. Our low incidence could be the result of the close follow-ups and the physical therapy (including ALE treatment) given to these patients [12].

Arm pain was still present five years after surgery, both at rest (20%) and during physical activity (21%), but the numbers of women with pain had significantly decreased since six months after surgery (Table II). We have previously reported that the intensity of arm-pain and sensation of heaviness two years after surgery was mainly low in these patients [12]. Similar results have recently been reported in a five-year follow-up study in Denmark, where 29% of the BCS developed chronic pain [16]. It has been suggested that BCS with chronic pain symptoms including neurological dysfunction such as sensation of heaviness, have been undertreated, and have obtained poor pain relief from their symptoms [21].

The shoulder function declined significantly the first six months, but improved to the baseline level at five years. Previous studies have also reported significant shoulder dysfunction in BCS, but patients given physical therapy shortly after surgery return a state of almost normal shoulder function [25]. As with ALE the first six months seems to be the best intervention period if one will prevent bad shoulder function.

The previously reported decline in physical activity level after breast cancer surgery [1,3] was not found in our study. The mean physical activity level at leisure time was similar to that at baseline, 126 ± 84 min per week, and did not decline significantly at six months or at five years after surgery (Table I). The recommended physical activity level has been defined as 150 min per week of moderate to vigorous intensity [26]. Among the 806 BCS in the American Health, Eating, Activity and Lifestyle Study, 32% had a physical activity level at the recommended 150 min per week [27]. Prior to surgery, 36% of the participants in our study had a physical activity level during leisure time above the recommended level of 150 min per week. Five years later, the physical activity level in 34% of the participants was above the recommended level. Fifty-one percent of the Norwegian general female population above 60 years of age, have reported that they are physical active during leisure time (brisk walking, bicycling etc)

Table V. Predictive factors for HRQoL scales at 5 years after surgery.

Physical functioning						
Factors	Univariate analysis			Multivariate analysis		
	<i>b</i> *	95% CI	p	<i>b</i> *	95% CI	p
Physical activity at leisure time (min per week) at baseline (prior to surgery)	0.039	0.012–0.067	0.005			
Physical activity at leisure time (min per week) at 6 months after surgery	0.076	0.039–0.113	<0.001	0.076	0.039–0.113	<0.001
Functioning						
Physical activity at leisure time (min per week) at baseline (prior to surgery)	0.036	0.002–0.070	0.038			
The HRQoL subcategory “Functioning” at baseline (prior to surgery)	0.165	0.007–0.323	0.041			
Duration of sick leave at 6 months after surgery (weeks)	–0.259	–0.483–0.034	0.024	–0.269	–0.494–0.045	0.019
Symptoms						
Duration of sick leave at 6 months after surgery (weeks)	0.211	0.030–0.392	0.023			
Pain in the affected limb during rest 3 months after surgery	0.148	0.024–0.272	0.020			
The HRQoL subcategory “Symptoms” at baseline (prior to surgery)	0.334	0.158–0.511	<0.001	0.258	0.065–0.441	0.009
Fatigue						
The HRQoL subcategory “Fatigue” at baseline (prior to surgery)	0.271	0.097–0.446	0.003			
Global Health						
The HRQoL subcategory “Global Health” at baseline (prior to surgery)	0.257	0.077–0.437	0.005	0.224	0.045–0.402	0.015
Duration of sick leave at 6 months after surgery (weeks)	–0.409	–0.667–0.140	0.003	–0.368	–0.634–0.102	0.007
Chemotherapy	–7.899	–15.050–0.748	0.031			

*b**: the estimated slope i.e. the mean change in the dependent variable (HRQoL dimensions) when the independent variable (factors) increases by 1 unit.

more than two times per week [28]. The reported activity level was lower than for the 34% of the BCS in our study that was above 150 min/week. The numbers of physical active BCS in our study is almost similar to the general population.

The HRQoL in our subjects was better than for the age-matched Norwegian female population [23], and is in accordance with the previously reported increase in HRQoL in disease-free physical active BCS [3,4]. Late morbidities after breast cancer affect several subscales of HRQoL [4–6,23]. The Functioning scale decreased significantly by –8.6 points (Table IV, Figure 2), which is in accordance with previous results [4–6]; however, the previously reported decrease in Physical Functioning values in BCS (for the same age group) was not found in our study [4] (Table IV, Figure 2). The Global Health status increased significantly by 7.3 points, from the baseline to five years after surgery (Table IV, Figure 2), and was more than 10 points above the mean value reported of 69.9 ± 25.8 for the general female population for the age group between 70 and 79 years of age, and five points above the general female population aged 60 to 69 years [23]. As previously reported, the women who participated in this study were included based on the

criteria of being able to participate in physical therapy rehabilitation with resistance exercise training at an outpatient clinic [12]. Patients who were too frail were excluded. This might be a reason for the high Physical Functioning and Global health status scores in our study when compared to the general population [23].

Chemotherapy was found to be a significant predictive factor for decreased Global Health status five years after surgery, as assessed by univariate analysis (Table V). This was in accordance with the results reported by Ganz et al.[29]; However, the multivariate analysis revealed that chemotherapy was not a significant predictive factor (Table V). Treatment with chemotherapy and high demands at work were reported to be of significance for symptom persistence 10 months after surgery [3].

Acute pain after surgery is a risk factor for developing chronic pain in BCS [29]. This observation is corroborated by univariate analysis of our material, showing that arm pain three months after surgery is a predictive factor for increased Symptoms at five years (Table V).

The physical activity level (at baseline and at six months after surgery), obtained by both univariate and multivariate analysis, was a significant predictive

factor for the Functioning and for the Physical functioning scales five years after surgery (Table V). The significant relationship between an increased physical activity level and increased HRQoL in BCS has been previously reported [3,29] and is further supported by our findings.

The duration of the sick leave after surgery appeared to be a significant predictive factor for both Functioning and the Global Health Status (Table V). Sick-listed and unemployed individuals in the general population have also reported lowered self-rated health and lowered social participation [30].

The 47 patients (23%) who were lost to follow-up at 5 years might be a limitation in our study. However, the lost cases did not affect the power or biased the results because intentionally the number of patients included were set high enough to allow this number of drop-outs without losing the necessary statistical power [12]. Furthermore, we have presented the results of change over time based on ANOVA for repeated measures, a favorable analysis for data at different time-points along the time axis because the numbers of significant-tests are reduced to one. However, we believe that the assessment of arm pain preoperatively would have enabled to examine changes in pain score more precisely. The necessary data to provide such results was not obtained.

Arm pain (36%) and a sensation of heaviness (32%) might be reduced by systematic registration and treatment shortly after surgery [12]. Our fairly low frequencies of ALE (13%) and recovery from shoulder motion impairments can probably be attributed to the physical therapy program in our study. Our data are, however, too limited to support a firm conclusion. All patients that have gone through axillary node dissection should be encouraged to a physical active life and treatment instituted as soon as ALE is detected. Future clinical practice should integrate measurements of ALE, pain and shoulder function during routine follow-up visits and adequate therapy for those with pain, beginning lymphedema and shoulder motion impairments.

Conclusions

Arm lymphedema, pain, and the sensation of heaviness in the limb were still present five years after surgery. Arm lymphedema was the only morbidity that continued to increase over time. The HRQoL temporarily declined, but later significantly improved from six months to five years. The significant predictive factors for HRQoL five years after surgery were: HRQoL prior to surgery, physical activity level at leisure time (both prior to and at six months after

surgery), and duration of sick leave after surgery (in weeks).

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