

# Associated risk factors of lower limb lymphedema after treatment of cervical and endometrial cancer

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**Abstract.** The scope of the study was to identify the associated risk factors of lower limb lymphedema development in cervical and endometrial cancer patients. We retrospectively analysed 326 patients: 186 cases (57.06%) with cervical cancer and 140 cases (42.94%) with endometrial cancer were treated in Surgery, Radiotherapy, Oncology and Gynaecology Clinics of 'St. Apostle Andrew' Emergency Clinical Hospital Galați over 9 years. Adjuvant radiotherapy was performed in 83.57% of endometrial cancer cases. Adjuvant chemotherapy was

performed in 45.16% of cervical cancer cases. Over 10 lymph nodes were removed in 74.73% of cervical cancer patients. Incidence of lymphedema was 15.05% in cervical cancer patients and 10% in endometrial cancer patients,  $P=0.06$ . Analysed risk factors for lower limb lymphedema occurrence were: Age, disease stage, radiotherapy, number of invaded lymph nodes (for cervical cancer patients), number of removed lymph nodes (for cervical cancer patients) and obesity. Multivariate analysis for associated risk factors of lower limb lymphedema development in cervical cancer showed that number of removed lymph nodes,  $OR=2.109$  (0.907-4.903),  $P<0.0001$ , number of lymph nodes with metastasis,  $OR=1.903$  (0.253-4.332),  $P=0.004$  and obesity,  $OR=1.713$  (0.226-2.967),  $P=0.006$  were found as statistically significant risk factors for lower limb lymphedema onset. For endometrial cancer patients, obesity,  $OR=1.518$  (0.721-2.75),  $P=0.0003$ , was the only associated risk factor with statistical significance for the lower limb lymphedema development. Lower limb lymphedema represents one of the adverse reactions of multimodal treatment in gynaecological cancers which affects patient's quality of life. Lower limb lymphedema occurrence is related with number of risk factors, the most important being removed lymph nodes, obesity and radiotherapy.

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*Abbreviations:* 95% CI, confidence interval; BMI, body mass index; BSO, bilateral salpingo-oophorectomy; BT, brachytherapy; CC, cervical cancer; CMT, chemotherapy; CT, computed tomography scan; EC, endometrial cancer; HR, hazard ratio; LA, lymphadenectomy; LLL, lower limb lymphedema; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio;  $\rho$ , PCC, Pearson correlation coefficient; PALA, para-aortic lymphadenectomy; PLA, pelvic lymphadenectomy; RT, radiotherapy; S, surgery; TAH, total abdominal hysterectomy; vs., versus

*Key words:* gynaecological cancers, endometrial cancer, cervical cancer, lymphedema, risk factors

## Introduction

Gynaecological cancers represent 16.3% of total malignant diseases, cervical cancer (CC) and endometrial cancer (EC) being the most common. The main therapeutic options are surgery (S) with pelvic lymphadenectomy (PLA) with or without para-aortic lymphadenectomy (PALA) and chemotherapy (CMT), external beam radiotherapy (RT), brachytherapy (BT). Lymphadenectomy with or without PALA is used in different stages. The association PLA with PALA increases the probability of adverse reactions.

Lower limb lymphedema (LLL) represents one of most debilitating adverse reactions occurring after multimodal

treatment of gynaecological cancers, surgery and radiotherapy. For many cases of gynaecological neoplasia, lymphadenectomy represents a part of the staging being in integral part of surgery, and this procedure is associated with LLL. In literature, incidence of lymphedema varies in very large limits, 1-67% after multimodal treatment (S, RT, CMT). These very large limits are due to lack of common criteria for lymphedema evaluation. Specialty literature uses many ways to define lymphedema, in arbitrary mode, from non-symptomatic to symptomatic lymphedema. The first published study trying to define lymphedema was by Kim *et al* (1) published in 2017. In this study the computed tomography scan (CT) for abdomen and pelvic areas was used as screening test for LLL occurrence (1). Among risk factors mentioned for LLL occurrence are number of removed lymph nodes, iliac lymph node excision, and adjuvant radiotherapy.

The present aimed to identify the risk factors associated with LLL occurrence after multimodal treatment for patients with cervical cancer and EC.

In general, lymphedema is caused by obstruction or interruption of lymphatic drainage, in distal segment, due to infections and malignancies. LLL represents a chronic complication and can lead to physical and psychological suffering (1,2) being one of the most important causes of poor quality of life in patients with gynaecologic malignancies after multimodal treatment (1). Lymphedema can be complicated by inflammation, infection, local skin or mucous membrane changes (including microbiome changes). The drugs used for treatment of lymphedema (systemic diuretics, tonic drugs for lymphatic vessels), AINS, or topical treatments (3,4) or for its complication (infections, comorbidities, pain) are also sometimes the source of adverse reactions with associated poor quality of life (5,6).

## Patients and methods

This is a retrospective study with 326 patients, 186 (57.06%) with CC and 140 (42.94%) with EC treated in the Surgery, Radiotherapy, Oncology, Gynaecology Departments of 'St. Apostle Andrew' Emergency Clinical Hospital (Galați, Romania), between 01/01/2007 and 31/12/2015. The study was approved by the Ethics Committee of 'St. Apostle Andrew' County Emergency Clinical Hospital. Informed consent was obtained from each patient prior to investigations, treatment and participation in the study. Patients with stage IIIB or IV disease, with other synchronous neoplasia, who presented lymphedema before surgery for pelvic cancer, with secondary neoplastic lesions, with profound venous thrombosis or who did not present at follow-up medical visits were excluded from study. Informed consent was obtained for each patient (7,8). The median follow-up period was 54 months (range 12-108 months).

Patients with lower limb volume increase >5% compared with the other lower limb were considered to have lymphedema. Clinical and therapeutic parameters are showed in Tables I and II, respectively.

**Statistical analysis.** Patient characteristics were compared using parametrical test, Student's t-test, Z-test (function of group size, for mean comparison) and non-parametrical

Mann-Whitney U test (for median comparison) (Table I). Multivariate logistic regression analysis was used to assess the risk factors associated as independent for occurrence of post-treatment LLL. Pearson's correlation coefficient (PCC) was used for bivariate correlation test. Statistical significance was set at  $P \leq 0.05$ . The statistical calculations were performed using XL-STAT software.

## Results

Median age was 53.5 years in CC group vs. 63 years in EC group ( $P < 0.0001$ ). Stage IIB of disease predominated in the CC group (78.49% of cases) and in EC group, the patients with stage II disease were more frequent (83.57% of cases). Squamous carcinoma was the most frequent histology in CC (82.8% of patients) vs. adenocarcinoma in EC (89.29% of cases),  $P < 0.0001$ . Tumor grade G2 predominated in both groups. Obesity was found in 10.22% of patients in CC and in 28.57% of cases in EC,  $P = 0.06$ .

Patient characteristics were compared using parametrical test, Student's t-test, Z-test (function of group size, for mean comparison) and non-parametrical Mann-Whitney U test (for median comparison) (Table I).

All CC patients underwent surgery, total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) and lymphadenectomy (LA). All EC patients underwent surgery, TAH with BSO without LA. Adjuvant RT was performed in 23.66% of CC patients and 83.57% of EC patients. BT was administered to 96.24% of CC patients and 16.43% of EC patients. None of EC patients received CMT and in CC group, adjuvant CMT was performed in 45.16% of the cases. In CC, 74.73% of cases had  $\geq 10$  lymph nodes removed and 25.27% of cases had  $< 10$  lymph nodes removed. In this group, 88.71% of patients had  $< 10$  lymph node metastasis and only 21 patients (11.29%) had  $\geq 10$  lymph node metastasis (Table II).

Comorbidities are presented in Table III. High blood pressure was the most frequent associated comorbidity found in 13.98% of CC patients and in 49.29% of EC patients. Obesity was present in 28.57% of EC cases and in 10.22% of CC cases. Other frequently associated comorbidities were diabetes mellitus type II in 24.29% of EC cases and secondary anaemia in 26.34% of CC patients. Coronary disease was finding in 9.14% of CC cases. Two CC patients were pregnant at the time of diagnosis (9).

The incidence of LLL was 15.05% of CC patients and 10% of EC cases,  $P = 0.06$ . LLL was unilateral in all patients enrolled in this study. In cervical cancer patients, 55.9% had left LLL and 44.09% had right LLL; the median time of LLL occurrence post-surgery was 4.5 months (range 2-18 months). In the EC group, 54.29% had left LLL and 45.71% had right LLL; the median time of LLL post-surgery occurrence was 2 months (range 1-4 months).

Univariate analysis for associated risk factors of LLL development in CC revealed that age under 50 years ( $P = 0.05$ ), neoadjuvant RT ( $P < 0.001$ ) and  $\geq 10$  lymph nodes with metastasis ( $P = 0.05$ ) were found to be the predictive risk factors with statistical significance (Table IV). Due to the limit of significance level ( $P = 0.05$ ) some risk factors such as age, number of lymph node metastasis from univariate analysis, we performed also multivariate analysis for these parameters.

Table I. Clinical parameters.

Parameter	Cervical cancer N (%)	Endometrial cancer N (%)	P-value
Median age (years)	53.5 (24-83)	63 (27-82)	<0.0001
TNM stage			
IA	-	9 (6.43)	0.703
IB	30 (16.13)	14 (10)	
IIA	10 (5.38)	Stage II: 117 (83.57)	
IIB	146 (78.49)		
Histopathology			
Squamous carcinoma	154 (82.8)	2 (1.43)	<0.0001
Adenocarcinoma	30 (16.13)	125 (89.29)	
Adenosquamous carcinoma	2 (1.08)	7 (5)	
Leiomyosarcoma	0	1 (0.72)	
Fibrosarcoma	0	5 (3.57)	
Grading			
G1	33 (17.74)	38 (27.14)	0.54
G2	59 (31.72)	75 (53.57)	
G3	94 (50.54)	27 (19.29)	
Obesity	19 (10.22)	40 (28.57)	0.06

N, number of cases.

Univariate analysis for associated risk factors of LLL development in EC group revealed that age >50 years ( $P<0.001$ ), adjuvant RT ( $P<0.001$ ) and obesity ( $P=0.001$ ) were found to be the predictive risk factors with statistical significance for LLL occurrence (Table V).

For patients with EC, LA was not performed, and consequently, the number of lymph nodes retrieved and numbers of metastatic lymph nodes were not analysed as independent risk factors.

Multivariate analysis for associated risk factors of LLL development in CC showed that number of removed lymph nodes, OR=2.109 (0.907-4.903),  $P<0.0001$ , number of lymph nodes with metastasis, OR=1.903 (0.253-4.332),  $P=0.004$  and obesity, OR=1.713 (0.226-2.967),  $P=0.006$  were found as statistically significant risk factors for LLL occurrence. The analytical method used was multivariate logistic regression. For EC patients, obesity, OR=1.518 (0.721-2.75),  $P=0.0003$ , was the only associated risk factor with statistical significance for LLL development (Table VI).

PCC for LLL indicates that the strongest correlation was found between LLL occurrence and number of removed lymph nodes for CC (PCC=0.713). The PCC values for CC cases also indicate a correlation between LLL occurrence and number of lymph nodes with metastasis, PCC=0.368 and obesity, PCC=0.163. In the EC group PCC values indicate strong correlation between obesity and LLL occurrence, PCC=0.689 (Table VII).

Comparative analysis of patients who developed LLL with cervical cancer vs. EC revealed that the only parameter that significantly varied was neoadjuvant RT, performed in

17.86% of CC cases with LLL vs. 100% of EC cases with LLL,  $P=0.01$ .

## Discussion

LLL represents one of the adverse reactions of multimodal treatment of gynaecological cancers (S, RT, CMT) which have a negative impact on quality of life. LLL has less known characteristics (time of occurrence, duration and evolution), is caused by a disruption/obstruction of the lymphatic system, in general, in proximal segment of thigh and is due to neoplasia and infections (10).

For many gynaecological malignancies, LA represents an integral part of staging and treatment and this procedure was associated with LLL occurrence. LLL incidence varies in very large limits in specialty literature, and is influenced by the gynaecological cancer sites; the highest incidence is in vulvar cancer and the lowest, in ovarian cancer (10).

A study by Ki *et al* (11), indicated the prevalence of LLL in cancer patients, function of anatomic origins: 9-70% in vulvar cancer, 1.2-47% in cervical cancer, 1.2-17.7% in EC and 7-40.8% in ovarian cancer.

The present study shows the involved risk factors of arm lymphedema occurring after breast cancer treatment are similar with risk factors which influence the LLL development after pelvic malignancies (12). These risk factors could be the number of removed lymph nodes and adjuvant radiotherapy.

A concrete method for lymphedema diagnosis has not yet been established. The physical examination performed by an experienced physician is the most common diagnostic

Table II. Therapeutic parameters.

Treatment performed total number of patients, N=326	Cervical cancer, N (%) N=186 (57.06%)	Endometrial cancer, N (%) N=140 (42.94%)
Surgery		
TAH+BSO+LA	186 (100)	140 (100) (without LA)
Radiotherapy		
Neoadjuvant	142 (76.34)	0
Adjuvant	44 (23.66)	117 (83.57)
BT	179 (96.24)	23 (16.43)
Chemotherapy		
Adjuvant	84 (45.16)	0
Neoadjuvant	0	
Number of removed lymph nodes		
<10	47 (25.27)	0
≥10	139 (74.73)	
Number of lymph nodes with metastasis		
<10	165 (88.71)	0
≥10	21 (11.29)	

TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; LA, lymphadenectomy; BT, brachytherapy; N, number of cases.

Table III. Associated comorbidities.

Associated comorbidities	Cervical cancer N=186 (%)	Endometrial cancer N=140 (%)
High blood pressure	26 (13.98)	69 (49.29)
Diabetes mellitus type II	8 (4.3)	34 (24.29)
Obesity	19 (10.22)	40 (28.57)
Hepatitis	9 (4.84)	11 (7.86)
Cirrhosis	2 (1.08)	0
Renal lithiasis	2 (1.08)	0
Biliary lithiasis	2 (1.08)	4 (2.86)
Pulmonary tuberculosis	2 (1.08)	0
Thyroid diseases	3 (1.61)	2 (1.43)
Anxious depressive syndrome	2 (1.08)	1 (0.71)
Coronary disease	17 (9.14)	7 (4.29)
Pregnancy	2 (1.08)	0

N, number of cases.

method. A screening method for early LLL detection is not yet established. Kim *et al* (1) was the first to use computed tomography scan (CT) as screening instrument for LLL risk factor identification in patients who underwent surgery for LA pelvic neoplasia. In that study, 511 patients with pelvic malignancies (cervical, uterine, ovarian and vulvar cancers) were analysed. Of those patients, 106 (20.7%) were diagnosed with LLL. The results of their study indicate that the risk factors for LLL occurrence after LA in gynaecological cancers

could be the number of lymph nodes retrieved (median >30), adjuvant pelvic radiotherapy (P<0.001), surgical intervention (open surgery or laparoscopy), long operation time, not using of intermittent pneumatic compression (1). Criteria for diagnosis or screening of LLL by imaging tests have not yet been established. The authors used, in arbitrarily way, the mean difference of subcutaneous layer thicknesses between preoperative and postoperative (after 1 year) CT scans, for the 106 patients with LLL. The authors measured the subcutaneous layer thicknesses over the Sartorius muscle of the right anterior thigh of the level of lesser trochanter of femur (1). The reference value was 3.77±3.14 mm and value was used as grouping criteria of patients.

In a study performed by Kim *et al* (13), adjuvant RT was significant associated with LLL lymphedema in patients with stage IIA FIGO cervical cancer, who performed radical surgery with LA. Their study enrolled 707 patients, and 12.6% of cases developed LLL. Number of resected lymph nodes was not found as a risk factor with statistical significance for LLL occurrence. Adjuvant RT was found a predictive risk factor for LLL development (OR=3.47; 95% CI, 2.086-5.788). Their study also concluded that patients need to be informed before treatment on the possibility of LLL occurrence and on the ways to prevent it (13).

In previous studies, risk factor analysis for LLL incidence identified that pelvic LA is a statistically significant factor, after the malignant diagnosis, which can interrupt the lymphatic flow (14-17).

In the study of Tada *et al* (14), 694 patients with cervical, ovarian and ECs were analysed. Among uterine and ovarian cancer patients who underwent pelvic LA and post-operative radiotherapy (OR=1.79; 95% CI, 1.20-2.67; P=0.006) was statistically significantly associated with LLL development.

Table IV. Univariate analysis for associated risk factors of LLL development in CC group (186 cases).

Analyzed parameter	Non lymphedema 158 (84.95%)	Lymphedema 28 (15.05%)	P-value
Age (years)			
≤50	62 (39.24)	19 (67.86)	0.05
>50	96 (60.76)	9 (32.14)	
Neoadjuvant radiotherapy (N=142)	119 (75.32)	23 (82.14)	<0.001
Adjuvant radiotherapy (N=44)	39 (24.68)	5 (17.86)	0.57
Number of removed lymph nodes			
<10	38 (24.05)	9 (32.14)	0.06
≥10	120 (75.95)	19 (67.86)	
Number of lymph nodes with metastasis			
<10	145 (91.77)	20 (71.42)	0.05
≥10	13 (8.23)	8 (28.57)	

LLL, lower limb lymphedema; CC, cervical cancer; N, number of cases.

Table V. Univariate analysis for associated risk factors of LLL development in EC group (140 cases).

Analyzed parameter	Non lymphedema N=126 (90%)	Lymphedema N=14 (10%)	P-value
Age (years)			
≤50	8	0	<0.001
>50	118	14 (100)	
Obesity	29 (23.02)	11 (78.57)	0.001
Adjuvant radiotherapy	103 (81.75)	14 (100)	<0.001

LLL, lower limb lymphedema; EC, endometrial cancer; N, number of cases.

Table VI. Multivariate analysis for associated risk factors of LLL development.

Risk factors	OR (95% CI)	P-value
Cervical cancer		
Number of removed lymph nodes	2.109 (0.907-4.903)	<0.0001
Number of lymph nodes with metastasis	1.903 (0.253-4.332)	0.004
Obesity	1.713 (0.226-2.967)	0.006
Endometrial cancer		
Obesity	1.518 (0.721-2.75)	0.0003

LLL, lower limb lymphedema; N, number of cases.

Table VII. Pearson's correlation coefficient.

Correlated parameters	Pearson's correlation coefficient	
	Cervical cancer	Endometrial cancer
Number of removed lymph nodes	0.713	-
Number of lymph nodes with metastasis	0.368	-
Obesity	0.163	0.689

N, number of cases.

Pelvic LA was not found as a risk factor for occurrence of lymphedema.

A study by Abu-Rustum *et al* (18) identified  $\geq 10$  resected lymph nodes during surgery for EC, being a risk factor for development of LLL. Their retrospective study was conducted over a period of 12 years and analysed 1,289 patients with EC. LLL occurred 5.3 months after surgery (range 1-32 months). Median follow-up period was 3 years. Age, weight, type of surgery, type of adjuvant RT and stage were not associated with LLL occurrence. Patients who had  $>10$  regional lymph nodes resected seemed to be at most significant risk for occurrence of leg lymphedema, after surgery for EC.

Kuroda *et al* (19) retrospectively analysed 264 patients with gynaecologic malignancies. LLL developed after a median period of 13.5 months. Regression analysis revealed that body mass index, BMI  $\geq 25$  kg/m<sup>2</sup> (HR=1.616; 95% CI, 1.030-2.535), pelvic LA with PALA (HR=2.323; 95% CI, 1.126-4.794), adjuvant RT (HR=2.469; 95% CI, 1.148-5.310) and lymphocyte formation (HR=1.718; 95% CI, 1.120-2.635), were independently associated with LLL occurrence. The data from their study showed that the occurrence rate of LLL increases logarithmically, from 32.8% at 3 years to 47.7% at 10 years.

In 2011, Ohba *et al* (20) published an article which analysed risk factors for lower-limb lymphedema after surgery for cervical cancer. A total of 155 patients with cervical cancer were evaluated with a median follow-up of 6.1 years. Thirty-one patients (20.0%) developed LLL. Supra-femoral node dissection (OR=9.5; 95% CI, 1.2-73.3; P=0.031) and adjuvant RT (OR=3.7; 95% CI, 1.2-10.9; P=0.019) were found to be independent risk factors).

Regarding risk factors for LLL occurring after treatment of pelvic malignancy, there are contradictory data.

There are some studies which identify that number of resected lymph nodes was not found as an independent risk factor for LLL occurrence, such as the study of Tada *et al* (14) and of Kim *et al* (13).

There are studies which, contrarily, identified that number of resected lymph nodes was an independent risk factor for LLL occurrence (18,21).

In the present study, multivariate analysis identified for cervical cancer group, risk factors associated with development of lymphedema as the number of resected lymph nodes (P<0.0001), number of lymph nodes with metastasis (P=0.004), obesity (P=0.006) and for EC, the only statically-significant risk factor was obesity (P=0.0003).

LLL is a chronic, progressive and incurable condition which often leads to disability. A recent study by Mirandola *et al* (22) showed an improvement in lower limb swelling with ameliorated quality of life after the overall physical activity pathway. Cancer is a chronic disease that induces important changes to the functional capabilities of the patients, the body image and the social or family role of the patients causing further emotional problems. Therefore, the role of a multidisciplinary team is crucial in the management of the patients (23).

In conclusion, LLL represents an adverse reaction of multimodal treatment for pelvic neoplasia, affects the quality of life for women treated for gynaecology cancers and all patients must be informed, before treatment initiation, on the possibility of LLL occurrence after the treatment and on the prevention

methods. The incidence of LLL is related with numerous risk factors, with the most important being the number of removed lymph nodes, obesity and adjuvant radiotherapy.

Limitation of our study is the retrospective aspect, thus there are no survival studies.

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### Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

LFR and ORC contributed to the design of the study, participated in the entire review process and prepared the manuscript. DCV, MNL, DF and NM contributed to the literature research, and the analysis and critical interpretation of the data. GS, CS and MC conceived the study and revised the manuscript. All authors read and approved the final version of the manuscript.

### Ethics approval and consent to participate

The study was approved by the Ethics Committee of 'St. Apostle Andrew' County Emergency Clinical Hospital (Galați, Romania). Informed consent was obtained from each patient prior to investigations, treatment and participation in the study.

### Patient consent for publication

Not applicable.

### Competing interests

All the authors declare that they have no competing interests.

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