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Early prevention of complex decongestive therapy and rehabilitation exercise for prevention of lower extremity lymphedema after operation of gynecologic cancer

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ABSTRACT

Objective: To investigate efficacy of early prevention of complex decongestive therapy and rehabilitation exercise for prevention of postoperative lower limb extremity lymphedema for patients with gynecologic cancer.

Methods: 109 female patients were randomly divided into two groups, the control group who only received routine treatment and the CDT group who received both CDT and rehabilitation exercise. For rehabilitation exercise, patients received additional rehabilitation exercise strategy including professional education and full range exercise of hip joint. The incidence of lower extremity lymphedema was recorded. A simple scale for patients' lower extremity lymphedema was designed. The diameter of low limbs (both thighs and calves) was also measured. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the Brief Fatigue Inventory (BFI) was used for measurement of quality of life.

Results: The incidence of lower extremity lymphedema was 15.09% cases of CDT group and 32.14% in the control group. K-M curve showed the lymphedema free time in CDT group was significantly longer. The subjective scores for heaviness of lower limbs, pain, numbness and dysfunction, as well as the diameters of both thighs and calves were lower in the CDT group. In both groups, the values of EORTC QLQ-C30-GHS and EORTC QLQ-C30-FS were significantly higher, and EORTC QLQ-C30-SS scores and BFI scores were remarkably lower.

Conclusion: Early prevention of CDT combined with rehabilitation exercise reduced incidence of lower limb extremity lymphedema and improved patients' quality of life, as well as reduced the cancer-related fatigue.

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1. Introduction

Both cervical cancer and endometrial cancer are common gynecological malignant tumor which affect millions of women.^{1–3} It is reported that about 527,624 new cases and 265,672 deaths are reported annually, and endometrial cancer is considered as the fifth common in female cancers.⁴ However, despite medical

development for chemotherapy and other treatment methods, currently, surgery is still a main strategy for treatment of gynecological cancers.^{5,6}

Studies show that lymphedema affects approximately 90 million people worldwide and surgery is one of the main causes of lymphedema, especially in cancer patients.^{7–9} Extremity lymphedema can cause a series of symptoms, including heaviness, pain, deficit of the extremities, sensory and anxiety.¹⁰ In gynecological surgery, disruption of pelvic drainage may result in accumulation of protein-rich lymph fluid in the lower extremity, and finally leads to lower extremity swelling.¹¹ The treatment methods for extremity lymphedema mainly contains surgical methods, conservative

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treatment like raising the affected limb and using bandages, and medications.^{12–14} The complex decongestive therapy (CDT) is a new developed, and a widely used method for extremity lymphedema in recent years.¹⁵ However, most studies reported its application to upper limb extremity lymphedema, and lower limb extremity lymphedema for gynecologic cancer is less concerned.

In the present study, we used both CDT and rehabilitation exercise for prevention of postoperative lower limb extremity lymphedema for patients with gynecologic cancer. It is found that early prevention of CDT combined with rehabilitation exercise reduced the incidence of lower limb extremity lymphedema and improved patients' quality of life, as well as reduced the cancer-related fatigue. This study might provide evidence for CDT and rehabilitation exercise in prevention and treatment of postoperative extremity lymphedema.

2. Methods and materials

2.1. Patients

The present prospective randomized controlled study included a total of 109 cases of female patients who received operation of cervical cancer, endometrial cancer or ovarian cancer in our hospital during April 2017 to July 2018. The inclusion criteria were as follows: 1) all patients were diagnosed as cervical cancer, endometrial cancer or ovarian cancer with FIGO stage II ~ III by imaging methods and histological analysis; 2) all patients had received surgical treatment such as radical mastectomy and pelvic lymphadenectomy; 3) the patients could complete the rehabilitation exercise below. The surgical procedures were all performed by the same team following standard protocol. The following patients were excluded, patients with other cancers except for cervical cancer, endometrial cancer and ovarian cancer, patients who showed recurrence or metastasis of cancer during the study period, patients who needed to change the treatment strategy during the period. The present study was approved by the ethic committee of Nantong First People's Hospital.

2.2. Grouping and treatment

For sample size bias, we used the formula:
$$\left(\frac{\pi_1(100-\pi_1)+\pi_2(100-\pi_2)}{(\pi_2-\pi_1)^2} \right) f(\alpha, \beta)$$
, and we estimated that the effective rates of method of routine nursing care is about 60% (rate of cases with no occurrence of no lymphedema), and about 90% for the method of CDT and rehabilitation exercise according to our previous experience. Thus, $\pi_1 = 0.6$, $\pi_2 = 0.9$, $\alpha = 0.05$, $\beta = 0.1$, $n_1 = n_2 = 38.5$. All patients were randomly divided into two groups using a computer-generated list by Rv. Uniform formula using SPSS software (SPSS Inc., Chicago, USA). All patients were consecutively enrolled during the study period within 24 h after the surgery. The control group included 56 patients who only received routine nursing care. The CDT group included 53 cases who received both CDT and rehabilitation exercise as well as health education. The treatment started from the first day after surgery.

For CDT, the patients received manual lymphatic drainage according to both reference and our own experience.^{16,17} Briefly, lotion was used on the affected limb and massage was conducted from the foot to the leg to make the lymph move. Then patients were asked to wear barrel bandage with a layer of cotton pad on the affected limb after manual lymphatic drainage. And the affected limb was bandaged under gradient pressure using low elastic bandage. The whole treatment lasted for 40 min. The patients received the treatment once a day for 20 d as a cycle. The treatment contained two cycles for 40 d.

For health education, the patients were asked to receive professional education to introduce the lymphedema and lymphatic return. And the physicians also emphasized how to avoid excessive lymph production, such as keeping skin clean and moist; wearing protective gloves when doing housework or gardening; wearing long sleeves or apply sunscreen to prevent skin sunburn; using insect repellent to avoid mosquito bites.

For rehabilitation exercise, patients were asked to receive full range exercise of hip joint. Briefly, patients were under supine position and relaxed for 1 min. Then patients would perform ankle flexion, dorsiflexion, varus and valgus, following with 360° surround motion. Then, patients were asked to perform flexion and extension of the knee joint, straight leg raising, flexion and extension of the hip joint, adduction and abduction. At last internal rotation and external rotation were also performed. The whole above motions were repeated for 15–20 times once. And the patients were asked to perform twice one day, at morning and night for each.

For both groups, routine nursing care and postoperative treatment were performed, including infection prevention, physical activities under the guidance of nursing, and psychological counseling.

Follow-up was conducted by telephone and outpatient visit. The treatment lasted for 40 d. The follow-up lasted for 1 year for all patients. The lower extremity lymphedema was examined by the criteria of the 2016 consensus document of the International Society of Lymphology.¹⁸

2.3. Subjective scores for lower extremity lymphedema

For subjective scores, we designed a simple scale for patients' lower extremity lymphedema. The list was designed for 4 points, heaviness of lower limbs, pain, numbness and dysfunction (limited joint movement and difficulty in walking). For each point, 0 represented no feeling and 5 represented the heaviest feeling. Two physicians were asked to do the examination in different time points of one day and the mean value was considered as the result. The subjective scores were measured before the treatment, as well as at 1 month, 3 months, and 1 year after treatment.

2.4. Measurement of diameter of low limbs

The diameter of low limbs (both thighs and calves) was also measured before the treatment, as well as at 1 month, 3 months, and 1 year after treatment. The thigh diameter was measured at the position of 10 cm above the patella. And the calve diameter was measured at the position of 5 cm above the ankle joint.

2.5. Measurement of quality of life and cancer related fatigue

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) was used for measurement of patients' quality of life 3 months and 1 year after the treatment. The EORTC QLQ-C30 included three subscales of the general health scale (EORTC QLQ-C30-GHS), the function scale (EORTC QLQ-C30-FS, including cognitive function, social function, emotional function, body function, role function) and symptom scale (EORTC QLQ-C30-SS, including fatigue, pain, nausea, vomiting, insomnia, dyspnea, anorexia, constipation, financial difficulties, diarrhea). For EORTC QLQ-C30-FS and EORTC QLQ-C30-SS, the mean value of all the scores were recorded. The Brief Fatigue Inventory (BFI) was used for measurement of cancer-related fatigue 3 months and 1 year after the treatment.

2.6. Statistical analysis

Continuous data were expressed by mean \pm SD. Chi square test was used to compare the counting materials and rates. Comparison between two groups was performed using the Student t-test. Kaplan–Meier curve was used for measurement of lymphedema free time. $P < 0.05$ was considered as statistically significant. All calculations were made using SPSS 22.0.

3. Results

3.1. Basic clinical characteristics for all patients

The present study included 109 cases who received operation of cervical cancer, endometrial cancer or ovarian cancer with 56 patients in the control group and 53 cases in the CDT group. The flow chart of the study was shown in Fig. 1, all patients who quit the study or lost follow-up were already excluded. Among all patients, 41 (37.61%) cases were with cervical cancer, 34 (31.19%) cases were with endometrial cancer and 34 (31.19%) cases were with ovarian cancer. The follow-up lasted for 1 year for all patients (Table 1). For surgical types of the patients, the cervical cancer patients received modified radical (mainly for FIGO IIA patients) or radical hysterectomy and pelvic lymphadenectomy according to patients' condition, and laparoscopic surgery was only used for FIGO IIA patients if proper (3 cases in the CDT group and 4 cases in the control group); endometrial cancer patients received radical hysterectomy plus bilateral pelvic lymphadenectomy; ovarian cancer patients received primary debulking surgery. No significant difference was found between the two groups.

3.2. Lower extremity lymphedema incidence, subjective scores and diameter of low limbs

To determine the efficiency of CDT and rehabilitation exercise for prevention of lower extremity lymphedema, the lower extremity lymphedema incidence was recorded within the whole study period, and subjective scores and diameter of low limbs were measured and collected. As shown in Table 2, lower extremity lymphedema occurred in 8 (15.09%) cases of CDT group, with a

Table 1
Basic clinical characteristics for all patients.

Variables	CDT group, n = 53	Control group, n = 56	P
Age, year	54.56 \pm 12.50	56.96 \pm 11.76	0.305
BMI, kg/m ²	23.66 \pm 2.37	23.78 \pm 2.20	0.776
Cancer type, n (%)			0.614
Cervical cancer	20 (37.73)	21 (37.50)	
Endometrial cancer	15 (28.30)	19 (33.93)	
Ovarian cancer	18 (33.96)	16 (28.57)	
FIGO stage, n (%)			0.882
II	25 (47.17)	27 (48.21)	
III	28 (52.83)	29 (51.78)	
Lymphadenectomy, n (%)			0.595
Yes	45 (84.91)	49 (87.50)	
No	8 (15.09)	7 (12.50)	
Radiotherapy, n (%)			0.972
Yes	33 (62.26)	35 (62.50)	
No	20 (37.74)	21 (37.50)	
Chemotherapy, n (%)			0.674
Yes	42 (79.25)	43 (76.79)	
No	11 (20.75)	13 (23.21)	

significant lower incidence rate than 18 (32.14%) cases of control group ($P = 0.014$ by Chi square test). The incidence time of lymphedema ranged from 6 (3–10) months for CDT group and 6 (1–11) months for control group. K-M curve showed the lymphedema free time of CDT group was significantly longer than the control group ($P < 0.05$, Fig. 2). The subjective scores for heaviness of lower limbs, pain, numbness and dysfunction, as well as the diameters of both thighs and calves were lower in the CDT group at 3 months and 1 year, however the difference was not significant (Tables 2–3). These results indicated that treatment of early CDT combined with rehabilitation could reduce the incidence of lower extremity lymphedema.

3.3. Quality of life and cancer related fatigue

At last, we compared the EORTC QLQ-C30 scores and BFI scores between the two groups of patients. Results showed that the EORTC QLQ-C30-GHS and EORTC QLQ-C30-FS scores were significantly higher, while EORTC QLQ-C30-SS scores were significantly lower in the CDT group ($P < 0.05$, Table 4). And the CDT group showed

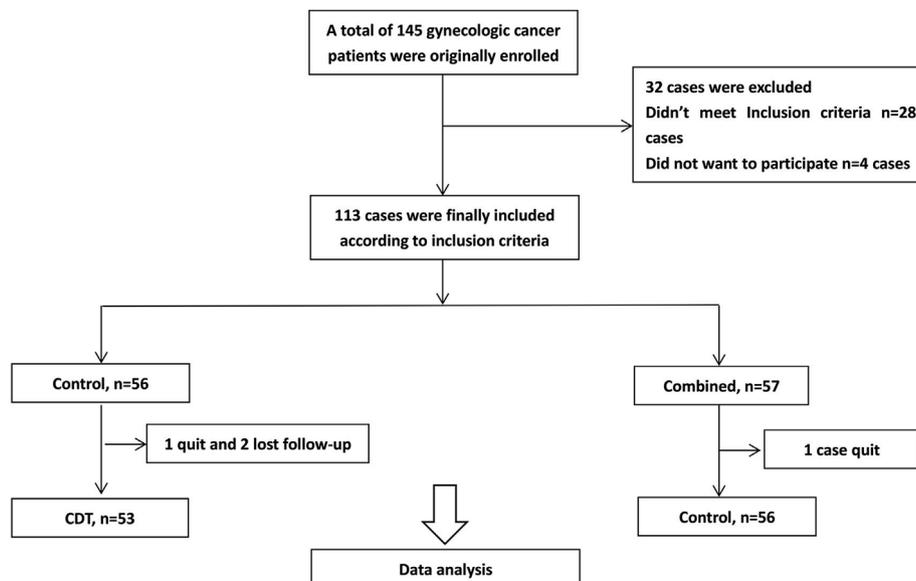
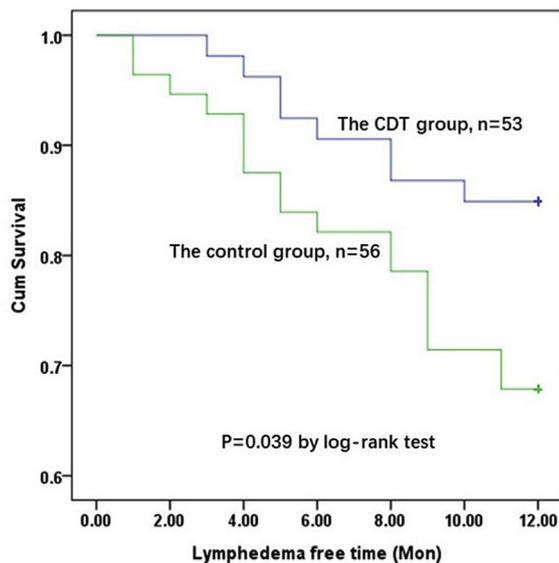


Fig. 1. Flow chart of the study.

Table 2
Subjective scores of low limbs.

Variables	CDT group, n = 53	Control group, n = 56	P
Heaviness			
Before study	1.16 ± 1.03	1.41 ± 0.98	0.216
1 mon	1.13 ± 0.83	1.46 ± 1.00	0.064
3 mon	1.24 ± 0.91	1.41 ± 0.94	0.357
1 y	1.52 ± 1.33	1.94 ± 1.51	0.131
Pain			
Before study	1.20 ± 0.90	1.28 ± 0.96	0.665
1 mon	1.28 ± 0.76	1.41 ± 1.20	0.513
3 mon	1.07 ± 0.91	1.39 ± 1.27	0.140
1 y	1.24 ± 1.29	1.53 ± 1.09	0.209
Numbness			
Before study	1.32 ± 0.80	1.16 ± 1.02	0.367
1 mon	1.18 ± 0.80	1.41 ± 1.14	0.246
3 mon	1.22 ± 0.86	1.46 ± 1.15	0.230
1 y	1.64 ± 1.31	1.92 ± 1.45	0.283
Dysfunction			
Before study	1.24 ± 0.89	1.30 ± 1.00	0.751
1 mon	1.00 ± 0.89	1.25 ± 1.03	0.181
3 mon	1.05 ± 0.86	1.39 ± 1.20	0.098
1 y	1.45 ± 1.06	1.78 ± 1.53	0.194

**Fig. 2.** K-M curve of the CDT and control groups.

markedly lower BFI scores than the control group ($P < 0.05$). These results suggested that the early application of CDT and rehabilitation exercise might also enhance the quality of life and reduce cancer related fatigue of the patients after gynecologic cancer surgery.

Table 3
Diameter of low limbs.

Variables	CDT group, n = 53	Control group, n = 56	P
Thighs, cm			
Before study	31.30 ± 4.47	30.25 ± 3.96	0.197
1 mon	30.79 ± 4.66	30.35 ± 4.37	0.616
3 mon	30.75 ± 4.70	30.80 ± 4.83	0.957
1 y	31.28 ± 4.63	33.14 ± 6.01	0.074
Calves, cm			
Before study	49.86 ± 4.75	51.03 ± 4.97	0.214
1 mon	50.28 ± 4.90	50.50 ± 5.30	0.825
3 mon	50.09 ± 4.93	50.35 ± 5.66	0.797
1 y	51.43 ± 6.46	52.10 ± 5.70	0.780

4. Discussion

Despite the surgical and chemotherapy methods for treatment of cancer, the extremity lymphedema after cancer operation is still a problem. Nowadays, many methods are used for treatment of extremity lymphedema. Cornelissen et al reported the efficacy of lymphatico-venous anastomosis in treatment of lymphedema and found lymphatico-venous anastomosis could lead to markedly improvement in quality of life and a high rate in stocking discontinuation.¹⁹ Mark et al showed that liposuction is effective in treatment of lymphedema.²⁰ Wen et al demonstrated that leukotriene B 4 antagonism could improve experimental lymphedema in both mice model and *in vitro*.²¹ However, most references focused on upper limb extremity lymphedema which occurred after breast cancer operation. Among the methods, the complex decongestive therapy is as widely used strategy to improve extremity lymphedema. However, few studies focused its application on prevention of lower limb extremity lymphedema. In the present research, we reported that early treatment of CDT combined with rehabilitation exercise reduced the incidence of lower limb extremity lymphedema, enhanced patients' life of quality and reduced patients' fatigue after surgery of gynecologic cancer.

CDT can be used in many conditions for treatment of extremity lymphedema. Sezgin et al showed CDT could improve upper limb functions in patients with breast cancer-related lymphedema.²² In a recent study, Cacchio et al demonstrated that CDT combined with diosmin, coumarin, and arbutin could enhance the efficacy of CDT alone in treatment of postoperative upper extremity lymphedema in breast cancer patients.²³ In advanced cancer, CDT was also effective for lymphedema in palliative care patients.²⁴ In this research, we demonstrated that the early application of CDT could reduce the incidence of lower limb extremity lymphedema for patients after gynecologic cancer surgery. Besides, CDT could also enhance patients' life of quality and reduce patients' fatigue. All these results indicated that CDT treatment has the potential as a preventive method for postoperative lymphedema.

Studies for rehabilitation exercise to treat cancer patients are also reported in several researches. Goo et al reported that rehabilitation program could improve patients' cardiopulmonary function, muscle strength and quality of life, and would not aggravate the lymphedema.²⁵ Do et al found that CDT combined with complex rehabilitation could enhance the patients' life of quality and improved lower-limb lymphedema for patients after gynecological cancer.²⁶ In the present research, we introduced a full range exercise of hip joint to improve patients' recovery. Besides, the combination of CDT and rehabilitation exercise showed good efficacy for prevention of extremity lymphedema.

The present study also has some limitations. The sample size of the research is limited and the study cases are from a single center.

Table 4
Quality of life and cancer related fatigue.

Variables	CDT group, n = 53	Control group, n = 56	P
EORTC QLQ-C30-GHS			
3 mon	69.71 ± 7.79	66.82 ± 6.70	0.022
1 y	69.24 ± 7.30	66.0 ± 6.46	0.016
ORTC QLQ-C30-FS			
3 mon	19.22 ± 5.05	21.83 ± 4.96	0.008
1 y	19.58 ± 4.49	23.67 ± 3.50	0.000
EORTC QLQ-C30-SS			
3 mon	64.18 ± 6.41	61.19 ± 6.27	0.015
1 y	65.43 ± 6.8	61.58 ± 5.82	0.002
BFI			
3 mon	2.33 ± 1.09	2.80 ± 1.18	0.036
1 y	2.18 ± 1.07	2.87 ± 1.16	0.002

The prevention effects are mainly from CDT or rehabilitation exercise need to further confirm. Whether combination of medications could further enhance the efficacy for treatment of extremity lymphedema is also unclear. All these need more studies to confirm.

In conclusion, this prospective randomized controlled study demonstrated that early treatment of CDT combined with rehabilitation exercise could reduce the incidence of lower limb extremity lymphedema, improve patients' quality of life and reduce the cancer-related fatigue. This study might provide more clinical evidence for application of CDT and rehabilitation exercise in treatment of postoperative extremity lymphedema for cancer patients.

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