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DOES INITIAL ROUTINE USE OF A COMPRESSION GARMENT REDUCE THE RISK OF LOWER LIMB LYMPHEDEMA AFTER GYNECOLOGICAL CANCER TREATMENT? A RANDOMIZED PILOT STUDY IN AN ASIAN INSTITUTION AND REVIEW OF THE LITERATURE

Y.K. Hnin, L.X. Ong, C.C.-C. Tsai, S.S. Ong, S.G. Yee, B.A. Choo, J.J.H. Low

Division of Gynaecologic Oncology (YKH,JJHL) and Department of Radiation Oncology (BAC) National University Cancer Institute; Department of Rehabilitation (LXO,CCCT,SSO,SGY), National University Hospital, Singapore

ABSTRACT

This is a randomized pilot study evaluating the effectiveness of customized compression garments (CG) in reducing the risk of lower limb lymphedema (LLL) in gynecological cancer patients. Patients who completed pelvic node dissection or radiation were routinely educated on reducing the risk of LLL by good skin care and manual lymphatic massage. After baseline lower limb volume perometry and clinical assessment, they were randomized to customized compression garment (CG) for 6 weeks (26 patients) or observation (30 patients). Both groups were followed up for 2 years and the primary outcome was the development of LLL. LLL incidence in the control group was 13.3% (4 of 30 patients) compared to 7.7% (2 of 26 patients) in the CG group. However the difference was not statistically significant (P=0.496). In the control group, 10.7% (3/28) who underwent node dissection developed LLL vs 7.7% (2/26) in the CG group. Among patients with node dissection plus radiation, LLL incidence was 14.3% (1/7) in the control group vs 12.5% (1/8) in the CG group. The mean onset of LLL was 12 months; compliance to CG wearing was high and QOL scores were similar in both groups. Customized low-compression CG worn for 6 weeks may have a possible benefit in reducing the risk of LLL when added to patient education on risk reduction although statistic significance was not achieved in this small pilot study. A larger multi-center study would be justified to expand these findings.

Keywords: Lower limb lymphedema, gynecologic cancer, compression garments, perometry

Pelvic or inguinal lymphadenectomy is standard of care in primary surgical staging in appropriate cases of cervical, uterine, ovarian, and vulvar cancers due to the risk of regional nodal metastases. Pelvic or inguinal radiation also plays an important role in the primary or adjuvant treatment of gynecological cancers. Despite the good oncological outcomes of such established treatment modalities, post-treatment sequelae are not insignificant, in particular the morbidity and disability resulting from lower limb lymphedema (LLL) which can have long term impact on the quality of life of survivors. Issues of limb and lower pelvic discomfort, heaviness, difficulties with physical mobility and pain along with financial implications and cost of treatment arise (1). It erodes a woman's sense of full recovery,

provokes loss of self-esteem, and may deepen anxiety and depression. Advances in functional imaging and sentinel node technology have helped minimize lymphadenectomy or radiation to a certain extent only. As such, risk reduction and management of LLL remains an area of high priority where lymphadenectomy and pelvic/inguinal radiation are still vital parts of gynecological cancer treatment.

In a survey of 803 gynecologic cancer survivors, Beesley et al found that a significant proportion of women experienced LLL, with the highest prevalence (36%) among vulvar cancer survivors and the lowest prevalence (5%) among ovarian cancer survivors (2). Another cohort study by Ryan et al noted that the diagnosis of LLL was made in 18% of the study population of gynecological cancer patients, and as high as 47% among vulvar cancer patients (3). Lymphedema has been reported to occur within days and up to 30 years after treatment for breast cancer (4). Eighty percent of patients experience onset within 3 years of surgery, while the remainder develop edema at a rate of 1% annually (5). In the study by Ryan et al, 84% developed LLL within the first 12 months (3).

It is well understood that risk reduction and early detection of lymphedema are key in its management. In its early mild stages, lymphedema must be managed appropriately to prevent the condition from progressing to the advanced and chronic stage where it is debilitating and irreversible. The gold standard in the treatment of lymphedema is complex decongestive therapy (CDT) which includes manual lymphatic drainage, compression bandages, and compression garment, but there is no consensus on how to best reduce the risk of its onset. A Cochrane review in 2004 evaluated 3 well-designed randomized studies on physical therapies to reduce lymphedema of the limbs and concluded that wearing of compression garment was beneficial but there is weak evidence to support the additional use of multi-layer bandaging (6). The study conducted by Lee et al recommended the use of custom-made compression garments in lymphedema management (7). Only 1 trial included patients with LLL (8). There is a paucity of well-designed studies specifically looking at risk reduction of LLL in gynecological cancer patients. In addition, such measures that are effective for the upper limbs may not necessarily be sufficient for the lower limbs which are in a dependent position far more than the arms and bear the full weight of the patient. Therefore, the primary risk reduction of LLL remains a major challenge. This study aims to evaluate the effectiveness of customized compression garments (CG) in reducing the onset of LLL in gynecological cancer patients in an Asian academic institution.

MATERIAL AND METHODS

A randomized pilot study was carried out among gynecological cancer patients at the Division of Gynaecologic Oncology, National University Cancer Institute Singapore (NCIS), between June 2014 and Dec 2016. Approval was obtained from the Ethics Committee of National University Health System, Singapore and the study was funded by a grant from NCIS. Participants were selected based on the following selection criteria:

Eligibility Criteria

1. All patients who have undergone pelvic and/or inguinofemoral lymph node dissection for gynecological malignancy
2. All patients who have completed whole pelvis and/or inguinofemoral radiotherapy for gynecologic malignancy

Exclusion Criteria

1. Congenital or pre-existing lower limb lymphedema prior to cancer diagnosis
2. Acute cellulitis of the lower abdomen, mons pubis, or lower limb
3. Lower limb paralysis
4. History of compromised arterial blood flow of the lower limbs

Eligible participants were recruited after detailed explanation of the study and obtaining written consent. Using random block design, participants were randomly allocated into two groups, (1) Compression garment (CG) group – early intervention with customized CG, and (2) Control (Non CG) group – without early intervention of CG. Development of lymphedema of lower limbs (unilateral or bilateral) was the primary outcome in this study. Clinical data was collected from the hospital electronic medical records.

Intervention

At completion of surgical or radiation treatment, all patients of both groups were seen by the team physiotherapists and occupational therapists to counsel and educate the patient on lymphedema, including precautions to reduce the risk of developing lymphedema through skin and nail care as well as exercises to promote lymphatic drainage. Participants were taught how to perform manual lymphatic drainage for their lower limb by physiotherapists. A lymphedema advice booklet was also given to each patient.

All patients underwent a baseline limb volume assessment. The Perometer 400T (Juzo®, Cuyahoga Falls, OH) used in this study is an optoelectronic volumetry device developed to calculate limb volume (LV) using infrared light. The perometer maps a three-dimensional graph of the limb using numerous rectilinear light beams. A three-dimensional image of the limb is generated from the data and LV is calculated using a modification of the disc method. The data is then used to calculate the LV. A clinical assessment is also made at baseline to exclude any pre-existing lymphedema.

Quality of life was accessed with tumor-specific FACT (Functional Assessment of Cancer Therapy) questionnaire for all patients as baseline and at each assessment point. Two physiotherapists and 2 occupational therapists carried out interventions together with the attending gynecological oncologist. The physiotherapists and occupational therapists involved in the study had specialized experience and training in LLL treatment. Only study members were aware of group allocations. The study was not blinded on both sides, except that subjects were randomly allocated at the beginning.

Compression Garment (CG) Group

Patients randomized to the early intervention (CG) group were reviewed by the occupational therapist at the beginning of study and individually-tailored customized CG were made for each patient which extends from waist to ankles (*Fig. 1*). The CG is made of a single layer of Powernet® fabric (Fabric number P-11117, material composition Nylon 68% and Spandex 32%) and the estimated compression level of the garment is approximately

Fig. 1. Example of customized compression garment utilized in the study

14-21 mmHg. Patients were told to wear the CG for at least 6 weeks. They were also asked to fill in the frequency and duration of wearing CG each day in a log book. A one-time questionnaire collecting their feedback regarding the CG was completed at the end of 6 weeks.

Follow-up

The patients were reviewed by the study team every 3 months in the first year and then every 4 months in the second year. At each visit, limb volume assessment with perometer and clinical assessment for lymphedema, as well as quality of life was assessed. On alternate visits, reinforcement on lymphedema education and physiotherapy management was given to all participants of both groups.

Diagnosis of LLL

The best method for LLL diagnosis has not yet been established. However the most accurate method of diagnosis is still based on physical examination performed by an experienced lymphedema specialist (9). For the purpose of this trial, objective volumetric assessment was calculated using infrared optoelectronic perometer. Perometric diagnosis of LLL is defined as the whole perometer percentage change >15% (10). The eventual diagnosis or exclusion of LLL was based on clinical assessment by the study team. This was especially important in mild cases of lymphedema with clinically obvious pitting edema but insufficient increase in perometer volume to meet the 15% criteria.

Statistical Analysis

Descriptive statistics (counts, percentages) were used to summarize demographic characteristics and all data were analyzed using SPSS version 22.0. Comparison of means between test and control groups and differences in proportions were tested with Chi-square test. Based on a background prevalence of 15-20% of LLL, allowing 3% dropout and power of 90% to detect a difference of 20% in the rate of LLL between intervention and control groups, a sample size of 90 would be required, however, the study accrued only 27 and 31 subjects in each group due to limited recruitment rate.

RESULTS

A total of 58 patients were recruited into the study from June 2014 to Dec 2016. Of these, 27 were randomized to CG group and 31 to the control (non-CG) group. One patient from each group dropped out of the study after the initial assessment visit, leaving 26 and 30 patients in each group, respectively.

Clinical Characteristics

Table 1 shows the demographic and clinical characteristics of both groups of patients. They were similar in terms of age, BMI, treatment characteristics, and follow up duration. *Table 2* shows the number of patients who developed LLL in both groups. The incidence of LLL in the control (non-CG) group (4 cases, 13.3%) appears higher than in the intervention CG group (2 cases, 7.7%). However, this difference was found to be not statistically significant (Odds Ratio 0.49, P=0.496).

In the control group, 3 out of 28 patients (10.7%) who underwent node dissection developed LLL, while in the CG group, the incidence was 7.7% (2 of 26). Among the patients who underwent both node dissection and pelvic radiation in the control group, 1 of 7 (14.3%) developed LLL whereas 1 of 8 (12.5%) in the CG group developed LLL. In both groups, the mean onset of LLL was within 12 months and all cases of LLL developed within 18 months. The likelihood of developing LLL was higher in patients with node dissection and radiation than with node dissection alone, as expected (5.6%, 9.5% vs 12.5%, 14.3%).

TABLE 1
Patient Characteristics

Demographic factors	CG group (n=26)	Control group (n=30)
Mean Age (range)	49.6 yrs (24-66)	47.8 yrs (27-66)
Mean BMI (range)	25.8 (18.5-33.7)	24.4 (18-35.6)
Primary cancer Cervix Uterus Ovary Synchronous (ovary and endometrium)	 2 (7.7%) 11 (42.3%) 12 (46.1%) 1 (3.9%)	 5 (16.7%) 14 (46.7%) 10 (33.3%) 1 (3.3%)
Stage 1 2 3 4	 23 (88.5%) 1 (3.8%) 2 (7.7%) 0	 22 (73.3%) 4 (13.3%) 4 (13.3%) 0
Treatment Pelvic LND alone Pelvic LND + chemotherapy Pelvic LND + Pelvic radiation Pelvic LND + Pelvic radiation + chemotherapy Pelvic radiation alone	 13 (50%) 5 (19.2%) 6 (23.6%) 2 (7.7%) 0	 13 (43.3%) 8 (26.7%) 6 (20.%) 1 (3.3%) 2 (6.7%)
Mean no. of lymph nodes removed (range)	46.5 (5-50)	23 (8-59)
Mean follow-up (months) (range)	29 (13-49)	22 (15-48)
LND - lymph node dissection		

TABLE 2
Incidence of LLL in Both Groups

	CG group (n=26)	Control group (n=30)
No. (%) with LLL	2 (7.7%)	4 (13.3%) (OR 0.49, P=0.496)
Mean age (yr) (range)	60.5 (60-61)	45.5 (36-54)
Mean BMI (range)	29.3 (26.6-32)	24.3 (16.9-32.5)
Stage 1 2 3 4	 1/23 1/1 0/2 0/0	 1/22 2/4 1/4 0
Treatment LND without Radiation LND with Radiation Radiation without LND	 1/18 1/8 0/0	 2/21 1/7 1/2
Mean onset (mth) (range)	10.5 (6-15)	8.3 (6-12)
Unilateral	0	3
Bilateral	2	1

Compliance and Patient Feedback on Compression Garments

Patients in the intervention group demonstrated good compliance in terms of wearing the CG supplied. Six patients (23.1%) wore the CG every day and 81% wore the CG for at least 5 days per week (*Table 3*). In terms of duration of usage, 84.6% wore it for more than 7 hours per day. A mean of 71.8% of the patients (range 17%-21%) gave positive feedback (rated "Good" or "Great") on the benefit, cosmesis, comfort, color, design and quality of the customized compression garments. The most common complaint was the CG being hot, itchy or tight to wear in our warm and humid weather.

TABLE 3
CG Usage – Frequency per Week and Average Duration per Day

Frequency of usage per week	No. (%)
2-3 days/wk	2 (7.7%)
>4 days/wk	3 (11.5%)
>5 days/wk	12 (46.2%)
>6 days/wk	6 (23.1%)
Non-respondents	3 (11.5%)
Average duration per day	**No. (%)**
>10 hr	11 (42.3%)
>7 hr	11 (42.3%)
3-6 hr	1 (3.8%)
Non-respondents	3 (11.5%)

Quality of Life Scores

Table 4 shows the mean and range of FACT (Functional Assessment of Cancer Therapy) QOL scores for both the CG and control groups at each assessment point. Both groups had similar QOL scores along all the assessments points.

TABLE 4
Mean and Range of FACT Quality of Life Scores in the Two Groups at Each Assessment Point

Mean QoL Score (Range)	CG group		Control group	
	Mean Score	Range	Mean Score	Range
Visit 0	139.8	104-170	140.5	89-171
Visit 1	143.2	92-170	148.2	108-172
Visit 2	145.2	109-170	153	123-172
Visit 3	153	124-172	154.6	118-172
Visit 4	155.4	117-172	157.1	136-172
Visit 5	158.3	133-172	156.6	140-172
Visit 6	156.8	125-172	157.5	140-172
Visit 7	158.6	128-172	156.4	133-172
Visit 8	161.1	147-172	156.5	140-172

DISCUSSION

LLL is a major source of morbidity in gynecological cancer patients who have undergone pelvic or inguino-femoral lymph node dissection and/or radiotherapy. Such treatments can cause the anatomical obliteration of lymphatic transport which is required to handle the presented load of microvascular filtrate including plasma protein and cells that normally leak from the bloodstream into the interstitium (11). Mild lymphedema can be managed but when more severe or chronic, treatment itself can be morbid, inconvenient and may need long care with psychosocial support.

The majority of research on lymphedema has been on the upper limb following treatment for breast cancer including lymphedema risk stratification for upper limb (12,13) and even a website for risk calculation (http://riskcalc.org/BreastCancerArmLymphedema/). Much less is known about LLL as an outcome of gynecological cancer treatment as there are fewer studies that focus on LLL. Its incidence in the literature ranges from 9-41% (14,15). The study from Sydney reported that 84% of women developed LLL in the first 12 months after treatment (3). Other retrospective studies have shown that 80% develop within 3 years of treatment (16,17). In our study, the incidence of LLL was 13.3% in the control group and the mean onset of LLL was 8.3 months with all patients developing it within 12 months. The lower incidence was likely due to the lack of patients with groin node dissection or radiation which would be at highest risk.

The sequelae of LLL are significant as it can erode a woman's sense of full recovery from gynecologic cancer, negatively affect her body image and self esteem, deepen depression and evoke anxiety issues about developing large body proportions (18,19). There are even fewer studies, if any, on the primary risk reduction of LLL in gynecological cancer patients in the Asian context. As such, this should be an area of high priority in cancers where lymphadenectomy or radiotherapy are a vital part of cancer treatment. In the area of breast cancer, primary risk reduction measures to avoid upper limb lymphedema, such as axillary lymph node staging with sentinel node biopsy instead of an axillary lymphadenectomy, have been very successful. The use of sentinel node biopsy in the staging of vulvar cancers, may also decrease the risk of developing lymphedema but vulvar cancer is relatively rare in Asia. Sentinel node mapping for endometrial carcinoma has become increasingly popular in recent years, however, the surgical management of endometrial cancer is still fraught with controversy. Questions still remain as to which approach is associated with the most useful information to guide adjuvant therapy, at the lowest cost of surgical morbidity, and ideally associated with the best survival (20). The technology is even less established in the other gynecological cancers like cervical and ovarian cancer which are common in Asia.

Some studies have evaluated surgical techniques in reducing LLL in gynecological cancers. In vulvar malignancy, a meta-analysis of the reported studies on sparing the long saphenous vein in inguinal node dissection suggests a reduced rate of lymphedema (21). Other authors have evaluated the role of prophylactic microsurgical lymphatic venous anastomosis after groin node dissection with resultant LLL rates of 7.4% (22) to 12.5% (23). A study from Sapporo, Japan evaluated the effect of preserving the circumflex iliac lymph nodes (CILNs) (24). The incidence and frequency of LLL was significantly lower in the preserved group than in the non-preserved group. While the authors concluded that this is a simple and effective approach for reducing the risk of LLL after lymphadenectomy, they also cautioned about the risk of leaving behind metastatic disease in the undissected CILNs. A proof-of-concept study evaluating the feasibility of identifying the lower-limb drainage nodes during pelvic lymphadenectomy for endometrial cancer (25) appears promising in preserving the lymphatic drainage pathways of the lower limbs decreasing the risk of LLL.

Traditionally, the non-surgical methods have been the mainstay of lymphedema risk reduction and treatment with more studies published on upper limb swelling. Upper body exercise has been found to be safe in women treated by axillary lymphadenectomy and evidence supports the use of prophylactic physiotherapy to reduce the onset of lymphedema (26,27). A single blinded clinical trial in women after axillary lymphadenectomy showed a significant reduction of lymphedema with manual lymphatic drainage (26). The Cochrane review which evaluated 3 well-designed randomized studies on physical therapies to reduce lymphedema concluded that wearing of compression garment was beneficial (6). The study by Lee et al recommended the use custom-made compression garments in lymphedema management (7). The author noted that inappropriate, ill-fitting garments contribute to an increase in edema and poor limb shape, associated with discomfort, intolerance and therefore non-compliance with wearing garments. The selection and fitting of the correct garment can therefore affect outcomes and the patients' quality of life.

A study published by Hansdorfer-Korzon et al found that class 1 compression garment could reduce the risk of truncal lymphedema on the operated side in females who underwent mastectomy and axillary node dissection. The results suggest that when properly fitted, class I compression corsets not only are an effective treatment for lymphedema but also could be used for reducing the onset of lymphoedema in patients who underwent node dissection or radiotherapy. In another randomized feasibility study using class 1 compression stockings after groin dissection, the incidence of clinically significant lymphedema was not different between both groups; however, there was a greater increase in mean leg volume in the control group (29). Stuiver et al published a randomized trial to assess the efficacy of class II compression stockings for the prevention of lymphedema in cancer patients following groin dissection (30). No significant differences were observed between groups in the incidence of edema or median time to occurrence. The authors did not state if the stockings were customized to fit individual patients' limbs.

The above data would seem to suggest that compression stocking should not only be customized for a proper fit to individual patients' limbs, the degree of compression may also play an important part. Compression level of 14-21mmHg (31-33) may be preferred over higher compression levels for primary risk reduction. One possibility is that these are less compressive in the normal limb and allow lymphatic circulation to establish new collateral channels from the lower limbs back to the central circulation. This should be contrasted with treatment of established LLL where there is evidence that high compression stockings (30-40 mmHg) are effective; generally, the highest level of compression that the patient can tolerate (20-60 mmHg) is likely to be the most beneficial for treatment as well as maintenance therapy (11).

In our study, the use of a properly customized 14-21 mmHg compression garment worn for 6 weeks after treatment resulted in a 7.7% incidence of LLL compared to 13.3% in the control group. Although the incidence appears lower than the control group, it was not statistically significant (OR 0.49, P=0.496) most likely due to the low prevalence and a larger cohort would be needed to achieve statistical power. The mean onset of LLL was roughly similar in both groups 10.5 months vs 8.3 months. The CG were well tolerated and compliance rate among users was high despite our warm climate, most likely due to counselling and the customized fitting for each patient. Another shortcoming is that our CG omits the foot, beginning compression at the ankle. Although this made the CG more comfortable and functional increasing compliance, it may contribute to edema in the foot without any compression on that area. For future study, we will consider including a pair of compression socks as well.

The sample size of this pilot study is too small to draw any statistical conclusion

but there may be still a possible benefit for customized CG in reducing the risk of LLL in gynecological cancer patients. The results are also in support of other published data. A larger multi-center study would be justified to expand these findings. A larger study population will also allow for stratification of variables like weight gain and patient activity level which could have a confounding effect on the outcome. With the development of evidence-based risk mitigation and patient selection, high risk patients can be identified for early referral and treatment.

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CONFLICT OF INTEREST AND DISCLOSURE

All authors declare no competing financial interests exist.

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A/Prof Jeffrey Low
Division of Gynaecologic Oncology
1E Kent Ridge Road,
NUHS Tower Block level 12, Dept of O&G
Singapore 119228
Tel: +65 6772 2682
Fax: +65 67794753
Email: Jeffrey_Low@nuhs.edu.sg