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PREDICTIVE FACTORS OF RESPONSE TO PHASE I COMPLETE DECONGESTIVE THERAPY IN UPPER EXTREMITY LYMPHEDEMA FOLLOWING BREAST CARCINOMA IN IRAN

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ABSTRACT

Post-mastectomy chronic lymphedema as a complication of breast cancer treatment is primarily managed with Complete Decongestive Therapy (CDT). We examined various factors for correlating with results of Phase I CDT treatment in controlling the upper extremity lymphedema. Study population consisted of patients with lymphedema referred to the Lymphedema Clinic of the Iranian Breast Cancer Research Center for control of arm edema. After obtaining the demographic and clinical data, patients were treated with CDT for 2 - 3 weeks. One hundred and thirty seven patients (mean age ± SD; 53.5 ± 10 years) were studied. In 48.7% of patients, the affected arm was the dominant limb. Fifty percent of patients experienced lymphedema during the first year after surgery, and mean duration of lymphedema was 35 ± 43 months. Mean volume reduction was 43% ± 14.87% (p = 0.03). There was a significant relationship between the percent of volume reduction and initial lymphedema volume (p=0.003) as well as duration of lymphedema (p=0.002). Our results demonstrate that Phase I CDT treatment is very effective for post mastectomy lymphedema, and particularly if it is provided in earlier stages of disease. In addition, CDT also has an important role in reducing clinical symptoms and improving limb function. In the appropriate setting, Phase I CDT has been an effective method of controlling post mastectomy lymphedema in this Iranian population.

Keywords: breast cancer, lymphedema, CDT, predicting factors, Iran

Early detection of breast carcinoma and effective adjuvant therapies are currently enabling breast cancer survivors to live longer. However, upper extremity lymphedema, a common sequela of breast cancer treatment, is a chronic problem for many survivors (1). Treatment of lymphedema is difficult, multidisciplinary in nature, and even in the best outcomes, is costly and time consuming (2). To date, there is no cure for breast cancer-associated lymphedema, although various methods, including conservative and operative techniques, have been described for the treatment of lymphedema (3-10). The goals of lymphedema therapy are to reduce swelling, preserve volume reduction, prevent medical comorbidities, improve the cosmesis of the affected limb, and enhance patient adherence and comfort.

The 2009 Consensus Document of the International Society of Lymphology (ISL) blends a worldwide spectrum of protocols for

the diagnosis and treatment of lymphedema. Nevertheless, with the lack of optimally conducted clinical trials, emerging technologies, approaches, and discoveries, and varying individual and national standards for treatment of lymphedema, no single evaluation and treatment protocol was endorsed resulting in a spectrum of approaches representing the consensus of the international community (11). Despite a variety of physical interventions proposed for controlling symptoms and minimizing complications of lymphedema, uniform agreement regarding a standard treatment of lymphedema has not been reached.

Complete Decongestive Therapy (CDT), including manual lymphatic massage, multilayer compressive bandaging, and the use of compressive garments, has become the standard care for the control of acquired lymphedema (9). Despite the fact that CDT is widely used in clinical practice as a noninvasive treatment for lymphedema, it is unclear whether certain demographic or clinical characteristics of patients, or whether deviation from the traditional CDT approaches, will affect treatment outcomes. An American Cancer Society review and Leal Study revealed the outcome of CDT was less optimal in the later stages of lymphedema due to adipose and fibrotic changes within the tissue (12-13). In a French study investigating clinical and paraclinical criteria predicting responses to CDT, venous insufficiency and continuing lymph node evidence of scintigraphic activity four hours after lymphoscintigraphy showed significant correlation (14). Other studies have suggested duration of post-cancer treatment lymphedema and body mass index (15), patient's compliance and latency (number of months from surgery to onset of lymphedema) (16), and stage of lymphedema (17) as predictive factors of CDT effectiveness. Although the effectiveness of CDT for treatment of lymphedema worldwide has been established, the previously mentioned studies report conditions under which CDT is more or less effective. The aim of this study was to evaluate the results of CDT treatment among Iranian women with post mastectomy upper limb lymphedema and to examine potential factors influencing the results of CDT in this population.

MATERIAL AND METHODS

Study Population

All patients with post mastectomy lymphedema referred for treatment to the Lymphedema Clinic of the Iranian Breast Cancer Research Center in 2008 were eligible to enter the study. Excluded were those with active malignancy, breast cancer recurrence, active infection, bilateral disease or bilateral lymphedema, venous insufficiency, low physical activity and unable to perform daily tasks, history of previous treatment for lymphedema, neuromuscular diseases especially in arms, any absolute contraindications for CDT, or female athletes with higher than normal physical activity,

Phase I (intensive phase CDT)

CDT daily treatment was administered 5 days a week for 10-15 sessions in accordance with recommendations by the International Society of Lymphology. Phase I consisted of skin care, 45 minutes of a specific light manual massage (manual lymph drainage; MLD with Vodder technique), remedial exercises, and compression applied by multilayered short-stretch bandages (Lohmann Rauscher lymphedema bandage set).

Measurement Tools

Demographic and clinical characteristics were obtained from a questionnaire, through personal interview, and from data recorded in the pathology report.

The volume of edema was measured by water displacement method. The edema volume (defined as the volume difference

TABLE 1
Demographic and Clinical Characteristic of Patients and Comparison of Means of Volume Reduction in Subgroups

Characteristic	Category	No. (%)	Percent of Volume reduction (Mean± SD)	p-value
Marriage status				0.084
	Unmarried	22 (16.1)	47.21±11.46	
	Married	115 (83.9)	42.18±15.36	
Occupation				0.611
	Employee	17 (12.4)	44.71±14.84	
	Household	120 (87.6)	42.74±14.93	
Education				0.517
	Less than high school	64 (46.7)	43.87±14.53	
	High school and higher	73 (53.3)	42.21±15.24	
Disease Staging				0.575
	I	12 (8.8)	43.11±18.6	
	II	53 (38.7)	43.06 ±16.38	
	III	42 (30.7)	41.28 ±13.38	
	IV	9 (6.6)	50.63 ±12.83	
	Unknown	21 (15.3)	42.87 ±12.33	
Type of Surgery				0.682
	Modified Radical Mastectomy	111 (81)	42.73±14.99	
	Breast preservation	26 (19)	44.07±14.62	
Radiotherapy				0.346
	No	13 (9.6)	46.55 ±20.29	
	Yes	124 (90.4)	42.58 ±14.19	
Chemotherapy				0.815
	No	16 (11.7)	43.81 ±14.62	
	Yes	121 (88.3)	42.88 ±14.97	
Hormone therapy				0.225
	No	13 (9.6)	46.26 ±14.53	
	Yes	124 (90.4)	42.26 ±14.92	
Affected limb = Dominant side				0.351
	No	73 (53.3)	44.11 ±15.89	
	Yes	64 (46.7)	41.72 ±13.64	
Co-morbid diseases				0.303
	No	109 (79.6)	42.32 ±15.14	
	Yes	28 (20.4)	45.58 ±13.77	
Duration of lymphedema				0.018
	≤2 years	84 (61.3)	45.35 ±15.59	
	>2 years	53 (38.7)	39.23 ±12.94	
BMI				0.648
	< 30	77 (56.2)	42.47 ±13.96	
	≥ 30	60 (43.8)	43.65 ±16.07	

TABLE 2
Quantitative Demographic and Clinical Characteristic of Patients and Their Correlation with Volume Reduction

Characteristics	Range (cm^3)	Mean ± SD	Pearson Correlation	p-value
Age (years)	26 - 84	53.5±10	-0.12	0.888
BMI	18.9 - 44.5	29.7 ± 4.65	0.028	0.742
Starting Volume of edema (cm^3)	240 - 4200	1230.5± 714	0.184	0.032
Time between surgery to lymphedema occurrence (years)	0 - 15	2.5 ± 3.47	0.109	0.2

between affected and unaffected arms) was recorded at the initial session and the final session of Phase I. The percent volume reduction (PVR) was calculated comparing these volumes.

Subjective symptoms (pain, heaviness and paresthesia) were recorded on a four point scale questionnaire ranging from 0 - 3, 0 indicating no symptoms and 3 indicating severe intensities. The score of these symptoms was assessed at the start and end of treatment.

Statistical Analysis

Mean volume reduction of edema in different categorical and continuous variable subgroups were compared using the Student's t- test, ANOVA, and correlation coefficient, respectively. The Wilcoxon test was used for measuring change of symptom scores after treatment. Two-sided p-values less than 0.05 indicated statistical significance. Statistical procedures were performed using the SPSS, version 17.0.

RESULTS

One hundred and thirty seven patients with post-mastectomy lymphedema were recruited to the study. Approximately 84% of them were married; the mean ± SD age of patients was 53.5 ± 10 years with range of 26 to 84. Seventy three patients (53.3%) had a high school or higher education level, and others were less than high school levels. 26 patients (19 percent) underwent breast conserving surgery (*Table 1*).

The initial volume of edema was 1230.5 ± 714 (mean ± SD) (cm^3) with a range of 240-4200, and after completing Phase I CDT, this was reduced to 682.2 ± 399 with the range of 30 to 2010. In addition, the PVR Phase I was 43 ± 14.9 (range of 11.1 to 88.9).

Using univariate analysis, it was found that both lymphedema duration (>2y versus ≤ 2y) and starting volume of edema was significantly correlated with PVR. Other variables examined with univariate analysis are shown in *Tables 1 and 2* and were not significant. Considering the importance of demographic and clinical factors and the significant p-values obtained in univariate analysis, all variables with p-value equals or less than 0.2 were entered into multivariate analysis. Multivariate linear regression showed lymphedema duration (>2y versus ≤ 2y) and starting volume of edema to have a statistically significant effect on PVR (*Table 3*).

TABLE 3
Factors Correlated to Percent of Volume Reduction

Variable	Beta	Standard Error	p-value
Constant	39.58	2.461	<0.001
Lymphedema Duration (>2y vs. ≤2y)	-8.225	2.589	0.002
Starting Volume of Edema	0.005	0.002	0.003

TABLE 4
Comparing Symptom Changes Due to CDT

L-Dex Ratio *†	Mean ± SD[a]	Median	Range Minimum	Range Maximum
Healthy	-1.0 + 3.6	-0.6	-9.7	7.7
At Risk	-0.1 + 6.0	-0.4	-9.6	36.9
Lymphedema	30.9 + 27.1	26.9	0.9	115.0

[a] SD: Standard Deviation; * Mean Scores differ significantly at p<0.001 between healthy and lymphedema group by the Tukey multiple comparisons of means; † Mean Scores differ significantly at p<0.001 between lymphedema and at-risk group by the Tukey multiple comparisons of means.

Changes in severity of main clinical symptoms (pain, heaviness and paresthesia) after CDT are shown in *Table 4.*

DISCUSSION

This study found a significant volume reduction after Phase I of CDT. Reduction in pain, paresthesia, and heaviness was remarkable after treatment compared to before CDT. Since introduction of CDT as an effective intervention for the treatment of secondary postmastectomy lymphedema, several case series have been reported in the literature to support the effectiveness of this technique in reducing the volume of swelling. While the reported results are promising, few studies have focused on searching for predictors of efficiency of CDT.

Percentage reductions of lymphedema volume and measurement methods often vary among studies. Perimetric measures and water displacement are the most frequently used methods and are reported to exhibit both excellent reproducibility with an intraclass correlation coefficient >0.99 and an accuracy coefficient <0.3% (18). This study showed a mean volume reduction of the swollen arm of 548 ± 410 ml (43%) after CDT using water displacement. Also using water displacement measures, Hamner et al (9) and Haghighat (19), respectively, reported a mean volume reduction of 236.7 ml and 43.1% (±13.7) after the end of Phase I of CDT. Two different studies reported mean volume reductions of 404 ± 33 ml (36%) at the end of CDT treatment (15) and 47% after one year (20) using perometry as a volume

measure. This study's results are reflective of the Phase I CPT literature, and the populations are therefore comparable.

Lymphedema has been shown to diminish quality of life in breast cancer survivors, with many reporting reduction of arm strength, limited mobility, and emotional distress (21-26). Pain and heaviness, also outcomes from lymphedema, are reportedly improved with lymphedema treatment. Hamner et al measured change in pain with CDT treatment in 76 breast cancer survivors with lymphedema. Average pain assessed with the Numeric Pain Scale (0-10) was 6.9 ± 2.3 before CDT and was reduced significantly to 1.1 ± 2.3 after CDT. Of the 76 patients with pain before therapy, 56 (76%) were pain-free after the CDT (9). Findings of the present study highlight the role of CDT in improving quality of life; as study patients revealed significant reduction in the post mastectomy related pain, heaviness, and paresthesia.

Evaluating the factors associated with effectiveness of CDT, patients with lymphedema duration less than 2 years had more volume reduction than those with duration greater than 2 years. The amount of edema volume prior to the treatment also influenced the result of the treatment. Vignes et al (15) reported that duration of lymphedema before intensive phase of decongestive physiotherapy and BMI were two predictors influencing reduction of lymphedema volume. No other clinical features or features of cancer treatment or treatment characteristics could be identified as predictors in that study. The present study did not find a relationship between the BMI and amount of volume reduction with treatment, but rather, the limb volume before the treatment had an independent effect on the amount of volume reduction following CDT treatment. Most other treatment techniques (e.g., microsurgery) also report greater success with patients who are treated early and with similar volumes.

Mondry et al studied demographics of patient's age, height, dominant upper extremity, date of onset of swelling, latency, surgery type and date, stage of cancer, previous or ongoing chemotherapy, hormonal therapy, and radiation therapy as predictive factors of the result of Phase I of CDT. They concluded that longer latency (the number of months from surgery to onset of lymphedema) was predictive of reduced girth, volume, pain and increased QoL. Using regression analysis, the grade of lymphedema predicted significantly the amount of volume reduction (16). Thomas et al did not find prior radiation therapy and extent of axillary dissection to significantly correlate with lymphedema volume reduction (27). This study reports most of the demographic and clinical characteristics identified in the Mondry study (*Tables 1,2*), but similar to other studies, there was no significant effect of these factors on CDT result. The fact that multiple studies in very different settings are finding similar results may indicate that many of the factors will never be correlated with treatment outcomes.

This study found no correlation between the presence of pain and the amount of limb volume before the initiation of CDT. But interestingly, the amount of volume reduced with CDT had a positive correlation with the presence of pain in the affected arm prior to CDT. It was observed that patients with a painful arm had greater compliance with treatment. This may be due to the fact that most of the patients with pain experienced pain reduction after the few days of CDT, which may have contributed to better adherence during the intensive and maintenance phases of CDT, resulting in greater volume reduction. Pain relief with CDT was also noted by Hamner et al (9). Although the study of pain reduction with CDT was not the primary purpose of this study, this outcome was an interesting result worthy investigations.

In conclusion, we found that Phase I CDT is a very effective treatment in post-mastectomy lymphedema in our population and especially if it is provided in the earlier stages. The use of Phase I CDT as an

effective method of controlling post-mastectomy lymphedema, accompanying clinical symptoms, and for improvement in limb function is supported.

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TABLE 4
Comparing Symptom Changes Due to CDT

Symptoms	Pre-CDT Score			After-CDT Score			p-value
	Range	Mean	SD	Range	Mean	±SD	
Pain	0-3	0.88	1	0-3	0.28	0.552	<0.001
Heaviness	0-3	1.42	1.027	0-3	0.47	0.642	<0.001
Paresthesia	0-3	0.64	0.984	0-3	0.28	0.565	<0.001

Editor's note: The article by Shahpar Haghighat "Predictive Factors of Response to Phase I Complete Decongestive Therapy in Upper Extremity Lymphedema Following Breast Carcinoma in Iran" Lymphology 46 (2013), 97-104 was published with Table 4 from the preceding article. The correct Table 4 is above. The Journal regrets this printing error.