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Incidence of Lower Limb Lymphedema in Post therapeutic Gynaecological Malignancies

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ABSTRACT

Introduction: Lower limb lymphedema (LLL) is one of the most disabling side effects of surgical and radiotherapy treatment for gynecological cancers (carcinoma of the cervix, carcinoma of the ovary, carcinoma of the endometrium, and carcinoma of the vulva). The incidence of lymphedema varies in gynecological cancers and patients undergoing radiotherapy and surgery. This prospective study aims to determine the incidence of lower limb lymphedema after surgery and radiotherapy in gynecological malignancies.

Methodology: A total of 512 subjects who undergo treatment for gynecological malignancies in the department of surgical oncology and / or radiotherapy were screened to find out the incidence of lymphedema by measuring limb circumference with inch tape and extracellular fluid (ECF) volume with bio-impedance analyzer at four intervals, before surgery/ radiotherapy, after surgery/radiotherapy, three months follow-up and six months follow-up. The limb circumference and ECF were used to find out the lymphedema.

Results: Turkey's pairwise comparison test was carried out to determine the incidence of lymphedema in both subjects (radiotherapy & surgery). The percentage of incidence of lymphedema in subjects who have undergone radiotherapy and surgical treatment with gynecological malignancies is 18.94% overall.

Conclusion: Many subjects developed lymphedema with post-treatment gynecological malignancies. It causes significant functional problems, emotional disturbances, adversely affecting the quality of life, and it also causes a financial burden to the family. Lymphedema can be diagnosed initially using a Bio-impedance analyzer and inch tape to minimize the complications and progression of the disease.

Keywords: Gynaecological malignancy, Bio-impedance analyzer, lowers limb lymphedema, incidence, extracellular fluid, limb circumference.

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INTRODUCTION

Lymphedema is an excessive accumulation of high protein fluid (lymph) in the interstitial spaces due to a disruption in regular lymphatic transport [1]. The lymphatic system is an open circulatory system and is essential for normal body functions; its role is to recover fluid passed into interstitial tissue from capillaries and carry it back to the systemic circulation. The lymphatic system functions are fluid balance, removal of plasma proteins, cellular debris, and immune defense mechanism.

The lymph is transported through the lymphatics primarily by the cyclic contraction of lymph capillaries, and the movement of lymph from distal to is influenced by the contraction and relaxation of muscles proximally. The lymphatics are absent in the brain, spinal cord, retina, bone, and cartilage. The lymph passes through several lymph nodes; during its movement, the first lymph node is called sentinel lymph node [2]. Lymphedema is a chronic disease that develops due to defects in lymph production or lymph transport, or lymph node dysfunction. Lymphedema can be divided into two types - primary lymphedema due to a defect in lymphatic system development and secondary lymphedema due to surgery, parasite infection, cancer, etc.

The most common cause of secondary lymphedema in cancer patients is lymph node excision in metastasis or post-radiation therapy fibrosis [3]. The distal leg part is affected initially, with proximal extension occurring without sparing feet. The initial symptom is usually painless swelling and a feeling of heaviness in the limb, especially at the end of the day. On examination, the swelling is seen as pitting edema, with time fibrosis in sub-cutaneous tissues causing nonpitting sign, i.e., stemmer sign positive (the inability to pinch the skin of dorsum of second toe between thumb and index finger) [4,5].

The risk factors for developing lower limb lymphedema [LLL] are the number of lymph nodes removed, the sight of lymph nodes removed, obesity, age, level of physical activity, mode of surgery, etc. The incidence of lymphedema is also influenced by number of lymph nodes removed during surgery [1, 6]. In addition, the incidence of lymphedema in endometrial cancers is 1.2-47%, cervical cancers 0-55%, ovarian cancers 4.7-4.8%, and vulvar cancers 30-70% [7].

The risk of developing LLL was more in vulvar cancers (47%) when compared to ovarian cancer (27%), uterine cancers (18%), and cervical cancers (18%) [3]. The mean time from surgery and/or radiotherapy to the occurrence of LLL was 4.6 months in ovarian cancer patients, 4.2 months in cervical cancer patients, and 6.8 months for endometrial cancer patients. Physiological studies like lymphoscintigraphy or lymphangiography help diagnose lymphedema. Clinically several methods are available to assess the lymphedema occurrence, i.e., plethysmography (water displacement measurement), limb circumference measurement, perometry, bio-electrical impedance analysis, etc.

In the limb circumference method, the limb is kept

in a horizontal position, and the measurement of the circumference of a limb is at specific landmarks [12]; afterward, the total circumference can be converted into the volume by using the formula. Perometry is an optoelectronic measuring method using infrared radiation light that passes perpendicular to the leg to measure the excessive volume and gives accurate results to find out lymphedema. A bio-impedance analyzer can measure the extracellular fluid volume, which passes current with different frequencies transmitted into the tissues. This method is beneficial for diagnosing early lymphedema [14].

The management of lymphedema consists of correct diagnosis, staging of lymphedema, and patient education. The treatment for lymphedema includes surgical and non-surgical methods. The surgical techniques include physiological and reductive methods, i.e., lymphatic venous anastomosis, lymph node transfer, lymphadenectomy, liposuction, etc. These physiological procedures try to restore the normal lymphatic flow by creating new connections between the lymphatic and venous systems. In addition, complete decongestive therapy (CDT), which includes Manual lymphatic drainage, pneumatic compression therapy, compression bandaging, skin care, compression garments, and lymphatic exercises, has effectively treated lymphedema⁴. The present study is conducted to determine the incidence of lower limb lymphedema in different types of gynecological malignancies.

Study design: Prospective randomized study

Study population: The subjects who came to the surgical oncology and radiotherapy departments were screened for biopsy-proven malignancy of Ca. Cervix / Ca. Ovary / Ca. Vulva / Ca. Endometrium

Study setting: From the departments of surgical oncology & radiotherapy.

Ethical considerations: The present study is approved by the ethical committee, SVIMS, Tirupathi (No-1084 of 2020).

Study duration: The present study was conducted for two years, i.e., from December 2020 to November 2022.

Inclusion criteria: Subjects with biopsy-proven gynecological malignancies (Ca. endometrium, Ca. cervix, Ca. ovary, Ca. vulva), undergoing surgery and /or radiotherapy, age: 35-65 years, unilateral lymphedema (left or right) were included for the study.

Exclusion criteria: Subjects who are not willing to participate in the study, age below 35 yrs and above 65 yrs, history of treatment for any cancer, Patients who have had prior lower extremity vascular surgery, history of chronic lower limb swelling, Neo-adjuvant chemotherapy and Pre-existing lower limb lymphedema were excluded from the study.

Materials: Non-elastic Inch tape to measure the lower limb circumference at prefixed reference points on a wooden board in centimeters and a Bio-impedance analyzer [N20]

to measure the extracellular fluid volume in liters.

METHODOLOGY

All the subjects were undergone an initial assessment of measuring limb circumference with inch tape at five reference points (i.e., 10 cm below the lateral malleolus, 10cm above, 20 cm above, 30 cm above, and 40 cm above the lateral malleolus over the prefixed reference points on the wooden board respectively (figure-1) and extracellular fluid (ECF) volume by using bioimpedance analyzer (fig -2), the parameters are measured before giving the treatment.

The values of limb circumference and extracellular fluid were measured in all the subjects after surgery at the time of discharge, after completing the radiotherapy treatment, and after three months and six months of follow-up, respectively. Suppose there is any change in limb circumference >2cm difference with inch tape at any level during a reassessment or a 20% increase in ECF volume with a bioimpedance analyzer. In that case, the subject is diagnosed with lymphedema. Based on the clinical findings staging of lymphedema according to the International Society of Lymphology as mentioned below (Table-1).

Table 1: According to the International Society of Lymphology, lymphedema can be classified into four stages [7].

Stages		Presentation
0	latent /subclinical condition	No noticeable swelling
		No pitting
		A feeling of heaviness
		Existing months/years before over-swelling occurs
I	Spontaneously reversible (Acute phase)	Pitting swelling
		Visible swelling, edema
II	Spontaneously irreversible (chronic phase)	Pitting swelling
		Hardened and thickened tissue
III	Lymphostatic Elephantiasis (End stage)	Absence of pitting swelling
		Enlarged and obvious swelling of the affected limb
		Hardness , thickness and toughness of skin
		Lymph leaking through damaged skin

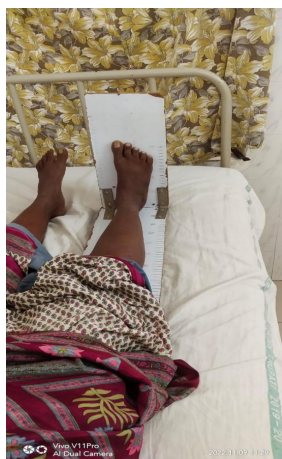


Figure: 1



Figure: 2

Figure (1, 2): The above figures show the measurement of limb circumference at five different reference points with the Non-elastic inch tape using a wooden board and extracellular fluid volume with a bioimpedance analyzer.

The present study, 512 subjects were screened from the radiotherapy and surgical oncology departments. The subjects with Ca cervix, Ca ovary, Ca endometrium, and Ca vulva are 324, 140, 37, and 11, respectively (Bar diagram). Among the 512 subjects, 265 patients underwent surgery (51.57%), 124 patients underwent radiotherapy (24.21%), and 123 patients underwent both surgery and radiotherapy (24.02%). Among the 324 subjects of Ca. Cervix, 62, among 140 patients of Ca ovary, 27, among 37 patients of Ca endometrium, six and among 11 patients of Ca vulva, two developed lymphedema (Table-2).

Table 2: Different types of gynecological malignancies with types of treatment and development of lymphedema in each type of malignancy.

Type of malignancy	Treatment type	Lymphedema developed	%	Total
Carcinoma cervix (324)	Radiotherapy(109)	21	19.26	62
	Surgery(105)	20	19.04	
	Radiotherapy& surgery(110)	21	19.09	
Carcinoma ovary (140)	Surgery(140)	27	19.28	27
Carcinoma endometrium(37)	Radiotherapy(4)	01	0.25	06
	Surgery(20)	02	0.1	
	Radiotherapy& surgery(13)	03	23.07	
Carcinoma vulva(11)	Radiotherapy(11)	02	18.18	02
Total-512				97

Data Analysis and Results

The collected data is entered in Microsoft Excel for tabulation and analysis. Statistical analysis is carried out by using IBM SPSS 19.0 version software. All subjects' mean age was 53.27 years, and their BMI was 23.25. 'Turkey' s pairwise comparison test was carried out to determine the incidence of lymphedema in both subjects (radiotherapy & surgery). In addition, a comparison of limb circumference and extracellular fluid volume at four-time intervals was made for all the subjects (table 4&5).

In the present study, subjects undergoing surgery and/or radiotherapy were taken to determine the incidence of lower limb lymphedema. From baseline to 6 months follow up in patients undergoing surgery and radiotherapy. As mentioned in the above graph, radiotherapy patients had more ECF than surgery. At level 1, there is a significant change in the limb circumference from the baseline after six months of follow-up in subjects with radiotherapy/surgery. At levels 2 and 3 compared to baseline, the limb circumference increases significantly after 3 and 6

months of follow-up. At level 4, compared to baseline and discharge, there is a significant change in limb circumference after 3 and 6 months. At level 5, there is a mild change in limb circumference from baseline to 6 months follow-up. Although the extracellular fluid volume gradually increased from baseline to 6 months follow-up in both radiotherapy and surgery subjects, more change was observed in radiotherapy compared to surgery. The percentage of incidence in Ca cervix – 19.13%, Ca endometrium - 16.21%, Ca ovary – 19.28%, and Ca vulva – 18.18% (Table-3). The incidence rate is higher in the cervix and ovary subjects than in the ovary and vulva.

Graph 1: Development of lymphedema among each gynecological malignancy:

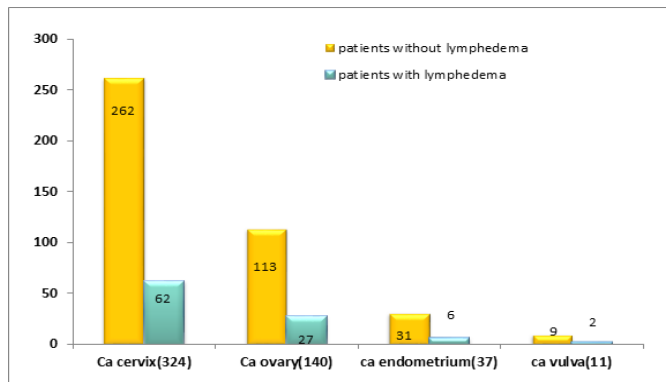


Table 3: The below table shows the incidence of lower limb lymphedema in different cancers with respective to the time period of 2 years.

Type Of Cancer	Total Screened	Incidence Of Lymphedema	Incidence % (Without Time Period)	Incidence % (Inclusion Of Study-2 Years)	Incidence Rate Out Of 1000 Subjects (Inclusion Of Study-2 Years)
Ca .Cervix	324	62	19.136	9.57	96
Ca .Endo-metrium	37	6	16.216	8.11	81
Ca .Ovary	140	27	19.286	9.64	96
Ca .Vulva	11	2	18.182	9.09	91

Graph 2: Shows ECF values across various timelines among subjects who have undergone surgery/ radiotherapy

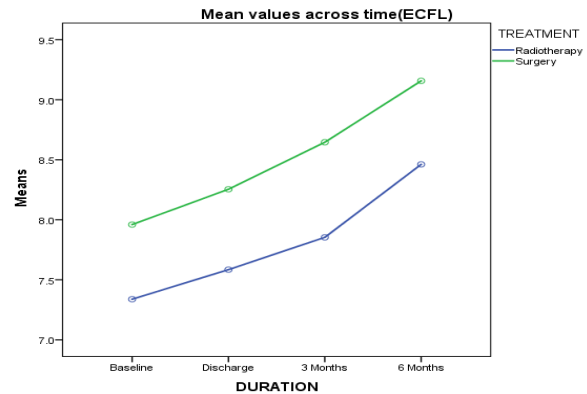


Table4: Table represents mean and standard deviation values of limb circumference at five levels and ECF volume at 4-time intervals in subjects who underwent surgery

		Surgery							
		BASE LINE		DISCHARGE		3 MONTHS		6 MONTHS	
LEV-ELS	POSI-TIONS	MEAN	STD	MEAN	STD	MEAN	STD	MEAN	STD
L1	RIGHT	20.667	1.373	20.694	1.369	21.250	1.556	21.694	1.670
	LEFT	20.714	1.619	20.629	1.592	20.914	1.502	21.343	1.662
L2	RIGHT	19.667	2.084	20.028	2.591	20.139	1.959	20.889	2.039
	LEFT	19.543	2.034	19.886	2.553	20.057	1.999	25.971	3.634
L3	RIGHT	25.417	3.565	25.444	3.597	25.639	3.634	26.194	3.512
	LEFT	25.457	3.567	25.457	3.567	25.771	3.590	25.971	3.634
L4	RIGHT	28.556	4.010	28.556	4.010	28.611	4.009	28.778	3.972
	LEFT	28.714	4.149	28.686	4.192	28.829	4.183	29.086	4.224
L5	RIGHT	32.000	3.950	32.000	3.950	32.000	3.950	32.222	3.758
	LEFT	32.143	3.866	32.143	3.866	32.200	3.976	32.400	3.972
ECF (L)		7.960	1.259	8.254	1.152	8.646	1.114	9.157	1.130

Table 5: Table represents mean and standard deviation values of limb circumference at levels and ECF volume at 4 time intervals in subjects who underwent radiotherapy

		Radiotherapy								F-value	p value
		BASE LINE		DISCHARGE		3 MONTHS		6 MONTHS			
LEVELS	POSITIONS	MEAN	STD	MEAN	STD	MEAN	STD	MEAN	STD		
L1	RIGHT	20.231	1.945	20.231	1.945	20.731	1.867	21.231	1.883	82.023	0.000*
	LEFT	20.231	1.681	20.231	1.681	20.615	1.813	21.308	1.995	76.136	0.000*
L2	RIGHT	19.654	2.331	19.692	2.346	20.038	2.218	20.846	2.395	66.149	0.000*
	LEFT	19.538	2.533	19.577	2.501	20.038	2.391	26.423	4.130	416.8	0.000*
L3	RIGHT	25.500	3.952	25.462	3.911	25.462	3.911	25.962	3.955	40.885	0.000*
	LEFT	25.577	4.130	25.615	4.167	25.846	4.106	26.423	4.130	45.187	0.000*
L4	RIGHT	28.654	4.223	28.654	4.223	28.731	4.220	28.962	4.209	21.118	0.000*
	LEFT	28.885	4.493	28.885	4.493	28.962	4.503	29.231	4.394	24.365	0.000*
L5	RIGHT	32.654	4.749	32.654	4.749	32.654	4.749	32.692	4.748	5.504	0.022*
	LEFT	32.423	4.768	32.423	4.768	32.500	4.844	32.615	4.784	16.274	0.000*
ECF(L)		7.338	0.876	7.585	0.772	7.854	0.723	8.462	0.764	406.225	0.000*

DISCUSSION

Lower lymphedema [LLL] is a chronic condition affecting women treated for gynecological malignancies. It can be asymptomatic or symptomatic, like limb heaviness, pain, decreased range of motion of joints, discomfort, and difficulty in daily activities. Lymphedema due to cancer treatment arises from anatomical obliteration during operative procedures or irradiation of the cancer area. Injury to the pelvic lymphatic system affects excess fluid absorption and decreases membrane permeability, accumulating fluid and proteins in extracellular spaces with consequent swelling [6,7]. Chronic edema can lead to cellular fibrosis, and prolonged pooling of proteins causes cellulitis and lymphangitis [9]. LLL causes functional problems that negatively affect gynecological cancer survivors' daily living, work, emotional state, and overall quality of life. The LLL also affects psychological, such as anxiety and depression.

Prevention and early detection of lymphedema in patients undergoing treatment for gynecological malignancies should be an integral part of comprehensive cancer therapy [6]. Lymphedema may cause a significant burden to the patients, family, and health care system because it is chronic and incurable [9]. Noori Khalid et al. [10] 201 studied the incidence of lower limb lymphedema after a year follow-up period, which was 43.5%. Hopp EE et al. 2016 studied that the incidence of lower limb lymphedema was 12.8% in endometrial cancers [11]. Kiey et al. 2012 stated that pelvic node dissection increased the risk of lower limb lymph edema after surgery compared to no pelvic node dissection [12]. Rustrum A et al. 2007 stated that the number of lymph nodes removed greater than 10 increases the risk of lower limb lymphedema in uterine cancers. Fuller et al. documented that the removal of greater than 25 lymph nodes leads to the development of lower limb lymphedema in cervical cancers. Bigla N et al. [7] in 2017, studied the incidence of lymphedema in endometrial cancers is 1.2 -47%; in cervical cancers, it is 0-55%; in ovarian cancers, 4.7-4.8% and vulvar cancers 30-70%.

Therefore, lymphedema is gradually increasing in patients with gynecological malignancies. Among the 97 subjects, 59 had Grade-2 lymphedema, and 38 had Grade-1 lymphedema. In addition, among the 97 subjects, 74 developed unilateral lymphedema, and 23 developed bilateral lower limb lymphedema. Most subjects who developed bilateral lymphedema were due to the removal of pelvic and iliac lymph nodes during the surgery. Removing both iliac and pelvic lymph nodes increases the risk of developing lower limb lymphedema.

The above studies also state that the incidence of lymphedema is higher in patients undergoing surgery/radiotherapy, which is in line with the present study. The early identification of lymphedema can be done through regular follow-up of the patients and patient education about lymphedema before the treatment. In our study, the incidence of lower limb lymphedema was 18.94% (39% are

grade-1 and 61% grade-2).

CONCLUSION

A significant percentage of subjects developed lymphedema with post-treatment gynecological malignancies. The overall percentage of incidence of lymphedema in the present study is 18.94%. The incidence of lymphedema is more in cervical and ovarian cancers when compared with the other types.

A bio-impedance analyzer or inch tape can identify early detection of lymphedema and helps to minimize the progression of lymphedema. In addition, the patient's education about lymphedema in the initial phase of treatment is also important to minimize the complications like infections and trauma, which will help the cancer survivors lead better lives.

Conflict of interest: Nil

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Limitations

1. Extended follow-up may be required to determine surgery and/or radiotherapy complications.
2. The collected samples are not equal (i.e., fewer subjects are present in carcinoma endometrium and vulva).
3. The quality of life of subjects with lymphedema needs to be evaluated.

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