Published in final edited form as:

Cancer. 2021 January 15; 127(2): 300–309. doi:10.1002/cncr.33184.

Health-Related Quality of Life Outcomes for the LEAP Study - CALGB 70305 (Alliance): A Lymphedema Prevention Intervention Trial for Newly Diagnosed Breast Cancer Patients

Michelle J. Naughton, PhD[1], **Heshan Liu, MS**[2], **Drew Seisler, MS**[2], **Jennifer Le-Rademacher, PhD**[2], **Jane M. Armer, PhD**[3], **Jill M. Oliveri, DrPH**[1], **Jeffrey A. Sloan, PhD**[2], **Karen Hock, PT**[1], **Michael Schwartz, MD**[4], **Gary Unzeitig, MD**[5], **Marianne Melnik, MD**[6], **Lisa D. Yee, MD**[7], **Gini F. Fleming, MD**[8], **John R. Taylor, MA**[9], **Charles Loprinzi, MD**[10], **Electra D. Paskett, PhD**[1]

[1.]The Ohio State University Comprehensive Cancer Center, Columbus, OH

[2.]Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN

[3.]University of Missouri – Sinclair School of Nursing and Ellis Fischel Cancer Center, Columbia, MO

[4.]Mount Sinai Medical Center, Miami Beach, FL

[5.]Doctor's Hospital of Laredo, Laredo, TX

[6.]Cancer Research Consortium of West Michigan, Grand Rapids, MI

[7.]City of Hope, Duarte, CA

[8.]University of Chicago Comprehensive Cancer Center, Chicago, IL

[9.]Alliance Protocol Operations Program Office, Chicago, IL

Correspondence: Michelle J. Naughton, Ph.D., Division of Cancer Prevention and Control, The Ohio State University, 1590 North High Street, Suite 525, Columbus, OH 43210-1240, Tel: 614-293-6390 Fax: 614-293-5611, michelle.naughton@osumc.edu.

Author Contributions:

Michelle J Naughton: Conceptualization, methodology, writing – original draft and writing – review and editing.
Drew Seisler: Data curation, formal analysis, visualization, writing – original draft and writing – review and editing.
Heshan Liu: Data curation, formal analysis, visualization, writing – original draft and writing – review and editing.
Jennifer Le-Rademacher: Data curation, formal analysis, visualization, writing – original draft and writing – review and editing.
Jane M Armer: Conceptualization, methodology, validation, writing – original draft and writing – review and editing.
Jill M Oliveri: Conceptualization, methodology, project administration, supervision, visualization, writing –review and editing.
Jeff A Sloan: Data curation, formal analysis, visualization, writing – original draft and writing – review and editing.
Karen Hock: Conceptualization, methodology, supervision, validation, and writing – review and editing.
Michael Schwartz: Investigation, supervision, and writing – review and editing.
Gary Unzeitig: Investigation, project administration, supervision, and writing – review and editing.
Marianne Melnik: Investigation, supervision, and writing – review and editing.
Lisa Yee: Conceptualization, investigation, and writing – review and editing.
Gini Fleming: Conceptualization, investigation, and writing – review and editing.
John R Taylor: Conceptualization, funding acquisition, project administration and writing – review and editing.
Charles Loprinzi: Conceptualization and writing – review and editing.
Electra D Paskett: Conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, visualization, writing – original draft and writing – review and editing.

Disclaimers: None

ClinicalTrials.gov Identifier: NCT00376597

Conflict of Interest Statement: Dr. Loprinzi reports grants from NCI during the conduct of the study. Dr. Paskett reports grants from Merck Foundation and Pfizer during the conduct of the study.

Poster presentation at the International Society for Quality of Life Research (ISOQOL). October 26, 2018. Dublin, Ireland.

[10.]Mayo Clinic, Rochester, MN

Abstract

Background: Lymphedema is a side effect of breast cancer treatment, causing swelling and pain in the arm and hand. We tested two lymphedema prevention interventions and their impact on health-related quality of life (HRQL) in a group-randomized trial in 38 U.S. cooperative group sites.

Methods: Patients were recruited before breast surgery. Sites were randomized to lymphedema-prevention education only (EO) or EO with exercise and physical therapy (LEAP). Lymphedema was defined as a ≥10% difference in arm volume at any time from baseline to 18-months post-surgery. HRQL was assessed using the Functional Assessment of Cancer Therapy–Breast plus 4 lymphedema items (FACT-B+4). Longitudinal mixed model regression analysis, adjusting for key demographic and clinical variables, examined participants' HRQL by: 1) intervention group, and 2) lymphedema status.

Results: 547 patients (56% LEAP) were enrolled and completed HRQL assessments. Results showed no differences between the interventions in preventing lymphedema (p=0.37) or HRQL (i.e., FACT-B+4 total score, p=0.8777). At 18 months, the presence of lymphedema was borderline significantly associated with HRQL (p=0.0825). However, African-Americans reported greater lymphedema symptoms (p=0.0002) and better emotional functioning (p=0.0335) than other race/ethnicities. Lower HRQL during the intervention was associated with younger age (p=<0.0001), ECOG performance status >0 (p=0.0002), ≥1 positive lymph node(s) (p=0.0009), ≤high school education (p<0.0001), chemotherapy (p=0.0242), and having only axillary node dissection or sentinel node biopsy, as compared to both (p=0.0007).

Conclusions: The tested interventions did not differ in preventing lymphedema or in HRQL outcomes. African-American women reported greater HRQL impacts due to lymphedema symptoms than other race/ethnicities.

Precis:

Two tested lymphedema prevention interventions did not differ in preventing lymphedema or in quality of life outcomes. African-American women, however, reported greater lymphedema symptoms than other race/ethnicities.

Keywords

lymphedema; breast cancer; quality of life; symptoms; race

INTRODUCTION

Lymphedema is often reported following breast cancer surgery and is characterized by swelling and/or pain in the arm or hand on the same side as the affected breast[1–5]. Symptoms can also include tightness, numbness, and decreased range of motion[1]. Lymphedema affects between 20–94% of women[2] and results from a malfunction of the lymph system causing excess fluid to collect in the affected area[2]. Rates of lymphedema have changed over time, reflecting a shift in treatment techniques, yet estimates suggest

close to one million women are still affected by lymphedema symptoms[4]. Common risk factors for the development of lymphedema include the type of lymph node surgery (axillary dissection vs. sentinel node biopsy), the type of treatment (mastectomy vs lumpectomy, radiation, chemotherapy), and the number of positive lymph nodes involved. Patient characteristics associated with lymphedema include a higher body mass index (BMI) and the presence of infection[6–10].

Prior research has consistently reported poorer health-related quality of life (HRQL) among women with lymphedema[11–18], affecting both their physical and mental health. Decreased strength and function of the arm can disrupt daily activities and fine motor skills[15], resulting in poorer functional capabilities. For some, the swelling and continual reminder of breast cancer can increase feelings of anxiety and depression[1]. Across studies, poorer HRQL in women with lymphedema has been associated with younger patient age (<40 years), surgical and other treatment characteristics, and minority race[16]. However, swelling has not been found to be related to swelling of the dominant versus non-dominant arm[14]. In general, those with more severe swelling report worse physical functioning and poorer mental health than those with less severe swelling[13]. A linear dose relationship was also found in one study between decreasing HRQL scores and increasing number of lymphedema-related arm symptoms[15]. In addition, research has shown that any potential increases in HRQL after breast reconstructive surgery may be negated when lymphedema is present[11]. When controlling for factors affecting HRQL, such as BMI, clinical and demographic characteristics, and decreased range of motion, lymphedema has still been found to be significantly associated with lower HRQL scores[18]. Longer time since treatment, however, is associated with better HRQL among patients[12].

There have been intervention studies focusing on breast cancer survivors with lymphedema aimed at reducing their swelling and improving function[19–23], but few studies have been aimed at preventing lymphedema occurrence. In 2006, the Cancer and Leukemia Group B (CALGB) initiated a Phase III, group randomized clinical trial to prevent lymphedema among women after surgery for breast cancer (protocol # CALGB 70305; ClinicalTrials.gov identifier: NCT00376597) (Paskett et al., in press). This trial compared the effectiveness of two interventions: 1) lymphedema prevention education only (EO); or 2) education + exercise (including use of a compression sleeve) titled the Lymphedema Education and Prevention (LEAP) group. In this paper, we report on a planned secondary endpoint, participants' HRQL by intervention group and lymphedema status, adjusting for key demographic and clinical variables known to be associated with lymphedema in this population. CALGB is now a part of the Alliance for Clinical Trials in Oncology.

METHODS

Participants

Eligible participants included women newly diagnosed with breast cancer (stage I – III), aged 18 years or older, with no prior history of lymphedema, carcinoma in situ, lobular carcinoma in situ, ductal carcinoma in situ or invasive breast cancer. Patients who received neoadjuvant chemotherapy were eligible if pre-surgery measurements and self-reported assessments were completed prior to their first chemotherapy treatment. Eligible patients

also had to have medical clearance to participate in a mild exercise program and have an upper arm size that accommodated a standard-size elastic compression sleeve and gauntlet. Patients who underwent bilateral mastectomies or axillary node dissection (ALND) and/or radiation bilaterally were ineligible. Patients were recruited from 38 CALGB and National Clinical Trials Network sites across the United States (U.S.) between December 2006 and September 2013, with follow-up continuing until December 2015. Sites were randomly assigned to one of the two intervention groups: 1) education only (EO) or 2) education + exercise with physical therapy (LEAP). All patients at a participating institution were assigned to the same intervention group to minimize contamination bias. The trial was approved by the Institutional Review Board (IRB) of each participating site, and each participant signed an IRB-approved, protocol-specific written informed consent in accordance with federal and institutional guidelines.

Participant Measures

Participants were recruited at their first pre-operative visit, using a two-step eligibility process. In Step 1, eligible participants were consented and registered to the study prior to surgery, so that baseline measurements could be collected. Baseline measurements of height, weight, range of motion, and arm circumference were taken by a trained institutional nurse pre-surgery or pre-neoadjuvant systemic treatment, as applicable. Participants completed self-reports of demographics, lymphedema knowledge, body image, self-efficacy[24], fear of cancer recurrence, self-reported pain and swelling, HRQL[25], and adherence to lymphedema prevention practices. These assessments were repeated after surgery and at 6- (by mail), 12-, and 18-months post-surgery.

In Step 2, women were randomized to one of the two study intervention groups only if they had either axillary node dissection or sentinel node biopsy. All eligible participants registered to Step 2 met with a trained lymphedema prevention educator to review lymphedema etiology, signs, symptoms, treatments, and preventive self-care practices (i.e., education only [EO] intervention). Participants randomized to the LEAP intervention also received a physical therapy-focused intervention, in which they were assessed by a physical therapist and instructed in an individualized exercise regimen involving breathing, stretching, strengthening, and ROM exercises varying the amount of weight used, body position and number of repetitions performed based on the participant's ability (i.e., lymphedema education plus exercise). Participants were instructed to perform these exercises daily, using an instructional video for home use. LEAP participants also were given 2-pound hand weights for use during daily exercises and an elastic compression sleeve and gauntlet (Juzo Class I 20–30mmHg) to wear during exercise, air travel, and/or vigorous activity. At both 12- and 18-months post-surgery, participants in both groups met again briefly with the study educator. Study educators also contacted participants by phone at 9- and 15-months post-surgery to reinforce prevention practices, answer questions, and remind participants of upcoming study appointments. Adherence to the exercise components were self-reported using study calendars throughout the 18-month trial period.

Outcome Measures

Lymphedema was defined as: 1) limb volume increase of ≥ 10% in the affected arm between the pre-operative and 12- or 18-month visits, after controlling for percentage change in BMI; or 2) a diagnosis of lymphedema by a participant's physician at any time following the post-operative assessment (up to 18 months post-surgery)[26–29].

HRQL outcomes were assessed using the Functional Assessment of Cancer Therapy–Breast plus 4 lymphedema items (FACT-B+4)[25]. This 42-item scale is comprised of 6 subscales: physical, emotional, functional, and social well-being, other concerns related to breast cancer, and lymphedema symptoms (4 items). Individual scores are calculated for each of the subscales, as well as a total score comprised of all items across the 6 subscales. The subscale and total scores are transformed to a scale from 0–100, with higher scores indicating better HRQL/functioning. The FACT has demonstrated sensitivity to change over time and meets all requirements for use in oncology clinical trials, including ease of administration, brevity, reliability, and validity[25].

Statistical Methods

In order to investigate the impact of the interventions on the participants' quality of life over the 18-month study period, mixed-model regression analysis was used to examine differences in FACT scores by intervention group assignment (EO versus LEAP), adjusting for demographic variables (race, age, education) and clinical/treatment variables (Eastern Cooperative Oncology Group [ECOG] performance status [PS] at baseline, immediate reconstructive surgery, definitive primary surgery, number of positive lymph nodes, chemotherapy [yes/no], type of node surgery, and time since surgery). In addition, to assess the general impact of lymphedema status (yes/no) on HRQL at 18-months post-recruitment, linear regression analysis was used adjusting for the same demographic and clinical/ treatment variables as listed above, as well as for intervention group assignment and baseline HRQL scores.

Data collection and statistical analyses were conducted by the Alliance Statistics and Data Center (SDC). All analyses were completed on the study database frozen on April 30, 2016. Data quality was ensured by review of data by the Alliance SDC and by the study chairperson following Alliance policies. The trial was monitored at least twice annually by the Data and Safety Monitoring Board.

RESULTS

A total of 554 participants were enrolled in the main trial (56% in LEAP; 44% in the EO intervention). Main trial results indicated that there were no significant differences between the two intervention groups in preventing the occurrence of lymphedema. Lymphedema-free rates were 58% in the EO and 55% in LEAP (p=0.73). Kaplan-Meier estimates of 18-month lymphedema-free probabilities were also similar (84% EO vs. 81% LEAP) (Paskett et al., in press). The HRQL data were examined, however, in order to investigate whether there were any HRQL impacts (either positive or negative) to participating in the interventions that might inform the study results.

Of the 554 total participants, 547 completed at least the baseline FACT-B+4 and were included in the HRQL analyses. Participants' demographic and clinical characteristics are provided in Table 1. On average, the women were 57.6 years old, non-Hispanic White, with approximately 75% having completed at least some college/training after high school. The majority of the women were either employed (52%), retired (24%) or homemakers (11%). There were several significant differences between the two study arms in several demographic factors. The LEAP participants had a higher level of educational attainment than women in the EO group (p=0.0321). However, the EO intervention had a higher proportion of African-American (p=0.0368) and Hispanic/Latina participants (p<0.0001) than the LEAP group. The higher proportion of Hispanic/Latina and African-American women was due primarily to one recruitment site that treated, and thus enrolled, primarily underrepresented minorities, which caused an imbalance in the racial/ethnic composition between the two intervention arms.

In terms of clinical characteristics, there were few significant differences between the EO and the LEAP participants, with the exceptions that more women in the LEAP intervention had immediate reconstructive surgery (19.8% vs. 9%, p=0.0005) and were PgR receptor status positive (71.5% vs. 62.4%, p=0.048) than the EO participants. Performance status (PS) was borderline significantly different between the two arms, with women in the EO group reporting a better PS than women in the LEAP group (p=0.062). Lastly, there were no significant differences at baseline between the intervention groups on the unadjusted FACT-B+4 total or subscale scores (Table 2).

Mixed model regression analyses indicated no significant differences by intervention group assignment on HRQL, as measured by the FACT-B+4 total score (p=0.8777) (Table 3). Worse HRQL over the 18 month study period was associated with an ECOG PS >0 (p=0.0002), being 6 months or less from breast cancer surgery (p=0.0001), ≥1 positive lymph node(s) (p=0.0009), no education beyond high school (p<0.0001), having had any chemotherapy (p=0.0242), having only axillary node dissection or sentinel node biopsy, as compared to both (p=0.0007), and younger age (p=<0.0001). In general, these factors associated with poorer quality of life for the FACT-B+4 total score, were mirrored in the subscale results (Appendix Table 3a). There was one notable exception, however, in the results for the lymphedema 4-item subscale. HRQL impacts for lymphedema symptoms were significantly worse for African-American women than non-Hispanic white participants or women of other race/ethnicities over the intervention study period (p=0.0002). However, African-American women reported better emotional functioning than non-Hispanic white or other racial groups (p=0.0335) during the 18 month study period.

To examine changes in the adjusted FACT-B+4 subscale and total scores during the trial, we plotted the change scores from pre-surgery to 18 months for each subscale, as well as for the total score (Figure 1). In general, there was some decline in quality of life domains from pre-surgery to 6 months, with some gradual improvement at 12 and 18 months. This pattern was seen particularly in the functional and additional concerns subscales, and the FACT-B+4 total score. However, it was notable that both the physical and the social functioning scores did not reach their pre-surgery levels by 18 months, indicating some lingering decrements in function. Similarly, lymphedema symptoms became prevalent at 6 months, with only some

modest improvement in symptoms at 12 and 18 months post-surgery. What was striking, however, was the positive increase in emotional functioning during the course of the study, beginning at month 6 and continuing through the end of the trial.

Lastly, in our final analysis, we examined the impact of developing lymphedema (yes/no) by 18-months post-surgery on the FACT-B+4 total (Table 4) and subscales scores (Appendix Table 4a), adjusting for baseline scores. The presence of lymphedema was only found to be borderline significantly related to the FACT-B+4 total score (p=0.0825), and the functional well-being subscale (p=0.094) at 18 months post-surgery, trending toward worse HRQL among the participants with lymphedema.

DISCUSSION

Lymphedema is an unwanted side effect of treatment for breast cancer. We examined the HRQL impacts of two lymphedema prevention interventions after breast cancer surgery. In the main trial, (Paskett et al., in press), lymphedema-free rates by 18 months were 58% vs 55% in the EO and LEAP groups, respectively. The LEAP intervention, which combined lymphedema education with daily exercise and the use of compression garments, was not found to be superior to the EO treatment arm. Low adherence to the LEAP intervention components may have been a factor in the lack of a significant difference between the two groups. Adherence to the LEAP exercises was approximately 50% overall, and 31% wore the elastic garments as prescribed. Primary reasons that the participants gave for not completing the daily prescribed exercises were lack of time (average of 45.9% across all exercises and time points), and low perceived benefit in completing the exercises (average of 19.2% across all exercises and time points). In addition, a study limitation was that exercise and sleeve use in the EO arm was not tracked in this study, so EO participants who engaged in these behaviors could not be accounted for in the analysis.

The results of the HRQL analyses were similar to the results of the main trial, and also indicated no significant differences in participants' HRQL by intervention group. During the 18-month study period, lower FACT-B+4 total scores were related to common clinical, treatment and demographic variables. In addition, the presence of lymphedema symptoms by 18 months was only found to be borderline significantly related to the participants' HRQL, suggesting that participants with lymphedema may not have been experiencing severe symptoms and/or had learned to manage these symptoms over the course of the study period using the EO intervention materials and information common to both study groups. It is also not known whether the EO participants used compression garments or completed any exercises on their own that may have assisted in reducing lymphedema symptoms, even if they did not prevent the occurrence of lymphedema.

As has been reported previously, worse HRQL in this study was associated with closer time to breast surgery and chemotherapy treatment[12,17]. We also observed that women with a higher number of positive lymph nodes and a higher ECOG PS were more likely to have lymphedema symptoms and worse HRQL, suggesting a relationship between lymphedema and higher stage disease. However, Beaulac et al (18) found that early-stage breast cancer

patients with lymphedema reported lower FACT-B scores compared to women without lymphedema.

In this trial, higher education and older age were associated with better HRQL, comparable to other related research[9,16], with the exception that younger age was not related to a worse global HRQL in research by Chachaj et al (14). Interestingly, we observed that women who had both axillary node dissection and sentinel node biopsy had higher HRQL than those who had only one procedure alone. This finding has not been reported previously in any HRQL study, and should be explored for possible reasons/mechanisms for this association. In addition, consistent with a systematic review by Pusic et al., our findings suggest that African-American women may have worse lymphedema symptoms compared to non-Hispanic White women[16]. Not only did these women in our study report greater lymphedema symptoms, they also reported better emotional functioning than non-Hispanic white or women in other racial groups. Examining lymphedema and HRQL in underrepresented minorities is under-studied and needs to be further explored to help improve the lives of these women following breast cancer surgery and treatment. Focusing on racial/ethnic minority women's HRQL will be important in future lymphedema studies to design more effective prevention and symptom intervention studies.

In summary, a group-randomized trial to test the effectiveness of two interventions to prevent lymphedema in women newly diagnosed with breast cancer had no major HRQL impacts – either positively or negatively – by intervention group. HRQL in the study arms tended to mirror some previous findings of lymphedema among newly diagnosed breast cancer patients. However, two important findings are apparent. First, women who had both axillary node dissection and sentinel node biopsy had higher HRQL than those who had only one procedure alone. This finding has not been reported previously in any study. Secondly, we found that African-American women experienced more severe lymphedema symptoms, but reported better emotional functioning than women of other racial/ethnic groups. Both of these findings should be further explored to reduce the comorbidity associated with breast cancer surgery and treatment, and improve patient HRQL.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support: Research reported in this publication was supported by the National Cancer Institute of the National Institutes of Health under the Award Number UG1CA189823 (Alliance for Clinical Trials in Oncology NCORP Grant), UG1CA189817, UG1CA189819, U10CA180790, U10CA180836, U10CA180850, and UL1TR001409, https://acknowledgments.alliancefound.org. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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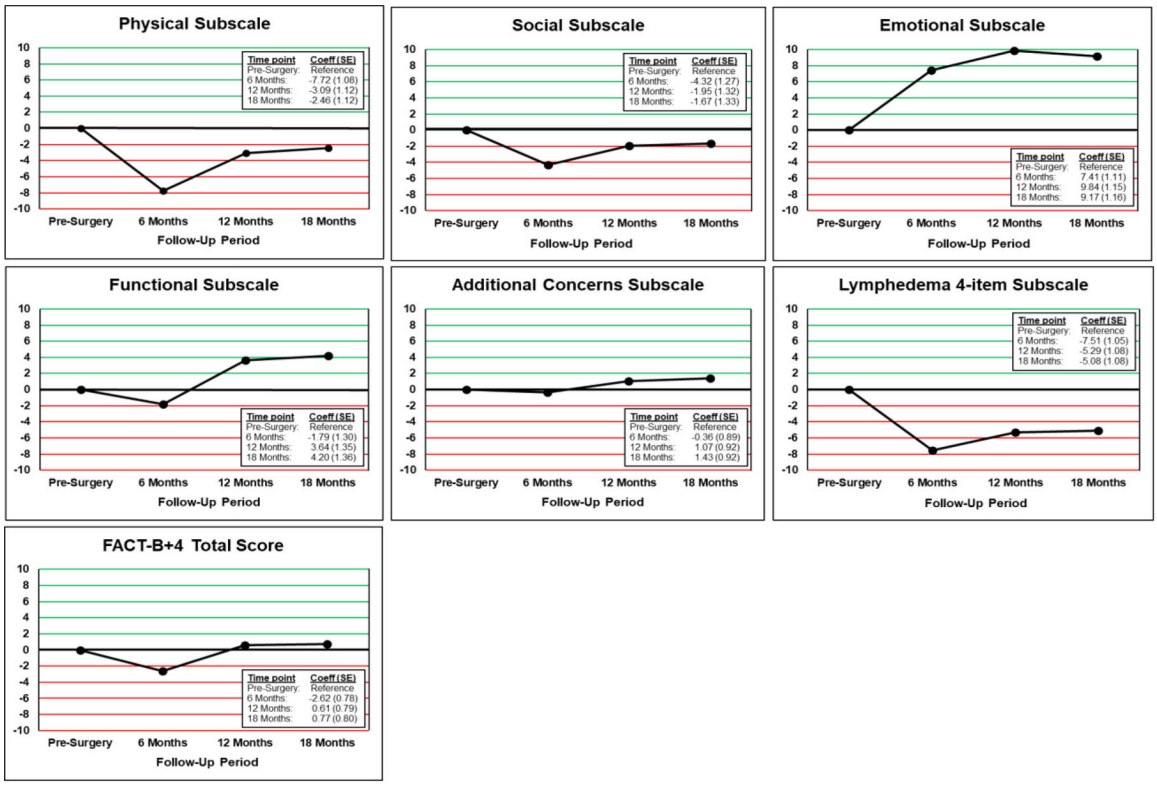

Figure 1.

Plots of Changes in Adjusted FACT-B+4 Subscale and Total Scores from Baseline to 18 Months

Table 1.

Baseline Demographic and Clinical Characteristics of Study Participants**

	Educational Only (N=238)	LEAP (N=309)	Total (N=547)	p value
Age				0.4067[1]
N	238	309	547	
Mean (SD)	58.0 (11.5)	57.4 (11.2)	57.6 (11.3)	
Range	(24.0–83.0)	(27.0–88.0)	(24.0–88.0)	
Race				0.0368[2]
African-American	37 (15.7%)	30 (9.9%)	67 (12.4%)	
Other (Asian, American Indian, Alaska Native, More than 1 race)	6 (2.5%)	17 (5.6%)	23 (4.3%)	
White	193 (81.8%)	256 (84.5%)	449 (83.3%)	
Ethnicity				<0.0001[2]
Hispanic or Latino	39 (17.0%)	10 (3.3%)	49 (9.2%)	
Non-Hispanic	190 (83.0%)	293 (96.7%)	483 (90.8%)	
Performance Status (PS)				0.0620[2]
0	193 (97.0%)	236 (91.8%)	429 (94.1%)	
1	6 (3.0%)	20 (7.8%)	26 (5.7%)	
2	0 (0.0%)	1 (0.4%)	1 (0.2%)	
Educational Background				0.0321[2]
< HS	19 (8.8%)	11 (3.6%)	30 (5.8%)	
HS Grad	38 (17.7%)	65 (21.3%)	103 (19.8%)	
Some college/Jr College	75 (34.9%)	90 (29.5%)	165 (31.7%)	
BA/BS College Degree	32 (14.9%)	64 (21.0%)	96 (18.5%)	
> BA/BS College Degree	51 (23.7%)	75 (24.6%)	126 (24.2%)	
Marital Status				0.8822[2]
Married	130 (61.0%)	188 (62.0%)	318 (61.6%)	
Separated/divorced/widowed	65 (30.5%)	93 (30.7%)	158 (30.6%)	
Single/never married	18 (8.5%)	22 (7.3%)	40 (7.8%)	
Employment Status				0.7279[2]
Disabled	16 (7.5%)	19 (6.3%)	35 (6.8%)	
Employed	117 (54.9%)	154 (50.7%)	271 (52.4%)	

	Educational Only (N=238)	LEAP (N=309)	Total (N=547)	p value
Homemaker	19 (8.9%)	38 (12.5%)	57 (11.0%)	
Retired	50 (23.5%)	74 (24.3%)	124 (24.0%)	
Student	2 (0.9%)	2 (0.7%)	4 (0.8%)	
Unemployed	9 (4.2%)	17 (5.6%)	26 (5.0%)	
Definitive primary surgery				0.9476[2]
Partial mastectomy/lumpectomy/excisional biopsy	152 (65.5%)	200 (65.8%)	352 (65.7%)	
Mastectomy, NOS	80 (34.5%)	104 (34.2%)	184 (34.3%)	
Type of axillary lymph node dissection				0.1058[2]
Axillary node dissection only	61 (25.6%)	63 (20.4%)	124 (22.7%)	
Both Axillary node dissection and sentinel node biopsy	74 (31.1%)	87 (28.2%)	161 (29.4%)	
Both missing	1 (0.4%)	0 (0.0%)	1 (0.2%)	
Neither axillary node dissection nor sentinel node biopsy	3 (1.3%)	1 (0.3%)	4 (0.7%)	
Sentinel node biopsy but axillary node dissection missing	1 (0.4%)	0 (0.0%)	1 (0.2%)	
Sentinel node biopsy only	98 (41.2%)	158 (51.1%)	256 (46.8%)	
Number of positive lymph nodes				0.0837[1]
N	217	295	512	
Mean (SD)	2.4 (5.2)	2.1 (5.5)	2.2 (5.3)	
Range	(0.0–41.0)	(0.0–60.0)	(0.0–60.0)	
Immediate reconstructive surgery				0.0005[2]
No	213 (91.0%)	247 (80.2%)	460 (84.9%)	
Yes	21 (9.0%)	61 (19.8%)	82 (15.1%)	
Receptor status, ER				0.3895[2]
Negative	55 (23.2%)	60 (19.4%)	115 (21.1%)	
Positive	182 (76.8%)	248 (80.3%)	430 (78.8%)	
Not Done	0 (0.0%)	1 (0.3%)	1 (0.2%)	
Receptor status, PgR				0.0479[2]
Negative	89 (37.6%)	87 (28.2%)	176 (32.2%)	
Positive	148 (62.4%)	221 (71.5%)	369 (67.6%)	
Not Done	0 (0.0%)	1 (0.3%)	1 (0.2%)	
HER-2/neu receptors				0.6619[2]

	Educational Only (N=238)	LEAP (N=309)	Total (N=547)	p value
Negative	193 (82.1%)	246 (80.4%)	439 (81.1%)	
Positive	39 (16.6%)	53 (17.3%)	92 (17.0%)	
Not Done	3 (1.3%)	7 (2.3%)	10 (1.8%)	
Pathologic primary tumor size				0.9151[1]
N	228	302	530	
Mean (SD)	2.2 (1.8)	2.4 (3.9)	2.3 (3.2)	
Range	(0.0–12.5)	(0.0–60.0)	(0.0–60.0)	
Grade				0.1691[2]
Low	55 (23.4%)	65 (22.2%)	120 (22.7%)	
Intermediate	90 (38.3%)	135 (46.1%)	225 (42.6%)	
High	90 (38.3%)	93 (31.7%)	183 (34.7%)	
Chemotherapy				0.4149[2]
Missing	4 (1.7%)	4 (1.3%)	8 (1.5%)	
No	138 (58.2%)	197 (63.8%)	335 (61.4%)	
Yes	95 (40.1%)	108 (35.0%)	203 (37.2%)	
Radiation prior to lymphedema diagnosis or within 18 months for those who were lymphedema-free				0.8570[2]
0 No	73 (30.7%)	97 (31.4%)	170 (31.1%)	
1 Yes	165 (69.3%)	212 (68.6%)	377 (68.9%)	
Body Mass Index (BMI)				0.9650[1]
N	238	309	547	
Mean (SD)	28.4 (6.0)	28.0 (5.4)	28.2 (5.7)	
Range	(18.0–57.9)	(16.4–53.3)	(16.4–57.9)	

** Not all participants answered all questions

[1] Kruskal Wallis (unadjusted)

[2] Chi-Square (unadjusted)

Table 2.

Comparisons of the Unadjusted Baseline FACT-B+4 Total and Subscale Scores by Intervention Group

	Education Only (EO) Intervention Group (N=238)		LEAP Intervention Group (N=309)		Total of All Participants (N=547)		p value (between intervention groups)	
	Baseline	**Month 18**	**Baseline**	**Month 18**	**Baseline**	**Month 18**	**Baseline**	**Month18**
Physical Subscale *							0.1213	0.7682
N	212	174	291	215	503	389		
Mean (SD)	90.1 (14.9)	87.5 (13.9)	89.2 (13.1)	86.4 (15.4)	89.6 (13.8)	86.9 (14.7)		
Median	92.9	92.9	92.9	92.9	92.9	92.9		
Q1, Q3	85.7, 100	82.1, 96.4	85.7, 100	78.6, 96.4	85.7, 100	82.1, 96.4		
Range	(0.0–100)	(7.1–100)	(0.0–100)	(3.6–100)	(0.0–100)	(3.6–100)		
Social Subscale							0.5884	0.1614
N	233	177	308	218	541	395		
Mean (SD)	85.7 (15.4)	84.4 (17.8)	84.6 (16.6)	82.5 (17.7)	85.1 (16.0)	83.4 (17.7)		
Median	91.7	92.9	89.3	87.5	89.3	89.3		
Q1, Q3	75.0, 100	75.0, 100	75.0, 100	75.0, 100	75.0, 100	75.0, 100		
Range	(17.9–100)	(14.3–100)	(25.0–100)	(25.0–100)	(17.9–100)	(14.3–100)		
Emotional Subscale							0.8511	0.0253
N	225	174	297	212	522	386		
Mean (SD)	73.8 (17.7)	85.7 (14.3)	73.7 (17.1)	83.5 (13.6)	73.7 (17.3)	84.5 (13.9)		
Median	75.0	87.5	75.0	83.3	75.0	87.5		
Q1, Q3	62.5, 87.5	79.2, 95.8	62.5, 87.5	79.2, 91.7	62.5, 87.5	79.2, 95.8		
Range	(20.0–100)	(25.0–100)	(20.8–100)	(25.0–100)	(20.0–100)	(25.0–100)		
Functional Subscale							0.6581	0.2696
N	238	177	307	220	545	397		
Mean (SD)	75.8 (20.2)	82.1 (16.4)	75.4 (19.3)	79.9 (18.1)	75.6 (19.6)	80.9 (17.3)		
Median	78.6	85.7	78.6	82.1	78.6	82.1		
Q1, Q3	64.3, 92.9	71.4, 96.4	64.3, 92.9	67.9, 92.9	64.3, 92.9	71.4, 96.4		
Range	(10.7–100)	(29.2–100)	(20.0–100)	(21.4–100)	(10.7–100)	(21.4–100)		
Fact G Total Score							0.6061	0.1239
N	209	172	287	210	496	382		
Mean (SD)	82.1 (12.9)	85.1 (12.1)	81.7 (12.4)	83.2 (12.7)	81.9 (12.6)	84.0 (12.5)		
Median	84.3	87.0	83.7	84.3	84.3	86.1		
Q1, Q3	75.8, 91.0	77.9, 95.4	74.5, 91.7	76.9, 93.5	75.0, 91.7	76.9, 94.4		
Range	(29.3–100)	(36.1–100)	(30.6–100)	(38.9–100)	(29.3–100)	(36.1–100)		

	Education Only (EO) Intervention Group (N=238)		LEAP Intervention Group (N=309)		Total of All Participants (N=547)		p value (between intervention groups)	
	Baseline	Month 18	Baseline	Month 18	Baseline	Month 18	Baseline	Month18
Additional Concerns Subscale							0.9286	0.4768
N	222	176	294	219	516	395		
Mean (SD)	67.7 (13.7)	70.1 (12.1)	67.7 (13.2)	69.1 (12.2)	67.7 (13.4)	69.5 (12.2)		
Median	67.5	71.5	67.5	72.5	67.5	72.5		
Q1, Q3	58.3, 77.5	62.5, 77.5	60.0, 77.5	60.0, 77.5	60.0, 77.5	62.5, 77.5		
Range	(20.0–100)	(22.5–100)	(27.5–100)	(35.0–100)	(20.0–100)	(22.5–100)		
Plus 4 Subscale							0.2310	0.1303
N	200	175	278	217	478	392		
Mean (SD)	95.3 (12.0)	91.7 (13.2)	94.7 (12.0)	89.5 (15.7)	94.9 (12.0)	90.5 (14.7)		
Median	100.0	100.0	100.0	93.8	100.0	100.0		
Q1, Q3	100, 100	87.5, 100	93.8, 100	87.5, 100	93.8, 100	87.5, 100		
Range	(25.0–100)	(31.3–100)	(18.8–100)	(18.8–100)	(18.8–100)	(18.8–100)		
FACT-B Total Score							0.3284	0.1730
N	200	172	284	209	484	381		
Mean (SD)	79.3 (9.8)	81.0 (10.6)	78.0 (11.0)	79.5 (10.9)	78.5 (10.5)	80.2 (10.8)		
Median	79.6	83.0	79.3	80.4	79.5	81.8		
Q1, Q3	74.6, 87.2	74.3, 89.2	72.0, 86.2	74.3, 88.5	73.0, 86.5	74.3, 88.5		
Range	(46.8–100)	(35.1–97.7)	(38.5–98.6)	(40.5–97.3)	(38.5–100)	(35.1–97.7)		
FACT-B+4 Total Score							0.2962	0.1626
N	191	172	271	209	462	381		
Mean (SD)	81.2 (9.0)	82.0 (10.1)	79.8 (10.3)	80.5 (10.6)	80.3 (9.8)	81.2 (10.4)		
Median	81.5	83.8	81.1	81.4	81.4	82.3		
Q1, Q3	76.8, 88.2	75.9, 89.9	74.4, 87.2	75.6, 89.0	75.6, 87.7	75.6, 89.6		
Range	(44.7–100)	(41.5–98.0)	(38.4–98.8)	(38.4–97.6)	(38.4–100)	(38.4–98.0)		

*Higher scores indicated better HRQL on the FACT-B+4 total and all subscale scores

Table 3.

Mixed Model Regression Analysis of the Impact of the Lymphedema Intervention Group, Clinical and Demographic Characteristics on Participants' Health-Related Quality of Life (i.e., FACT-B+4 total score) Over the 18 Month Study Period

Variable	Level	Estimate	Standard Error	P-Value	Overall P-Value
Lymphedema Intervention Group	LEAP	−0.2089	1.3476	0.8777	0.8777
	Education Only (EO)	Reference			
Immediate reconstructive surgery	Yes	−0.6987	0.9281	0.4595	0.4595
	No	Reference			
Definitive primary surgery	Mastectomy, NOS	1.3136	0.7948	0.1088	0.1088
	Partial mastectomy/lumpectomy/ excisional biopsy	Reference			
Race	African-American	−0.2886	0.9659	0.7668	0.7220
	Other	1.0089	1.4270	0.4842	
	White	Reference			
ECOG Performance Status	1 & 2	−7.5739	1.3944	0.0002	0.0002
	0	Reference			
Follow-up period	Pre-Surgery	Reference			0.0001
	6 Months	−2.6163	0.7760	0.0011	
	12 Months	0.6066	0.7972	0.4484	
	18 Months	0.7700	0.8008	0.3385	
Number of positive lymph nodes	1–3	−2.6191	0.8867	0.0048	0.0009
	4+	−4.3304	1.1191	0.0003	
	0	Reference			
Education	At least some college	3.1241	0.7765	0.0002	0.0001
	Post College work/degree	3.8446	0.8872	<.0001	
	HS Grad or less	Reference			
Chemotherapy	Yes	−1.7769	0.7440	0.0242	0.0242
	No	Reference			
Axillary Node Dissection	Axillary node dissection only	−2.1234	0.9360	0.0280	0.0007
	Sentinel node biopsy only	−3.9897	0.9768	0.0002	
	Both Axillary node dissection and sentinel node biopsy	Reference			
Age	1 more year	0.1829	0.02942	<.0001	<.0001

Table 4.

Linear Regression Model of the Impact of the Presence of Lymphedema on Participants' HRQL at 18 Months adjusted for Intervention Group, Demographic and Clinical Variables

Variable	Level	Estimate	Standard Error	P-Value	Overall P-Value
Lymphedema Intervention Group	LEAP	−0.6161	1.1482	0.5921	0.5921
	Education Only (EO)	Reference			
Immediate reconstructive surgery	Yes	−1.8887	1.5627	0.2281	0.2281
	No	Reference			
Definitive primary surgery	Mastectomy, NOS	1.1734	1.4323	0.4135	0.4135
	Partial mastectomy/lumpectomy/ excisional biopsy	Reference			
Race	African-American	−2.0784	1.6039	0.1964	0.3549
	Other	1.4292	2.8702	0.6190	
	White	Reference			
ECOG Performance Status	1 & 2	−4.2272	2.3780	0.0768	0.0768
	0	Reference			
Number of positive lymph nodes	1–3	0.8704	1.5469	0.5742	0.2989
	4+	−2.1654	2.1082	0.3055	
	0	Reference			
Lymphedema	Yes	−2.3175	1.3288	0.0825	0.0825
	No	Reference			
Education	At least some college	0.6585	1.3911	0.6364	0.4045
	Post College work/degree	2.0368	1.5706	0.1961	
	HS Grad or less	Reference			
Chemotherapy	Yes	−1.1679	1.3790	0.3980	0.3980
	No	Reference			
AND/SND Status	Axillary node dissection only	−0.4700	1.6435	0.7752	0.9123
	Sentinel node biopsy only	−0.6072	1.5351	0.6928	
	Both Axillary node dissection and sentinel node biopsy	Reference			
Age	1 more year	0.04319	0.05546	0.4369	0.4369
Baseline FACT-B+4 Total Score		0.6572	0.05971	<.0001	<.0001