The Breast 24 (2015) 75–81

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Original article

Health related quality of life improvement in breast cancer patients: Secondary outcome from a simple blinded, randomised clinical trial

María José Yuste Sánchez [a, *], María Torres Lacomba [a], Beatriz Sánchez Sánchez [a], David Prieto Merino [b], Soraya Pacheco da Costa [a], Ester Cerezo Téllez [a], Álvaro Zapico Goñi [a, c]

[a] Physiotherapy Department, Physiotherapy in Women's Health Research Group, Faculty of Physiotherapy, Alcalá de Henares University, E-28871 Alcalá de Henares, Madrid, Spain
[b] Clinical Trial Unit, London School of Hygiene & Tropical Medicine, London, UK
[c] Príncipe de Asturias University Hospital, Alcalá de Henares, Madrid, Spain

ARTICLE INFO

Article history:
Received 23 February 2014
Received in revised form
1 November 2014
Accepted 24 November 2014
Available online 10 December 2014

Keywords:
Quality of life
Breast cancer
Physiotherapy
Therapeutic education program

ABSTRACT

Objective: To determine the effectiveness of an early physiotherapy intervention for the prevention of secondary lymphoedema on health-related quality of life in women who also received an education program after breast cancer surgery.
Methods: One hundred and fifty three women diagnosed with unilateral breast cancer (stage I–II) treated with breast surgery, which included axillary lymph-node dissection, from Hospital Príncipe de Asturias, Alcalá de Henares, Madrid (Spain) were randomly assigned into two groups. Subjects in early physiotherapy group ($n = 76$) received a physiotherapy intervention combined with a therapeutic education program; women in the control group ($n = 77$) received only the therapeutic education program. Both interventions were delivered by two different physiotherapists of Physiotherapy in Women's Health Research Group at Physiotherapy Department of Alcala University. Health related quality of life was measured with EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires in 5 assessments: after surgery just before group interventions started (A_1), after the 3-week group interventions finished (A_2); and a follow-up period in 3 (A_3), 6 (A_4) and 12 (A_5) months after surgical intervention.
Results: Greater change in quality of life was observed for early physiotherapy group arm compared to control group, although no strong statistical evidence was found ($p > .05$) for most of the dimensions except for physical function and social function areas ($p < .003$).
Conclusions: The control group with therapeutic education program reported a clear improvement in the perception of quality of life. Adding early physiotherapy to the therapeutic education program did not show statistically significant changes in the global score or in most of the dimensions, but showed an improvement in the physical and social dimensions.

Introduction

Breast cancer is one of the most common malignant tumours and it affects 22.7% of women worldwide [1]. The global survival rate for breast cancer patients is between 78 and 88% after five years, and this tendency is rising over the years, due to the improvements in early detection and treatment [1–4].

Women with breast cancer undergoing treatment often have many psychological and physical adverse effects as a result of their cancer and the treatment for it. These effects have a negative impact on women's physical, emotional and social status and they experience a poorer quality of life (QoL) because of the disease and its treatment. Therefore, the interest on assessing breast cancer survivors' QoL, physical, emotional and social status impact has increased during the last few decades [5–8].

Breast cancer symptoms [9], type of surgical intervention [10–12], adjuvant therapies [13,14] and women's low economic level [11,15] are directly associated to decreased Health-Related Quality of Life (HRQoL). A review about QoL during breast cancer

* Corresponding author. Facultad de Fisioterapia, Universidad de Alcalá, Campus Externo. Ctra., Madrid-Barcelona km 33,600, 28071 Alcalá de Henares, Madrid, Spain.
E-mail address: marijo.yuste@uah.es (M.J. Yuste Sánchez).

http://dx.doi.org/10.1016/j.breast.2014.11.012
0960-9776/

treatment states that HRQoL perception is affected by different symptoms depending on the treatment the patients received [16]. In fact, although HRQoL improves over time after surgery, it does not reach values before surgery even after two or five years after breast cancer diagnosis [9–11,17–19].

After breast cancer surgery, the most frequent symptoms are pain, restricted shoulder and arm mobility, axillary web syndrome, arm muscle weakness and upper limb lymphoedema [10,19–32]. Over 70% of patients with axillary lymph node dissection and 40% of patients with sentinel lymph node biopsy report restricted arm mobility, shoulder pain, stiffness, oedema, axillary web syndrome, and a swollen feeling in breast and arm after surgery [22,33]. The sentinel node procedure may have a lower impact on shoulder functionality than axillary lymph node dissection, especially in the long term, around 72 months [10,12]. In general, these problems decrease over time and may limit patient's daily living activities and have a negative impact on their physical and psychological well-being [9,18].

A reduction in shoulder range of motion (ROM) affects basic activities of daily living and may hinder radiotherapy treatment. Many studies have examined the effect of physiotherapy in upper-limb dysfunction after breast cancer surgery [34], although only few of them have reported the effect of the interventions on HRQoL [35,36]. The objective of most of these studies was to improve shoulder ROM [34,36–38]. Just two of them aimed the prevention of lymphoedema through affected upper limb exercise intervention [39] and only one addressed vascular sequelae of immediate postoperative period (post-surgical oedema, axillary web syndrome, etc.) [40]. Most interventions described in the studies were compared to educational programs on lymphoedema prevention, patient and diet education, and counselling [41,42]. The potential ability of psychosocial interventions that include an education support on breast cancer treatment to enhance HRQoL [43–45], are usually performed during the care these patients, although most of the times they do not follow any established guidelines [43].

The aim of this paper was to determine the effectiveness of an early physiotherapy intervention for the prevention of secondary lymphoedema on the health-related quality of life in women who also received an education program after breast cancer surgery.

Material and methods

This paper reports a secondary analysis of the study named “Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blind, clinical trial”, which was carried out between May 2005 and December 2010 and approved by Hospital Príncipe de Asturias Ethical Committee of Clinical Research in Alcalá de Henares, Madrid (Spain) [40].

Subjects

The sample consisted of 153 women diagnosed with breast, >18 years old, diagnosed with stage I–II breast cancer who were operated of unilateral breast cancer surgery with axillary lymph-node dissection at Hospital Príncipe de Asturias, Alcalá de Henares, Madrid (Spain). Women who had bilateral breast surgery, with no axillary lymph-node dissection, or systemic disease or local or regional recurrence, as well as those who presented some contraindication for physiotherapy intervention were excluded from the trial. After signing the informed consent, participants were blinded randomly allocated either to the early physiotherapy group (EPTG) with 76 participants, or to the control group (CG) with 77 participants. The sample size was calculated according to the main objective of the clinical trial: prevention of lymphoedema in breast cancer survivors. Details on sample size calculations, randomisation and blinding have been explained in the paper with the primary analysis by Torres et al. [40].

Procedure

Physiotherapy intervention in EPTG was carried out by an experienced physiotherapist (Pt1) and included manual lymphatic drainage on chest and arm (third proximal to shoulder); scar massage; shoulder active kinesiotherapy, combined with functional activities; and proprioceptive neuromuscular facilitation exercise with no resistance. A therapeutic education program was added to the physiotherapy intervention and included information about breast cancer treatments and morbidity, lymphatic system function before and after surgery, and which factors may trigger upper limb lymphoedema, pain and reduced shoulder movement. In addition to that, participants were given skills to modify attitudes in order to improve habits that might prevent morbidity. Each participant was asked to complete a survey to assess knowledge about lymphoedema. In the CG, participants received the same therapeutic education program as in the EPTG, by another physiotherapist (Pt2) [46]. Before the study started, consensus meetings were carried out in order to ensure both physiotherapists (Pt1 & Pt2) performed the same therapeutic educational program.

All participants started each group intervention between the third and the fifth day after surgery and discharge from hospital. Both, EPTG and CG interventions consisted on 30–45-min sessions, 3 times a week, during 3 weeks.

Data collection was performed six times during Physiotherapy assessments by an experienced physiotherapist (Pt3) who used a form's purpose-designed for the study. Assessment timing was before surgical intervention just after randomisation (A_0), after surgical intervention (A_1) just before EPTG or GC interventions started, right after the 3-week intervention finished (A_2); and a follow-up period in 3 (A_3), 6 (A_4) and 12 (A_5) months after surgery. Pt3 was blinded to subject group allocation and participants were instructed not to reveal information about their intervention group.

If upper limb lymphoedema and/or pain occurred during the period of participatory monitoring, either in EPTG or CG, participants were treated according to the recommended physiotherapy protocols for each case [47,48]. No participant was treated out of the interventions established in the study.

Variables

Socio-demographic, anthropometric and personal data together with clinical antecedents and data regarding basal pathology, was collected before surgical intervention (A_0). Breast cancer therapy data (type and date of surgery, radiotherapy, chemotherapy, hormone therapy) were collected after surgical intervention (A_1).

HRQoL, was measured with the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) which is an integrated system for assessing the quality of life (QoL) of cancer patients participating in clinical trials and is intended to be supplemented by tumour-specific questionnaire modules. In this study, EORTC QLQ-C30 was supplemented by a breast cancer module questionnaire (EORTC QLQ-B23) [49,50]. Both questionnaires are validated to the Spanish population [51,52] and were self-filled by participants at five different moments during the study in A_1, A_2, A_3, A_4 and A_5. According to EORTC guidelines each scale or item ranges from 0 to 100. Higher scores for the functional scales represent a higher level of functioning and, higher scores for the symptoms represent a greater extent of symptoms [53].

Statistical analysis

Arithmetic mean and standard deviation, or median and interquartile range, were used as indexes of central trend and dispersion for quantitative variables of the sample distributions depending respectively on whether or not the distributions were assumed to be normal as determined with Kolmogorof-Smirnov (K–S) test. Absolute and relative frequencies in percentage terms were used for categorical variables. To estimate the effect of time and the intervention on the outcomes we used a separate ANOVA model for each outcome with repeated measures (within individuals) and random effects of the individual baseline:

$$Y_{i,t} = U_i + B_1 + I_1{}^*G_i + (B_2 + I_2{}^*G_i)T_2 + (B_3 + I_3{}^*G_i)T_3 + (B_4 + I_4{}^*G_i)T_4 + (B_5 + I_5{}^*G_i)T_5 + e_{i,t} \quad (1)$$

where $Y_{i,t}$ is the observed value of the outcome in individual (i) at moment (t). U_i is the random intercept for each individual, assumed normally distributed with mean 0. G_i is the trial arm of the individual (i) with values $G_i = 0$ for the control arm and $G_i = 1$ for the intervention arm. T_j ($j = 2–5$) are dummy variables for time that take value $T_j = 1$ for $j = t$ and $T_j = 0$ otherwise B_1 is the expected mean of the outcome of the individuals in the control group at post-surgical measurement (visit A_1). B_2 to B_5 are the effects of time in the control group, that is, the differences of outcome mean between post-surgical assessment and observations from A_2 to A_5. The terms $(B_2 + I_2)$ to $(B_5 + I_5)$ are the effects of time in the intervention group, (again, as differences of outcome mean from baseline). Therefore, the interaction coefficients I_2 to I_5 collect the effect of the intervention at each time period, (differences between the control and the intervention groups). Finally $e_{i,t}$ is a random error assumed normally distributed with mean 0 and constant variance. A p-value for the null hypothesis that the time has no effect at all on the outcome mean, and other p-value for the null hypothesis that the intervention does not have an effect at all was also provided. Statistical software R version 3.1 (copyright (2014) the R Foundation for statistical computing) was used for data analysis.

Results

Between May 2005 and December 2010, 153 women, who had unilateral breast cancer surgery with axillary lymph-node dissection at Hospital Príncipe de Asturias, Alcalá de Henares, Madrid (Spain), met the inclusion criteria and gave their informed consent, were included in the study. During the study, 6 participants dropped out, 2 in EPTG and 4 in CG for different reasons, such as, no intervention adherence or moving away from the city during the recovery period, either during the intervention or the follow-up assessments. Therefore, 147 women filled EORTC QLQ-C30 and EORTC QLQ-BR23 questionnaires and more than 95% of the all items were answered (Fig. 1).

Table 1
Post-surgical descriptive characteristics of the sample according to the intervention groups.

	Early physiotherapy group ($n = 74$)	Control group ($n = 73$)
Age (years)–Mean (SD)	53.3 (10.5)	53.6 (12.1)
Body mass index (kg/cm^2)–Mean (SD)	27.5 (5.3)	26.3 (4.4)
Sugical procedure–Number (%)		
Modified mastectomy	29 (39.2)	25 (34.2)
Lumpectomy	17 (23)	18 (24.7)
Quadrantectomy	28 (37.8)	30 (41.1)
Number of dissected lymph nodes–Mean (SD)	13.08 (5)	13.75 (5.5)
Operated side (%)		
Right	47.3	61.6
Left	52.7	38.4
Dominant side (%)		
Right	97.3	97.3
Left	2.7	2.7
Cancer treatment (%)		
Chemotherapy	79.45	88.8
Radiotherapy	75.3	79.2
Hormonal Therapy	57.5	66.6

Post-surgical descriptive characteristics of the sample are shown in Table 1, according to the intervention groups. Both groups were fairly homogeneous at post-surgical assessment.

Table 2 shows the effect of time on the outcome if no Physiotherapy is given, that is, the change in the outcome means at each measurement point. The p-values test whether time has no effect at all in the outcomes. All outcomes except "cognitive function" have very small p-values providing strong evidence that their means do change over time. These p-values have not been corrected for multiple testing, but even if one wants to apply the harsh Bonferroni correction multiplying each p-value by 21 (the number of tests), only three p-values will increase to become large (insomnia, financial difficulties and body image).

Table 3 shows the effect of the intervention (Physiotherapy) at each time point, that is, the difference between control and intervention groups at each measurement point. These are the values of the I_j parameters of the models. The p-values test whether the intervention has no effect at all in the outcomes and therefore the change over time would be the same in both arms of the trial. Most

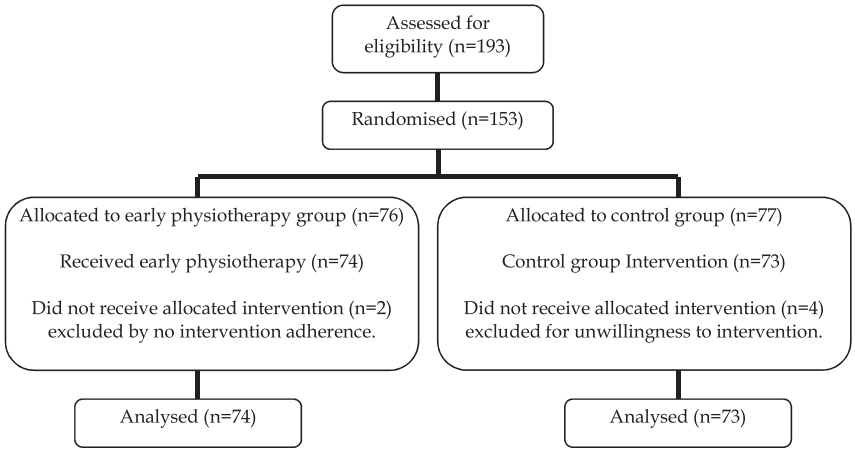

Fig. 1. Flow diagram progress of subjects through the phases of the study.

Table 2
Effect of time: Mean changes (difference) in outcomes from post-surgery measurement (A_1) to each time point (A_2 to A_5) if no Physiotherapy is given.

Coefficients of model [1]	B_2	B_3	B_4	B_5	*P* value
Areas	T3 weeks ($A_2 - A_1$)	T3.months ($A_3 - A_1$)	T6.months ($A_4 - A_1$)	T12.months ($A_5 - A_1$)	
Global*	10.5 (4.1 to 16.9)	4.5 (−1.8 to 10.9)	7.4 (1.1 to 13.8)	10.8 (4.5 to 17.2)	<0.00001
Physical*	6.9 (3.2 to 10.5)	5.4 (1.8 to 9.1)	5.5 (1.9 to 9.18)	5.8 (2.1 to 9.4)	<0.00001
Role*	13.2 (5.4 to 21.1)	17.1 (9.2 to 24.9)	16.0 (8.1 to 23.9)	21.2 (13.3 to 29.1)	<0.00001
Emotional*	7.3 (2.0 to 12.6)	9.2 (3.9 to 14.5)	11.5 (6.2 to 16.8)	13.8 (8.5 to 19.1)	<0.00001
Cognitive*	3.0 (−2.5 to 8.4)	−3.4 (−8.8 to 2.1)	−0.8 (−6.3 to 4.6)	−2.0 (−7.4 to 3.5)	0.10132
Social*	8.1 (2.1 to 14.1)	4.5 (−1.5 to 10.4)	2.4 (−3.6 to 8.3)	8.5 (2.5 to 14.5)	<0.00001
Fatigue**	−2.6 (−8.7 to 3.5)	8.0 (1.9 to 14.1)	−0.3 (−6.4 to 5.8)	1.2 (−4.9 to 7.3)	0.00008
Nausea, vomiting**	−5.5 (−9.7 to −1.2)	4.2 (0.0 to 8.5)	−3.3 (−7.6 to 0.9)	−5.0 (−9.3 to −0.7)	<0.00001
Pain**	−7.4 (−13.7 to −1.0)	−6.2 (−12.6 to 0.1)	−9.9 (−16.2 to −3.6)	−6.6 (−13.0 to −0.3)	0.00002
Dispnoea**	2.3 (−2.1 to 6.8)	9.9 (5.5 to 14.3)	5.3 (0.9 to 9.7)	6.5 (2.1 to 11.0)	0.00002
Sleep disturbance**	−3.4 (−11.1 to 4.4)	3.3 (−4.5 to 11.0)	−1.0 (−8.7 to 6.8)	−2.2 (−9.9 to 5.6)	0.00582
Apetite loss**	−0.4 (−7.0 to 6.3)	7.2 (0.6 to 13.8)	0.6 (−6.0 to 7.2)	−6.1 (−12.7 to 0.6)	0.00009
Constipation**	−12.5 (−19.9 to −5.0)	−0.24 (−7.7 to 7.2)	−7.8 (−15.3 to −0.4)	−13.0 (−20.5 to −5.6)	<0.00001
Diarrhoea**	−1.4 (−6.0 to 3.2)	6.7 (2.1 to 11.3)	5.7 (1.1 to 10.3)	2.0 (−2.6 to 6.6)	0.00001
Financial impact**	1.2 (−4.7 to 7.0)	2.2 (−3.7 to 8.1)	1.6 (−4.3 to 7.5)	2.0 (−3.9 to 7.9)	0.03925
Body image*	3.3 (−2.1 to 8.8)	−4.3 (−9.8 to 1.1)	−1.4 (−6.8 to 4.1)	2.2 (−3.3 to 7.6)	0.00684
Future perspectives*	2.74 (−4.8 to 10.3)	3.2 (−4.3 to 10.7)	14.6 (7.1 to 22.1)	5.9 (−1.6 to 13.5)	<0.00001
Fatigue**	−4.2 (−9.2 to 0.9)	15.9 (10.8 to 20.9)	5.5 (0.5 to 10.5)	−1.9 (−6.9 to 3.1)	<0.00001
Breast symptoms**	−7.7 (−13.2 to −2.2)	−13.1 (−18.7 to −7.5)	−12.4 (−18.0 to −6.9)	−10.2 (−15.8 to −4.6)	<0.00001
Arm symptoms**	−2.7 (−8.9 to 2.7)	−5.2 (−10.6 to 0.3)	−6.4 (−11.8 to −1.0)	−3.8 (−9.2 to 1.63)	<0.00001
Upset hair loss*	3.7 (−3.3 to 10.6)	5.0 (−2.0 to 12.0)	5.9 (−1.1 to 12.9)	9.1 (2.1 to 16.1)	0.00056
Sexual function*	−0.2 (−5.3 to 4.8)	−0.5 (−5.5 to 4.6)	−1.6 (−6.7 to 3.5)	−6.9 (−11.9 to −1.8)	0.00059
Sexual enjoyment*	−3.7 (−9.6 to 2.2)	0.0 (−5.9 to 5.9)	−3.2 (−9.1 to 2.7)	−4.1 (−10.0 to 1.8)	0.38473

*Functional scales, **Symptoms.

of the *p*-values are quite large and this does not provide any evidence of an effect of the intervention. Only for two outcomes (physical function and social function) the *p*-values are small enough and even if corrected by the Bonferroni method they would reach marginal levels of significance.

Discussion

This paper was developed within a randomised controlled trial of a Physiotherapy intervention combined with a Therapeutic Education program versus the Therapeutic Education program alone, to minimise the onset of lymphoedema after axillary lymph-node dissection for breast cancer therapy.

In this study, the average age of participants, around 53 years old, was similar to other breast cancer QoL studies where ages were from 44 to 60 [17,19,54,55]. Regarding surgery type and chemo and radiotherapy treatments, clinical data are representative of what occurs with breast cancer patients in developed countries and similar to those for other studies [17,39,54].

Values obtained at 12 months for both groups in EORTC-QLQC30 studied dimensions were higher than the reference values published by EORTC [56].This indicates that, in this study QoL improved substantially, in different proportions, in both groups in the different dimensions after 12 months.

In the present study, participants' therapeutic adherence and cooperation were high, since only 6 of 153 women dropped out during the process. Besides, the level of response in the questionnaires during assessments reached up to 95% of all items completed. Although not all studies about breast cancer provide this data, a 70% response level is generally considered to be high [17]. These facts may be due to the attention and monitoring carried out by the researchers and that the questionnaires were self-filled out by the participants with the researchers during the physiotherapy assessments, while in most HRQoL and breast cancer studies the questionnaires were sent by mail [9,10,18,19].

The ANOVA model showed greater clinical changes at 12 months for EPTG arm although no strong statistical evidence was found except for physical functioning and social functioning.

This fact may be explained by the physiotherapy intervention proposed in this study, as it seems to minimise the side effects of surgery and therefore improve physical functioning and have a positive impact on psychosocial well-being and social function, as noted in the literature [57–59].

As said before, reduced shoulder ROM is one of the most important factors for functional activity impairment in women after breast cancer surgery [32,33]. The effectiveness of physiotherapy interventions for the improvement of shoulder ROM and daily living activities after breast cancer surgery has been widely evidenced [34] and some authors suggest their implementation for these patients [60]. However, no statistically significant difference was found between groups in arm symptoms dimension, although there were clinical changes (Fig. 2). The most important clinical changes can be appreciated after group intervention and at 3 and 6 months follow-up. At 12 months, arm symptoms increased and this may be related to the results of the first analysis on the incidence of lymphoedema, which showed that the CG develops four times more lymphoedema than the EPTG between 6 and 12 months after surgery [40]. These results lead to the belief that lower incidence of lymphoedema in EPTG was a decisive influence on the HRQoL of participants as different studies describe the negative impact of lymphoedema on quality of life [61]. Therefore, this should be expressed in the results of arm symptom perception, but that was not so, may be explained by the instrument used to measure the HRQoL. In this study, a reliable and valid instrument to measure the impact on HRQoL were used, but these instruments do not seem to address all important-surgery-specific and psychometric issues of breast cancer surgery [7], and lymphoedema following breast cancer surgery [32,61,62]. Generic HRQoL instruments alone cannot be expected to detect subtle but perhaps clinically important changes before and after an intervention or change over time. For this reason, some authors recommend the use of a condition-specific instrument alongside a generic instrument [7,62]. The physiotherapy intervention in this study was performed for decrease sequelae of surgery related to upper limb function and lymphoedema. Therefore, specific instrument as Oxford Shoulder Score (OSS) [63] for shoulder dysfunction and Upper Limb

Table 3
Effect of treatment: Differences between intervention and control groups in the changes from post-surgery measurement (A_1) to each time point (A_2 to A_5). (p-values < 0.05 are in bold font).

Coefficients of model [1]	I_2	I_3	I_4	I_5	P value
Areas	T3.weeks ($A_2 - A_1$)	T3.months ($A_3 - A_1$)	T6.months ($A_4 - A_1$)	T12.months ($A_5 - A_1$)	
Global*	−3.4 (−12.4 to 5.6)	−3.5 (−12.4 to 5.5)	4.1 (−4.9 to 13.1)	7.3 (−1.6 to 16.3)	0.07801
Physical*	−0.1 (−5.2 to 5.1)	2.3 (−2.9 to 7.4)	5.6 (0.5 to 10.8)	8.6 (3.5 to 13.8)	**0.00295**
Role*	−3.6 (−14.7 to 7.5)	−1.7 (−12.9 to 9.4)	3.7 (−7.5 to 14.8)	3.1 (−8.1 to 14.2)	0.67013
Emotional*	1.1 (−6.4 to 8.6)	−2.1 (−9.6 to 5.4)	3.7 (−3.8 to 11.1)	6.1 (−1.3 to 13.7)	0.23114
Cognitive*	2.7 (−5.0 to 10.3)	5.3 (−2.4 to 12.9)	3.5 (−4.1 to 11.2)	5.6 (−2.1 to 13.3)	0.62201
Social*	−5.4 (−13.8 to 3.0)	−10.3 (−18.7 to −1.9)	3.4 (−5.0 to 11.8)	4.2 (−4.2 to 12.6)	**0.00298**
Fatigue**	−0.6 (−9.2 to 8.0)	−3.7 (−12.3 to 4.9)	−0.8 (−9.4 to 7.8)	−9.5 (−18.1 to −0.9)	0.17469
Nausea, vomiting**	−3.3 (−9.3 to 2.7)	−6.7 (−12.7 to −0.7)	−3.1 (−9.1 to 2.9)	−3.3 (−9.3 to 2.7)	0.31952
Pain**	1.9 (−7.0 to 10.8)	−1.6 (−10.5 to 7.3)	−2.8 (−11.7 to 6.11)	−4.4 (−13.3 to 4.5)	0.67840
Dispnoea**	−2.3 (−8.5 to 3.9)	−6.1 (−12.3 to 0.2)	1.7 (−4.6 to 7.9)	−6.0 (−12.2 to 0.2)	0.05117
Sleep disturbance**	−3.1 (−14.0 to 7.9)	−4.6 (−15.5 to 6.3)	−0.9 (−11.8 to 10.0)	−12.0 (−23.0 to −1.1)	0.21357
Apetite loss**	−5.6 (−14.9 to 3.8)	−8.0 (−17.4 to 1.3)	−4.3 (−13.6 to 5.1)	−4.1 (−13.4 to 5.3)	0.56593
Constipation**	0.0 (−10.5 to 10.5)	−7.9 (−18.4 to 2.6)	−5.9 (−16.4 to 4.6)	−4.9 (−15.4 to 5.6)	0.46670
Diarrhoea**	−0.1 (−6.6 to 6.5)	−0.7 (−7.2 to 5.8)	−2.5 (−9.0 to 4.0)	1.2 (−5.3 to 7.7)	0.86043
Financial impact**	1.8 (−6.5 to 10.1)	7.9 (−0.5 to 16.1)	−0.6 (−8.9 to 7.7)	−2.0 (−10.3 to 6.3)	0.16329
Body image*	1.3 (−6.4 to 9.0)	3.4 (−4.2 to 11.1)	5.8 (−1.9 to 13.4)	2.0 (−5.7 to 9.7)	0.64186
Future perspectives*	4.5 (−6.1 to 15.1)	5.8 (−4.8 to 16.4)	3.4 (−7.2 to 14.0)	10.7 (0.1 to 21.3)	0.38877
Fatigue**	3.4 (−3.7 to 10.5)	−1.8 (−8.8 to 5.3)	−1.6 (−8.7 to 5.5)	2.3 (−4.8 to 9.4)	0.51826
Breast symptoms**	2.8 (−5.1 to 10.7)	4.5 (−3.4 to 12.3)	3.2 (−4.7 to 11.1)	−1.3 (−9.2 to 6.6)	0.58873
Arm symptoms**	−2.1 (−9.7 to 5.6)	−8.2 (−15.9 to −0.5)	−7.7 (−15.4 to −0.1)	−7.0 (−14.7 to 0.7)	0.12971
Upset hair loss*	−0.5 (−10.4 to 9.4)	10.7 (0.9 to 20.6)	1.3 (−8.6 to 11.1)	−3.3 (−13.1 to 6.6)	0.06341
Sexual function*	5.0 (−2.2 to 12.1)	7.9 (0.7 to 15.0)	3.9 (−3.3 to 11.0)	5.5 (−1.7 to 12.6)	0.29199
Sexual enjoyment*	7.3 (−1.1 to 15.6)	3.6 (−4.7 to 11.9)	5.5 (−2.9 to 13.8)	3.2 (−5.1 to 11.5)	0.51866

*Functional scales, **Symptoms.

Lymphoedema 27 (ULL-27) [64] should be added to EORTC QLQ-BR23. At the time in which this study was developed, there were no validated Spanish versions of these questionnaires.

In the literature, many studies have been found that report the effects of physiotherapy and therapeutic exercise on improving HRQoL of breast cancer survivors. In most of these studies, interventions describe therapeutic exercise with the aim of improving the symptoms produced by the adjuvant therapy [65]. Only four studies which determine the effect of early physiotherapy and specific recommendations about self-care on HRQoL of women with breast cancer were found [35,36,38,39]. All of them applied an early physiotherapy intervention after surgery, and assert that physiotherapy is beneficial in functional and physical well-being without causing adverse effects in postoperative period but the beneficial clinical changes show no statistically significant differences between groups, although they are higher in the physiotherapy groups than in the educational groups. Gordon et al. [35] developed a trial to assess changes in HRQoL during 12 months on three independent prospective cohorts that received either early home-based physiotherapy intervention starting 4–5 days after surgery ($n = 36$); group-based exercise and psychosocial intervention starting 8 weeks after surgery ($n = 31$) and a non-intervention group ($n = 208$). Although no statistically significant differences between groups were found, better results were obtained in the early home-based physiotherapy group and the major clinical changes were obtained in functional well-being measured with the Functional Assessment of Cancer Therapy-Breast quality-of-life (FACT-B) and arm function measured with DASH. On the other hand, Pinto et al. [36] compared the effects of a rehabilitation program among women undergoing sentinel node biopsy ($n = 30$) versus complete axillary lymph node dissection ($n = 31$) on the QoL measured by FACT-B, 30 days and 6 months after surgery. The

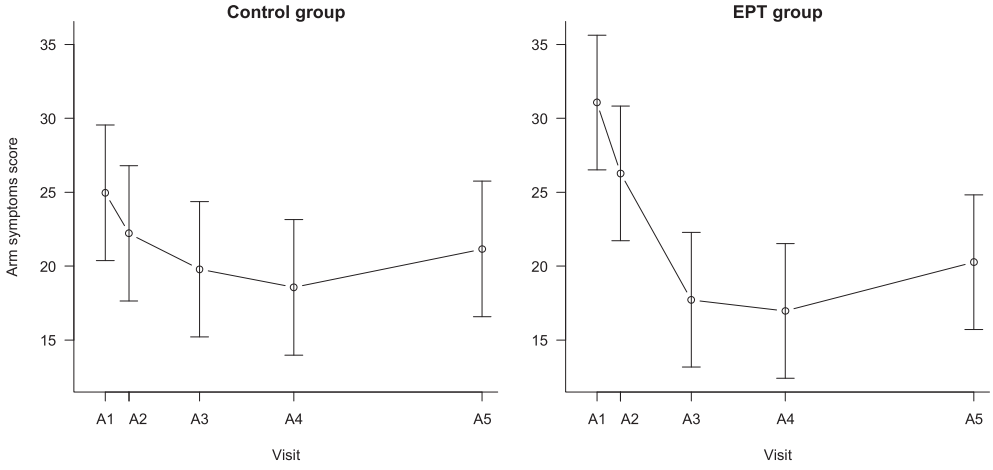

Fig. 2. Estimation mean and 95% confidence interval of arm symptoms scale from the ANOVA model at each visit. EPT group had Early Physiotherapy + Therapeutic Education Program. Control group only received Therapeutic Education Program. The visits (A1 to A5) are spaced in the graph according to their distance from surgery (post-surgery, 3 weeks, 3 months, 6 months and 12 months).

intervention consisted of physiotherapy exercises performed three times a week during four weeks (the authors did not include details) and educational sessions (advice on arm care and lymphoedema management and a booklet). Axillary lymph-node dissection group had better results in the trial outcome index (sum of physical well-being, functional well-being and breast cancer subscale scores), emotional well-being, and breast cancer subscale of FACT-B within 30 days. And the RESTORE trial developed by Anderson et al. [39] aimed to determine the effect of a moderate tailored exercise program ($n = 52$) based on upper and lower strength training and including a lymphoedema prevention module, on physical function and on arm volume on HrQoL measured with FACT-B, between 4 and 12 weeks after surgery during 6 months. They found better values in physical function measured by the 6-min walk test but no significant differences in the means of FACT-B subscales and FACT-B total scores were found when comparing to an education program alone for the prevention of lymphoedema ($n = 52$).

The results found in the present study are better, if they are compared to the prior studies, probably because the sample in the present study is larger and the physiotherapy intervention is more specific. None of the aforementioned studies included details about the physiotherapy techniques that were used for shoulder ROM recovery, no data on the vascular sequelae of surgery was reported, no details were added about the initial state of the upper limb function. In the Restore trial, the participants had probably already recovered their upper limb function after surgery, but the authors did not specify whether participants received some early treatment during the first month after surgery.

At last, Testa et al. [38] developed a study on 70 women divided in early physiotherapy group for increasing shoulder ROM and a control group and measured HRQoL with EORTC QLQ-30 and EORTC QLQ-BR23, shoulder ROM and pain after intervention, at 1, 6 and 12 months after surgery. They found statically significant differences in physical and social function. Although their methodology and results are very similar to the present study, there are no other details as this paper is an oral presentation and only the abstract was published, so far.

Therefore, as far as the authors know the present study is the first one which shows that a specific physiotherapy program in addition to an educational program in the immediate postoperative period is more beneficial that only an educational program in physical and social function, and these benefits remain at least for a year after surgery.

Limitations of study

This study has limitations regarding to the non-existence of a control group which did not receive any intervention. This is due to the fact that the availability of evidence concerning the benefits in terms of upper limb lymphoedema prevention [40,66,67] and the improvement in QoL which a therapeutic education program can bring to women who have had breast cancer surgery by means of axillary lymph-node dissection raise ethical problems [15,43].

The fact that the therapeutic education program was administered by different physiotherapists may have influenced outcomes, although consensus meetings were carried out before starting the study and the same graphic materials were used to ensure that both physiotherapists applied the same educational intervention.

The physiotherapy intervention of all participants who presented upper limb lymphoedema and/or pain in the monitoring phase could have an influence on the final results obtained after 6 months of monitoring.

And last, the sample was composed of participants from just one hospital which could result in a bias for study's external validity.

Conclusions

The control group with therapeutic education program reported a clear improvement in the perception of quality of life. The intervention receiving early physiotherapy combined with the therapeutic education program did not show statistically significant changes in the global score or in most of the dimension but showed an improvement in the physical and social dimensions.

Future studies should strive to use high-quality condition-specific patient reported outcome instruments to determine the impact of special conditions and its physiotherapy interventions on HRQoL of cancer survivors.

Clinical trial registry

This clinical trial is registered in the International Standard Randomised Controlled Trial Number Register: number ISRCTN95870846.

Funding

This study was funded by the Health Institute Carlos III (Protocol PI071124) of the Spanish Health Ministry.

Conflict of interest statement

The authors indicate no potential conflicts of interest.

Acknowledgements

We thank the staff and participants of the Gynaecology Service of Príncipe de Asturias University Hospital (Madrid) for their generous participation. The Physical Therapy Department of Alcalá University and Principe de Asturias Hospital provided the facilities for the study.

References

[1] International Agency for Research on Cancer. Cancermondial. Globocan. International Agency for Research on Cancer; 2002.
[2] Edwards BK, Noone AM, Mariotto AB, Simard EP, Boscoe FP, Henley SJ, et al. Annual report to the Nation on the status of cancer, 1975–2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. Cancer 2014;120(9):1290–314.
[3] De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE–5-a population-based study. Lancet Oncol 2014;15(1):23–34.
[4] López-Abente G. La situación del cáncer en España. Madrid: Área de Epidemiología Ambiental y Cáncer. Centro Nacional de Epidemiología. Instituto de Salud Carlos III. Ministerio de Sanidad y Consumo; 2005.
[5] Arraras JI, Meiriño R, Prujá E, Villafranca E, Valerdi JJ. La Calidad de vida en el paciente oncológico: estudios del Servicio de Oncología del Hospital de Navarra en el Grupo de Calidad de Vida de la EORTC. In: Anales del Sistema Sanitario de Navarra; 1998.
[6] Royo A. Calidad de vida en pacientes intervenidas de cáncer de mama. In: Departamento de Medicina Interna. Barcelona: Universidad Autónoma de Barcelona; 2011.
[7] Chen CM, Cano SJ, Klassen AF, King T, McCarthy C, Cordeiro PG, et al. Measuring quality of life in oncologic breast surgery: a systematic review of patient-reported outcome measures. Breast J 2010;16(6):587–97.
[8] McQuellon RP, Kimmick G, Hurt GJ. Quality-of-life measurement in women with breast cancer. Breast J 1997;3:178–86.
[9] Montazeri A, Vahdaninia M, Harirchi I, Ebrahimi M, Khaleghi F, Jarvandi S. Quality of life in patients with breast cancer before and after diagnosis: an eighteen months follow-up study. BMC Cancer 2008;8:330.
[10] Engel J, Kerr J, Schlesinger-Raab A, Sauer H, Holzel D. Axilla surgery severely affects quality of life: results of a 5-year prospective study in breast cancer patients. Breast Cancer Res Treat 2003;79(1):47–57.
[11] Pandey M, Thomas BC, Ramdas K, Ratheesan K. Early effect of surgery on quality of life in women with operable breast cancer. Jpn J Clin Oncol 2006;36(7):468–72.

[12] De Gournay E, Guyomard A, Coutant C, Boulet S, Arveux P, Causeret S, et al. Impact of sentinel node biopsy on long-term quality of life in breast cancer patients. Br J Cancer 2013;109(11):2783–91.
[13] Nicolussi AC, Sawada NO. Quality of life of breast cancer patients in adjuvant therapy. Rev Gaucha Enferm 2011;32(4):759–66.
[14] Ochayon L, Zelker R, Kaduri L, Kadmon I. Relationship between severity of symptoms and quality of life in patients with breast cancer receiving adjuvant hormonal therapy. Oncol Nurs Forum 2010;37(5):E349–58.
[15] Falagas ME, Zarkadoulia EA, Ioannidou EN, Peppas G, Christodoulou C, Rafailidis PI. The effect of psychosocial factors on breast cancer outcome: a systematic review. Breast Cancer Res 2007;9(4):R44.
[16] Munoz M. Quality of life during treatment in young women with breast cancer. Breast Cancer Res Treat 2010;123(Suppl. 1):75–7.
[17] Arraras JI, Illaramendi JJ, Tejedor M, Vera R, Prujá E, Marcos M. Quality of life in breast cancer patients assessed using the EORTC questionnaires. Oncología 2001;3(2):100–7.
[18] Casso D, Buist DS, Taplin S. Quality of life of 5–10 year breast cancer survivors diagnosed between age 40 and 49. Health Qual Life Outcomes 2004;2:25.
[19] Kootstra J, Hoekstra-Weebers JE, Rietman H, de Vries J, Baas P, Geertzen JH, et al. Quality of life after sentinel lymph node biopsy or axillary lymph node dissection in stage I/II breast cancer patients: a prospective longitudinal study. Ann Surg Oncol 2008;15(9):2533–41.
[20] Bergmann A, Mendes VV, de Almeida Dias R, do Amaral ESB, da Costa Leite Ferreira MG, Fabro EA. Incidence and risk factors for axillary web syndrome after breast cancer surgery. Breast Cancer Res Treat 2012;131(3):987–92.
[21] Hayes SC, Johansson K, Stout NL, Prosnitz R, Armer JM, Gabram S, et al. Upper-body morbidity after breast cancer: incidence and evidence for evaluation, prevention, and management within a prospective surveillance model of care. Cancer 2012;118(8 Suppl.):2237–49.
[22] Kootstra JJ, Dijkstra PU, Rietman H, de Vries J, Baas P, Geertzen JH, et al. 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 2013;139(1):125–34.
[23] Leidenius M, Leppanen E, Krogerus L, von Smitten K. Motion restriction and axillary web syndrome after sentinel node biopsy and axillary clearance in breast cancer. Am J Surg 2003;185(2):127–30.
[24] Moskovitz AH, Anderson BO, Yeung RS, Byrd DR, Lawton TJ, Moe RE. Axillary web syndrome after axillary dissection. Am J Surg 2001;181(5):434–9.
[25] Nesvold IL, Reinertsen KV, Fossa SD, Dahl AA. The relation between arm/shoulder problems and quality of life in breast cancer survivors: a cross-sectional and longitudinal study. J Cancer Surviv 2011;5(1):62–72.
[26] O'Toole J, Miller CL, Specht MC, Skolny MN, Jammallo LS, Horick N, et al. Cording following treatment for breast cancer. Breast Cancer Res Treat 2013;140(1):105–11.
[27] Schmitz KH, Speck RM, Rye SA, DiSipio T, Hayes SC. Prevalence of breast cancer treatment sequelae over 6 years of follow-up: the Pulling Through Study. Cancer 2012;118(8 Suppl.):2217–25.
[28] Torres Lacomba M, Mayoral Del Moral O, Coperias Zazo JL, Yuste Sanchez MJ, Ferrandez JC, Zapico Goni A. Axillary web syndrome after axillary dissection in breast cancer: a prospective study. Breast Cancer Res Treat 2009;117(3):625–30.
[29] Aerts PD, De Vries J, Van der Steeg AF, Roukema JA. The relationship between morbidity after axillary surgery and long-term quality of life in breast cancer patients: the role of anxiety. Eur J Surg Oncol 2013;37(4):344–9.
[30] Bosompra K, Ashikaga T, O'Brien PJ, Nelson L, Skelly J. Swelling, numbness, pain, and their relationship to arm function among breast cancer survivors: a disablement process model perspective. Breast J 2002;8:338–48.
[31] Torres Lacomba M, Mayoral del Moral O, Coperias Zazo JL, Gerwin RD, Goni AZ. Incidence of myofascial pain syndrome in breast cancer surgery: a prospective study. Clin J Pain 2010;26(4):320–5.
[32] Martins da Silva RC, Rezende LF. Assessment of impact of late postoperative physical functional disabilities on quality of life in breast cancer survivors. Tumori 2014;100(1):87–90.
[33] Hack TF, Cohen L, Katz J, Robson LS, Goss P. Physical and psychological morbidity after axillary lymph node dissection for breast cancer. J Clin Oncol 1999;17(1):143–9.
[34] McNeely ML, Campbell K, Ospina M, Rowe BH, Dabbs K, Klassen TP, et al. Exercise interventions for upper-limb dysfunction due to breast cancer treatment. Cochrane Database Syst Rev 2010;(6). CD005211.
[35] Gordon LG, Battistutta D, Scuffham P, Tweeddale M, Newman B. The impact of rehabilitation support services on health-related quality of life for women with breast cancer. Breast Cancer Res Treat 2005;93(3):217–26.
[36] Pinto e Silva MP, Sarian LO, Morais SS, Pace do Amaral MT, Freire de Oliveira MM, Derchain S. Implications of a postoperative rehabilitation program on quality of life in women with primary breast cancer treated with sentinel lymph node biopsy or complete axillary lymph node dissection. Ann Surg Oncol 2008;15(12):3342–9.
[37] Gordon LG, Scuffham P, Battistutta D, Graves N, Tweeddale M, Newman B. A cost-effectiveness analysis of two rehabilitation support services for women with breast cancer. Breast Cancer Res Treat 2005;94(2):123–33.
[38] Testa A, Iannace C, Di Libero L. Strengths of early physical rehabilitation programs in surgical breast cancer patients: results of a randomized controlled study. Eur J Phys Rehabil Med 2014;50(3):275–84.
[39] Anderson RT, Kimmick GG, McCoy TP, Hopkins J, Levine E, Miller G, et al. A randomized trial of exercise on well-being and function following breast cancer surgery: the RESTORE trial. J Cancer Surviv 2012;6(2):172–81.
[40] Torres Lacomba M, Yuste Sanchez MJ, Zapico Goni A, Prieto Merino D, Mayoral del Moral O, Cerezo Tellez E, et al. Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial. Bmj 2010;340. b5396.
[41] Blaise S, Villemur B, Richaud C, Rastel D, Bucci B, Evra V, et al. Designing a therapeutic education program for patients with lymphedema: live with lymphedema. J Mal Vasc 2012;37(1):1–8.
[42] Bosompra K, Ashikaga T, O'Brien PJ, Nelson L, Skelly J, Beatty DJ. Knowledge about preventing and managing lymphedema: a survey of recently diagnosed and treated breast cancer patients. Patient Educ Couns 2002;47(2):155–63.
[43] Dolbeault S, Cayrou S, Bredart A, Viala AL, Desclaux B, Saltel P, et al. The effectiveness of a psycho-educational group after early-stage breast cancer treatment: results of a randomized French study. Psychooncology 2009;18(6):647–56.
[44] Koinberg I, Langius-Eklof A, Holmberg L, Fridlund B. The usefulness of a multidisciplinary educational programme after breast cancer surgery: a prospective and comparative study. Eur J Oncol Nurs 2006;10(4):273–82.
[45] Matsuda A, Yamaoka K, Tango T, Matsuda T, Nishimoto H. Effectiveness of psycho educational support on quality of life in early-stage breast cancer patients: a systematic review and meta-analysis of randomized controlled trials. Quali Life Res 2014 Feb;23(1):21–30.
[46] FPSM. Physiotherapy in Women's Health Research Group. Patient's resources. 2005. Available at: http://www2.uah.es/fisioterapia_saludmujer/recursos_pacientes/index.html.
[47] Torres M. Drenaje Linfático manual. In: Torres M, Salvat I, editors. Guía de Masoterapia para Fisioterapeutas. Madrid: Médica Panamericana; 2006. p. 239–67.
[48] Ferrandez J, Bourassin A, Debeauquesne A, Philbert C. Étude prospective ambulatoire multipraticien du lymphoèdeme du membre supérieur après cancer de sein. À propos de 76 cas. Oncologie 2005;7:316–22.
[49] Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85(5):365–76.
[50] Fayers PM, Aaronson N, Bjordal K, Groenvold M, Curran D, Bottomley A. The EORTC QLQ-C30 scoring manual. 3rd ed. Brussels: European Organisation for Research and Treatment of Cancer; 2001.
[51] Arrarás JI. Cuestionario de Calidad de Vida de la EORTC para Cáncer de Mama EORTC QLQ-BR23. Psicol Conduct 2001;9(1):81–98.
[52] Arrarás JI. Cuestionario de Calidad de Vida de la EORTC QLQ-C30. Psycho-Oncology 2002;11:249–56.
[53] Teschke K, Trask C, Johnson P, Chow Y, Village J, Koehoorn M. Measuring posture for epidemiology: comparing inclinometry, observations and self-reports. Ergonomics 2009;52(9):1067–78.
[54] Kenny P, King MT, Shiell A, Seymour J, Hall J, Langlands A, et al. Early stage breast cancer: costs and quality of life one year after treatment by mastectomy or conservative surgery and radiation therapy. Breast 2000;9(1):37–44.
[55] Neil W, Scott PMF, Neil K, Aaronson A, Bottomley ADG, Mogens G, et al. EORTC QLQ-C30 reference values. Brussels: EORTC Quality of Life Group; 2008.
[56] Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. J Exp Clin Cancer Res 2008;27:32.
[57] Mehnert A, Veers S, Howaldt D, Braumann KM, Koch U, Schulz KH. Effects of a physical exercise rehabilitation group program on anxiety, depression, body image, and health-related quality of life among breast cancer patients. Onkologie 2011;34(5):248–53.
[58] Perkins HY, Baum GP, Taylor CL, Basen-Engquist KM. Effects of treatment factors, comorbidities and health-related quality of life on self-efficacy for physical activity in cancer survivors. Psychooncology 2009;18(4):405–11.
[59] Spence RR, Heesch KC, Brown WJ. Exercise and cancer rehabilitation: a systematic review. Cancer Treat Rev 2010;36(2):185–94.
[60] Shamley DR, Barker K, Simonite V, Beardshaw A. Delayed versus immediate exercises following surgery for breast cancer: a systematic review. Breast Cancer Res Treat 2005;90(3):263–71.
[61] Pusic AL, Cemal Y, Albornoz C, Klassen A, Cano S, Sulimanoff I, et al. Quality of life among breast cancer patients with lymphedema: a systematic review of patient-reported outcome instruments and outcomes. J Cancer Surviv 2013;7(1):83–92.
[62] Pinto M, Gimigliano F, Tatangelo F, Megna M, Izzo F, Gimigliano R, et al. Upper limb function and quality of life in breast cancer related lymphedema: a cross-sectional study. Eur J Phys Rehabil Med 2013;49(5):665–73.
[63] Dawson J, Fitzpatrick R, Carr A. Questionnaire on the perceptions of patients about shoulder surgery. J Bone Jt Surg Br 1996;78(4):593–600.
[64] Launois R, Megnigbeto AC, Pocquet K, Alliot F. A specific quality of life scale in upper limb lymphoedema: the ULL-27 questionnaire. Lymphology 2002;35(1–760):181–7.
[65] Scott DA, Mills M, Black A, Cantwell M, Campbell A, Cardwell CR, et al. Multidimensional rehabilitation programmes for adult cancer survivors. Cochrane Database Syst Rev 2013;3. CD007730.
[66] Box RC, Reul-Hirche HM, Bullock-Saxton JE, Furnival CM. Physiotherapy after breast cancer surgery: results of a randomised controlled study to minimise lymphoedema. Breast Cancer Res Treat 2002;75(1):51–64.
[67] Price J, Purtell JR. Prevention and treatment of lymphedema after breast cancer. Am J Nurs 1997;97(9):34–7.