Risk factors for lower limb lymphedema in gynecologic cancer patients

after initial treatment

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Abstract

Background: Most studies on lower limb lymphedema have been conducted in gynecologic cancer patients who underwent surgery for gynecologic malignancy. This study aimed to evaluate the risk factors for lower limb lymphedema development in gynecologic cancer patients who underwent initial treatment.

Methods: A retrospective cohort design was used to follow 903 gynecologic cancer patients who underwent treatment at Kurume University Hospital between January 1, 2013 and December 31, 2015. Data analyses were performed in 356 patients, and the patients were followed up until December 31, 2017. The model comprised 2 components to facilitate statistical model construction. Specifically, a discrete survival time model was constructed, and a complementary log-log link model was fitted to estimate the hazard ratio. Associations between risk factors were estimated using generalized structural models.

Results: The median follow-up period was 1,083 (range: 3–1,819) days, and 54 patients (15.2%) developed lower limb lymphedema, with a median onset period of 240 (range: 3–1,415) days. Furthermore, 38.9% of these 54

patients developed lower limb lymphedema within 6 months and 85.2%

within 2 years. International Federation of Gynecology and Obstetrics stage,

radiotherapy, and number of lymph node dissections ($\geq$28) were significant

risk factors.

Conclusion: Simultaneous examination of the relationship between lower

limb lymphedema and risk factors, and analysis among the risk factors

using generalized structural models, enabled us to construct a clinical model

of lower limb lymphedema for use in clinical settings to alleviate this

condition and improve quality of life.

Keywords: Lower limb lymphedema, Risk factor, Gynecologic cancer

Introduction

Most research on lower limb lymphedema (LLL) has been conducted in

gynecologic cancer patients after surgery for gynecologic malignancy.

Although studies on the causes of LLL in Japan and abroad have been

conducted in recent years, research is still lagging compared to that on upper

limb lymphedema [1, 2]. Patients with LLL suffer psychological damage

due to motor function disorders and physical handicapping and may develop

severe complications, such as cellulitis, which significantly worsen quality

of life (QOL).

In previous studies, postoperative radiotherapy [3-13] and the number of

lymph node (LN) dissections [9-10, 12-19] were recognized as risk factors

for LLL; however, reported risk factors differ between studies [20-21].

Although lymphedema development appeared in a literature review,

statistical analysis should simultaneously include the relationship between

lymphedema onset and risk factors, and the relationship between risk factors,

to determine the risk factors for lymphedema. To date, no study has included

a prediction model including the relationship between risk factors [1, 22].

This study aimed to estimate the "survival curve" of LLL in gynecologic

cancer patients after initial treatment using 5-year follow-up records, and to

construct a clinical pathology model of LLL development based on structural equation modeling where risk factors associated with LLL incidence and clinically interpretable relationships between risk factors can be simultaneously examined.

Patients and Methods

Study design and data source

A retrospective cohort design was used to follow up 903 gynecologic cancer (cervical, endometrial, ovarian, and fallopian tube) patients who underwent treatment at the Kurume University Hospital Gynecology Department between January 1, 2013 and December 31, 2015. Finally, after a 3-year accrual period, data of 356 patients were used for analyses, and patients were followed up until December 31, 2017. Patients who underwent initial treatment for gynecologic cancer, including surgery, chemotherapy, radiotherapy, or any combination, were included. The exclusion criteria are described in Fig. 1.

The presence or absence and time of onset of LLL depended on the judgment of the attending physician. The physician in charge diagnosed LLL through physical examinations, including those for the presence of

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left-right difference in lower limb thickness. This study was conducted with

the approval of the Kurume University Ethics Committee (number: 14063).

Risk Factors

Data on 19 risk factors were obtained from hospital medical records; they

were grouped into internal and external risk factors to facilitate the

construction of statistical models, as shown in Table 1. Patients' age and

body mass index (BMI) were recorded at initial treatment.

Statistical Analysis

Risk factors were dichotomized to facilitate the interpretation of model

parameters. Age was dichotomized with patients' mean age value at initial

treatment. BMI, an index of obesity, was dichotomized as ≥ 25 kg/m^2, using

a clinically reasonable cut-off value. Cases were categorized according to

the International Federation of Gynecology and Obstetrics (FIGO)

guidelines into 2 categories by severity: stages I-II and stages III-IV. A tree

model was applied as a method of binary conversion of LN clearance and

the number of LNs dissected was categorized as ≥ 28 and <28. In a previous

study [8], 31 LN dissections were used as data cut-off values, and in this

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study, 28 or more were determined to be appropriate cut-off values. In clinical practice, LN biopsy or LN dissection is selected depending on the risk of cancer LN metastasis. Thus, the number of LN varies, depending on the location, but the number of LN dissections cannot be adjusted in each area. Therefore, the value for each LN area was set to two values that performed or not performed.

For univariate analysis, the Cox proportional hazard model was used to estimate the hazard ratio of each risk factor on the incidence rate of LLL. Multiple complex relationships between risk factors affect the incidence of LLL [1]. To model the complexity of LLL development, the structural equation modeling approach was employed to examine the impact of the risk factors. The model comprised components; the first one is the survival model which estimated the hazard of risk factors, and the second one represented the complex relationship between risk factors. Specifically, the discrete survival time model was constructed by partitioning the follow-up period into 180-day intervals. Additionally, the complementary log-log link model [23] was fitted to estimate hazard ratio, while the association between risk factors was estimated using generalized structural models (GSEMs). The outline of the GSEM is described in the appendix. Data analysis was

performed using the SAS 9.4 TS Level 1 M3 statistical software (SAS

Institute Inc., NC, USA), JMP Ⓡ Pro13.2.1 (JMP is a product of SAS,

located at A Campus Drive, Cray, NC, USA), Stata/MP 14.0 (StataCorp LP

4905 Lakeway Drive College Station, TX 77845 USA), and the R version

2.15.2 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 2 shows patient characteristics categorized by type of gynecologic

cancer. All 356 patients were Japanese, with a mean age of 58.4 years

(median, 59.0 years; range: 18–95 years) and mean BMI of 23.2 kg/m^2

(median, 22.4 kg/m^2; range: 14.1–47.6 kg/m^2). Mean age at first treatment

(median, range) for cervical carcinoma, endometrial carcinoma, and ovarian

cancer, including fallopian tube cancer, was 54.8 years (median, 49 years;

range: 30–81 years), 61.6 years (median, 59.5 years; range: 44–86 years),

and 57.7 years (median, 60 years; range: 46–83 years), respectively.

FIGO for staging gynecological cancer was 63% during stage I (225

patients) and 17 % during stage III (61 patients). The types of therapy were

surgery (34 patients), chemotherapy and radiotherapy (29 patients),

 radiotherapy (18 patients), or surgery and radiotherapy (17 patients).

Specifically, there are two types of radiotherapy: external beam irradiation

and intracavitary brachytherapy. Endometrial or ovarian cancer is externally

irradiated, and cervical cancer is irradiated externally or with radiotherapy

combined with external and intracavitary brachytherapy. External beam

irradiation can irradiate the lesion, uterus, vagina, and pelvic LN area from

outside the body. However, intracavitary brachytherapy can be performed by

concentrating a high dose at the lesion site using a radiation source from the

uterus or vagina, while suppressing the radiation dose of other organs. There

are differences in the type of radiotherapy depending on the type of cancer,

such as external beam irradiation for endometrial/ovarian cancer, and

external beam irradiation after surgery or intracavitary brachytherapy

combined with externa beam irradiation. Although detailed data are not

shown, differences in radiotherapy by cancer type were not found to directly

affect the development of LLL (OR, 0.79; p=0.56). External beam radiation

was performed for the entire pelvis; total dose was 45–50.4 Gy (1.8 Gy, 25–

28 Fr). Conversely, surgery and a combination of surgery and chemotherapy

were performed on 90% of patients with endometrial and ovarian cancer.

 The Kaplan-Meier survival curve is shown in Fig. 2 where the median

follow-up period for 356 patients was 1,083 days (range: 3–1,819 days). A

total of 54 patients (15.2%) developed LLL with a median onset period of

240 days (range: 3–1415 days). Furthermore, 38.9% of them developed LLL

within 6 months and 85.2% within 2 years. In this study, the follow-up

period was set from 720 to 1,800 days, but LLL occurred 3 days after the

first treatment. Also, 7 out of 302 patients who did not develop LLL had a

follow-up period of less than 100 days, for reasons such as transfer after

initial treatment.

Table 3 shows the distribution of risk factors among patients with and

without LLL. The hazard ratio for each risk factor was obtained from a

univariate Cox proportional hazard model, and 95% confidence intervals are

also shown in Table 3. FIGO stage (III-IV), radiotherapy, and number of LN

dissections (≥28) were significant, with the level of significance being less

than 5%. Generalized structure equation modeling was employed to

construct a clinical model as shown in Fig. 3. This clinical model consisted

of 2 components. The first was a discrete time survival model to estimate

the hazard ratio among risk factors. FIGO stage (HR, 2.3; 95% CI: 1.2–4.2),

radiotherapy (HR, 2.2; 95% CI: 1.1–4.5), and the number of LNs dissected

(≥28) (HR, 1.9; 95% CI: 1.0–3.5) were found to be significant risk factors

for LLL development. Cancer types, inguinal LN dissection, pelvic LN

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dissection, para-aortic LN dissection, and LN metastasis have an indirect

effect on the onset of LLL and have no direct effects.

The relationships between risk factors were modeled in the second

component. Since all endogenous risk factors were binary, as shown in Fig.

3, logistic regression models were used to evaluate the interrelationship

among risk factors. Standard treatment for each gynecologic malignant

tumor includes surgery, chemotherapy, radiotherapy, or any combination, as

shown in Table 2. Thus, although standard therapy differs depending on the

type of cancer, the results in Table 3 indicate that cancer type has no

influence on LLL. The odds of receiving radiotherapy were 42.4 times

higher in patients with cervical cancer than in patients with other types of

cancer (95% CI: 29.5–60.9). Similarly, the odds of receiving radiotherapy

were 6.4 times higher among patients with FIGO stages III-IV than in those

with stages I-II (95% CI 4.4–9.3). Table 3 shows the incidence of LLL at

LN excision sites was 17.5% (29/166) in patients with inguinal LN

dissection (95% CI 0.87-3.04), 17 % (34/200) in patients with pelvic LN

dissection (95% CI 0.86-3.53), and 18% (15/83) in patients with para-aortic

LN dissection (95% CI 0.75-2.60). However, as shown in Table 4, the

probability of removing each LN with 28 or more LN resections compared

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to less than 28 is 5.9 times higher with inguinal LN (95% CI: 4.4-8.0). It is

4.0 times higher in pelvic LN (95% CI: 2.7-5.9) and 2.8 times higher in

para-aortic LN (95% CI: 2.1-3.6). Similarly, patients with cervical cancer

were 1.6 times more likely than patients with non-cervical cancer to have 28

or more LN resections (95% CI 1.3-2.1). There was no difference in the

incidence of LLL by individual site, but it was higher in cases of 28 or more.

Total LN dissections indicates the intensity (thoroughness) of the dissection,

and it was confirmed that inguinal LN dissection was performed in cases

where thorough dissection was required. A high proportion of LLL was

observed when inguinal LN dissection was performed indirectly. Other odds

ratios are shown in Table 4. All parameter estimates in Table 4 were

obtained simultaneously based on GSEM.

Discussion

The accumulation of scientific information on the developmental history of

LLL has been delayed because priority was given to treating gynecological

cancer. Hence, this study main focused on reporting the incidence of LLL

development and its clinical risk factors based on sound scientific methods.

This study differs from previous reports in that the risk factors for LLL

development in patients treated for gynecologic cancer (cervical cancer, endometrial cancer, and ovarian cancer including fallopian tube cancer) were examined without limiting the treatment method. Although there are differences in standard treatment depending on the type of cancer, the results of the univariate analysis did not directly affect the occurrence of LLL according to type of cancer. Therefore, we analyzed the risk factors directly related to LLL occurrence, regardless of the type of cancer. As a result, the number of LNs dissected (≥28) was a significant risk factor for LLL development regardless of site and extent of LN dissection. Nine out of 54 cases of LLL showed recurrence. However, the relationship between recurrence as a pelvic mass and occurrence of LLL could not be denied in only one case of recurrence. Therefore, globally, it can be presumed that the occurrence of LLL is due to treatment. This result supports the notion that sentinel LN biopsies result in lower incidence of LLL by not performing unnecessary LN dissections. Sentinel LN is defined as a LN where cancer cells reach LN metastasis through the tumor and the lymph vessel connected to it. Therefore, if cancer metastasis has not occurred in the sentinel LN, it is believed that there is a high possibility that it has not spread to other LNs, and there is no other metastasis. Therefore, in order to reduce the number of

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LN resections recognized as a risk factor for the development of LLL less than 28, the presence of metastasis to sentinel LNs [29, 30] is confirmed, and the significance of dissection biopsy is high. In the future, sentinel LN biopsy should be actively introduced to reduce the incidence of LLL. According to the literature, there are limited records of patients after surgery. Although there are reports on the incidence and timing of postoperative LLL, there is no clear report on the incidence and timing of LLL in gynecologic cancer treatment after initial treatment, including treatments other than surgery.

For example, Kim et al. [5] reported 1-year and 3-year prevalence rates of 42.7% and 78.7%, respectively, with a median onset time of 11 months. Our 5-year follow-up records indicated similar prevalence rates based on the Kaplan-Meyer estimate. Additionally, Graf et al. [27] reported an estimated prevalence of LLL of 32% 1 year after surgery and 58% 8 years after surgery. Hareyama et al. [28] reported that the cumulative incidence of patients who underwent lymphadenectomy was 12.9% at 1 year, 20.3% at 5 years, and 25.4% at 10 Years. The reported risk factors from many previous studies [3–21, 27–28] were mainly based on postoperative patients with limited and specific treatments. In contrast to the findings from previous

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studies, we evaluate risk factors based on all patients who received initial

treatment for gynecologic cancer, where initial treatment was defined as

either surgery, chemotherapy, radiotherapy, or any combination therapy.

From the results of this study, regardless of the type of treatment, it is clear

that LLL occurs in about 15% of patients within 2 years of initial treatment.

Therefore, accurate information can be provided to patients.

Previous studies [3,6,9–21] have reported postoperative radiotherapy and

the number of LN dissections as risk factors for LLL. However, some

studies have reported that the location of the LN is a risk factor. For

example, Kuroda et al. [4] studied pelvic lymphadenectomy (PLA) in

patients with or without para-aortic lymphadenectomy (PALA) and reported

BMI ($\geq$25), PLA+PALA, and postoperative radiation therapy as the risk

factors. In contrast, Oba et al. [6] reported that suprafemoral node dissection

and postoperative radiation therapy are risk factors for the development of

LLL. However, a study on postoperative cervical cancer patients reported

that pelvic and para-aortic lymphadenectomy and the number of LNs are not

risk factors. Todo et al. [8] examined the effect of removing circumflex iliac

nodes up to the distal external iliac nodes (CINDEIN) in patients with

uterine corpus malignancies. It was reported that adjuvant radiation therapy,

resection of more than 31 LN, and removal of CINDEIN are risk factors for

the development of LLL. These findings were mainly based on

postoperative patients who received limited and specific treatment. Unlike

previous studies, this study included all patients who received initial

treatment for gynecologic cancer, regardless of surgery. This includes

patients who had been treated with chemotherapy or radiation therapy and

who had not undergone surgery. Therefore, it is speculated that

lymphadenectomy did not directly affect the development of LLL.

As shown in Table 2, although the maximum number of LN dissections in

cervical cancer is small, compared to those in endometrial cancer and

ovarian cancer, the average number of LN dissections in cervical cancer was

higher than that in cervical cancer and ovarian cancer. The reason is that

pelvic LN dissection is usually performed in cervical cancer, but in

endometrial/ovarian cancer, pelvic LN dissection or para-aortic LN

dissection may not be performed for low-risk patients who do not have

cancer metastasis at each LN site. In some cases, LN dissection was omitted,

and only LN biopsy was performed, and the reason for this study may be

that there were many low-risk patients with endometrial/ovarian cancer. LN

biopsy randomly collects one or two LNs to see if there is cancer LN

metastasis. However, LN dissection is performed when the cancer is likely

to have spread to it as the LNs in the cancerous area are removed for the

purpose of preventing recurrence; the number of LN dissection inevitably

increases. As shown in Table 3, LN excision and cancer type at each site did

not directly affect the onset of LLL. However, as shown in Table 4, when

each LN excision site and cancer type had 28 or more LN excisions it had

an indirect effect on LLL. Although detailed data are not shown here,

differences in surgery by cancer type were not found to directly affect the

development of LLL (Fisher's exact test $p = 0.57$). However, as shown in

Table 4, the incidence of LLL was high when there were 28 or more LN

dissections. Therefore, I thought that the model in Fig. 3 was appropriate.

The novelty of our findings on risk factors may be explained by the

different analytical approaches. Kimura et al. [1] suggested the importance

of considering the relationship between risk factors from a clinical

viewpoint. As risk factors were often highly correlated, multivariate Cox

regression analyses were likely faced with the issue of multi-collinearity.

The generalized structural equation model proved to be a useful analytical

tool to help avoid this difficulty and examine the relationship among risk

factors simultaneously.

The limitations of our study was single-center medical record data and the number of patients may have been insufficient to confirm the effects of cancer types. Another limitation is the lack of data on the severity and extent of LLL development.

In this study, the risk factors directly affecting LLL development were FIGO progression stage (III-IV), number of LNs dissected ($\geq$28), and radiotherapy (performed). Simultaneous examination of the relationship between LLL and risk factors, and among the risk factors using GSEM, enabled us to construct a clinical model of LLL development, which can be used in the clinical setting. It will also provide information to alleviate the incidence of LLL and improve patient QOL.

Conflicts of interest: The authors declare that they have no conflicts of

interest.

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Appendix: Fitting the Cox Proportional Hazard Model via the

Generalized Structural Equation Model

Let T_i be onset time of lymphedema for i-th patient $(i = 1,...,n)$. Onset time is interval censored if we only know event occored within time interval $\tau_{r-1} < T_i \leq \tau_r$ $(r = 1,...,m)$. If event or censoring occored in time interval a, hazard function $h(a)$ for i-th subject is defined as $h(a_i) = P(T_i = a_i | T_i > a_i - 1)$.

Then, i-th subject's contribution to the likelihood, L_i, is

$$L_i = \prod_{r=1}^{a_i} h(r)^{Y_{ir}} (1 - h(r))^{1-Y_{ir}}$$

Hear, Y_{ir} is an indicator variable defined as $Y_{ir} = 0$ if $r < a_i$ and $Y_{ir} = \delta_i$ if $r = a_i$ where δ_i is censoring indicator (=1 if onset lymphedema, otherwise= 0).

It can be shown that $\log\{-\log h(r \mid X_i)\} = \alpha_r + X_i'\beta$ if we assume proportional hazard model $h(r \mid X_i) = h_0(r)\exp(X_i'\beta)$ where X_i is a vector of risk factors, $\alpha_r = \log\{\log S_0(r) - \log S_0(r-1)\}$ and $S_0(r) =$ baseline survival function [24,25].

Let μ_{ir} is expectation of Y_{ir}, $E(Y_{ir}) = \mu_{ir}^{(Y)}$, then survival analysis of lymphedema is modeled as $g_1(\mu_{ir}^{(Y)}) = \alpha_r + X_i'\beta$ where g_1 is complimentary log-log link function. Effect of expogeneous risk facort W_i on endogenious risk factors X_i will be modeled as $g_2\left(\mu_i^{(X)}\right) = \gamma'W_i$ where $\mu_i^{(X)}$ is mean vector of X_i and g_2 is an appropriate link function for X. $\left\{g_1\left(\mu_{ir}^{(Y)}\right), g_2\left(\mu_i^{(X)}\right)\right\}$ are simulteniously modeled under genelazied structural equation models [26].

Fig. 1　Subject selection and follow-up flow diagram

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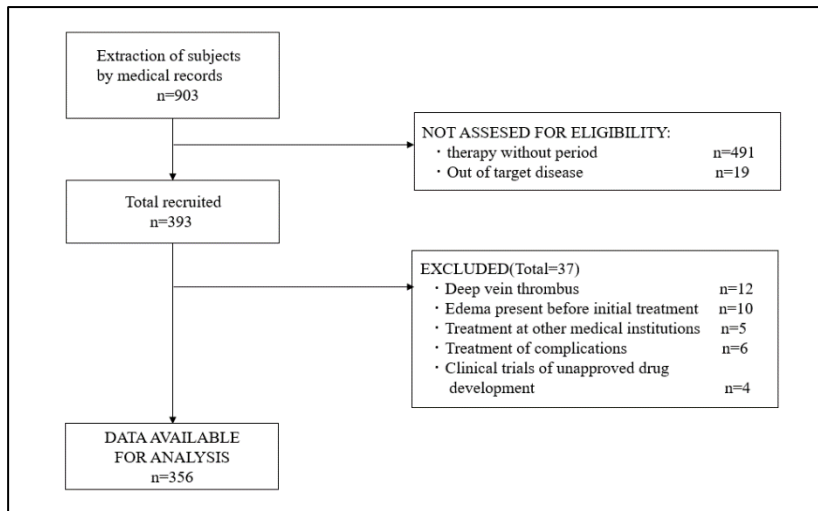
Fig. 2 Kaplan-Meier of plot of the cumulative incidence of lower limb lymphedema (LLL)
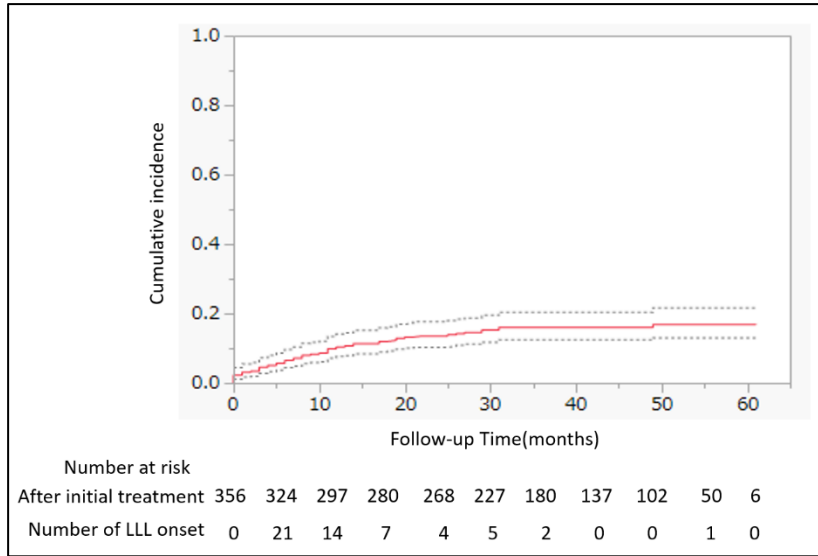
Fig. 3 Risk Factor Model of lower-limb lymphedema (LLL)
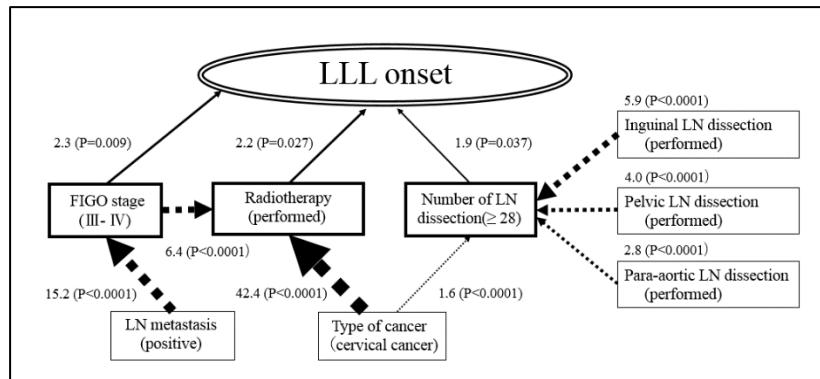
The solid arrow is the hazard ratio. The thickness of the solid arrow expresses the strength of the relationship. The dotted arrow is the odds ratio.
FIGO international federation of gynecology and obstetrics, LN lymph node

Table 1 Possible Risk Factors used for statistical analysis

Risk factors group	Risk factors
Internal risk factors	
Patient background	Age*, BMI*, Complication and Medical history[†], family history[†], Delivery history*,
Disease progress status	Type of gynecological cancer[‡], FIGO staging[‡], Lymph node metastasis,
External risk factors	
Method of treatment	Surgery, Chemotherapy, Radiotherapy, Type of therapy,
Operative therapy relation	Type of surgery, Number of LN resection, Inguinal LN dissection,
	Pelvic LN biopsy, Pelvic LN dissection,
	Para-aortic LN biopsy, Para-aortic LN dissection

* At the time of initial treatment, if height and weight data do not exist, data at the time closest to the initial treatment day are adopted.

[†]Data on the occurrence of diabetes, hypertension, and other cancers.

[‡]If the diagnosis results differ before and after treatment, the diagnosis after treatment regarding endometrial and ovarian cancer.

BMI body mass index, FIGO international federation of gynecology and obstetrics, LN lymph node, CI confidence interval

Table 2 Patient characteristics by type of gynecological cancer

Caracteristics	Cervical N=121(34%)	Endometrial N=151(42.4%)	Ovarian and tube N=84(23.6%)	All N=356(100%)
Age*(year), Mean±SD	54.8±15	61.6±10.7	57.7±14.8	58.4±13.6
BMI* (kg/m²), Mean±SD	22.0±4.0	24.7±4.6	21.9±4.3	23.2±4.5
Stage (FIGO), n(%)				
I	73(60%)	113(75%)	39(47%)	225(63%)
II	25(21%)	7(4%)	11(13%)	43(12%)
III	13(11%)	21(14%)	27(32%)	61(17%)
IV	10(8%)	10(7%)	7(8%)	27(8%)
†Type of therapy,n(%)				
Sur only	34(28%)	78(52%)	27(33%)	139(39%)
Chemo only	2(2%)	0(0%)	1(1%)	3(1%)
Rad only	18(15%)	0(0%)	0(0%)	18(5%)
Sur and Chemo	14(11%)	62(41%)	54(64%)	130(36%)
Chemo and Rad	29(24%)	1(1%)	1(1%)	31(9%)
Sur and Rad	17(14%)	5(3%)	0(0%)	22(6%)
Sur and Chemo and Rad	7(6%)	5(3%)	1(1%)	13(4%)
Number of LN resections				
Mean±SD	27.5±15.7	22.8±18.8	23.2±20.5	24.0±18.7
Min-Max	0-67	0-88	0-97	0-97

*At the time of initial treatment, †The type of treatment is the treatment received between the initial treatment
after the diagnosis of a gynecologic malignancy and the end of the follow-up.

after diagnosis of a gynecological malignancy and the end of follow-up. Sur is abbreviation of Surgery.

Chemo is abbreviation of Chemotherapy. Rad is abbreviation of Radiotherapy.

SD standard deviation, BMI body mass index, FIGO international federation of gynecology and obstetrics,

LN lymph node, Min minimum values, Max maximum values

Table 3 Influence of factors on the absense or presence of Lower limb lymphedema

variables	variable category	absence N=302(84.8%)	presence N=54(15.2%)	Hazard ratio 95%CI
age(years), n(%)	≥ 58	168(55.6)	30(55.6)	0.59-1.73
	< 58 [reference]	134(44.4)	24(44.4)	
BMI(kg/m²), n(%)	≥ 25	86(28.5)	13(24.1)	0.44-1.54
	< 25 [reference]	216(71.5)	41(75.9)	
Medical history and complication*, n(%)	Yes	112(37.5)	15(27.8)	0.38-1.25
	No [reference]	187(62.5)	39(72.2)	
Family history, n(%)	Yes	56(18.5)	9(16.7)	0.44-1.84
	No [reference]	246(81.5)	45(83.3)	
pregnancy*, n(%)	Yes	249(83.3)	42(77.8)	0.37-1.33
	No [reference]	50(16.7)	12(22.2)	
Stage(FIGO), n(%)	III -IV	66(21.9)	22(40.7)	1.42-4.20
	I - II [reference]	236(78.2)	32(59.3)	
Type of cancer, n(%)	Cervical	100(33.1)	21(38.9)	0.51-1.91
	Endometrial	133(44.0)	18(33.3)	0.33-1.31
	Ovarian and Tube [reference]	69(22.9)	15(27.8)	
Surgery, n(%)	Yes	260(86.1)	44(81.5)	0.35-1.38
	No [reference]	42(13.9)	10(18.6)	
Chemotherapy, n(%)	Yes	153(50.7)	24(44.4)	0.45-1.32
	No [reference]	149(49.3)	30(55.6)	
Radiotherapy, n(%)	Yes	65(22.0)	19(35.2)	1.09-3.35
	No [reference]	237(78.0)	35(64.8)	
Type of therapy, n(%)	Combination therapy	166(55.0)	31(57.4)	0.57-1.67
	Monotherapy [reference]	136(45.0)	23(42.6)	
Type of surgery†, n(%)	Total hysterectomy	177(76.3)	29(76.3)	0.12-6.55
	Modified radical hysterectomy	8(3.5)	2(5.3)	0.11-13.14
	Radical hysterectomy	42(18.1)	6(15.8)	0.09-6.28
	Others [reference]	5(2.2)	1(2.6)	
Inguinal LN dissection, n(%)	Yes	137(52.7)	29(65.9)	0.87-3.04
	No [reference]	123(47.3)	15(34.1)	
Pelvic LN biopsy, n(%)	Yes	52(20)	6(13.6)	0.28-1.58
	No [reference]	208(80)	38(86.4)	
Pelvic LN dissection, n(%)	Yes	166(63.8)	34(77.3)	0.86-3.53
	No [reference]	94(36.2)	10(22.7)	
Para-aortic LN biopsy, n(%)	Yes	94(36.2)	16(36.4)	0.53-1.79
	No [reference]	166(63.9)	28(63.6)	
Para-aortic LN dissection, n(%)	Yes	68(26.2)	15(34.1)	0.75-2.60
	No [reference]	192(73.9)	29(65.9)	
Number of LN dissection‡ n(%)	≥ 28	95(36.8)	25(36.8)	1.14-3.77
	< 28 [reference]	163(63.2)	19(43.2)	
LN metastasis	Positive	41(15.8)	11(25.0)	0.89-3.49
	Negative [reference]	219(84.2)	33(75.0)	

*Data missing:n(%)→3(1%), †Data missing:n(%)→34(11.2%), ‡Data missing:n(%)→2(1%)

Total hysterectomy is the routine procedure for endometrial cancer, ovarian cancer, severe dysplasia, or invasive cervical cancer stage IA1. Bilateral oophorectomy is usually performed. Also, pelvic or para-aortic lymph node dissection is also performed. Depending on the status of the disease, para-aortic lymph node dissection may or may not be performed. Modified radical hysterectomy is the routine procedure for stage IA2 invasive cervical cancer. It is positioned between total and radical hysterectomy. Bilateral oophorectomy is usually performed. Pelvic or para-aortic lymph node dissection may or may not be performed depending on the status of the disease.

Radical hysterectomy is the routine procedure for stage IB2 invasive cervical cancer. It involves the removal of the uterus, cervix, and the upper one-third of the vagina along with the cardinal ligament. Additionally, pelvic lymph node dissection and biopsy of para-aortic lymph nodes must be performed. Bilateral oophorectomy is usually performed.

BMI body mass index, FIGO international federation of gynecology and obstetrics, LN lymph node, CI confidence interval

Table 4 Estimate of model parameter on the risk factors moodel

Comporment 1 Outcome (Time to event)	Coefficient	Hazard Ratio	95%CI	p-value
Direct effect of "lymphedema onset"				
FIGO (III-IV)	0.824	2.3	1.2-4.2	0.009
Radiotherapy (perfomed)	0.804	2.2	1.1-4.5	0.027
Number of LN dissection (≥ 28)	0.64	1.9	1.0-3.5	0.037

Comporment 2 Outcome (Yes / No)	Coefficient	Odds Ratio	95%CI	p-value
Direct effect of "FIGO stage (III-IV)"				
LN metastasis (positive)	2.722	15.2	11.4-20.2	<0.001
Direct effect of " Radiotherapy (performed)"				
Type of cancer (Cervical cancer)	3.748	42.4	29.5-60.9	<0.001
FIGO (III-IV)	1.854	6.4	4.4-9.3	<0.001
Direct effect of "Number of LN resection (≥ 28)"				
Inguinal LN dissection (+)	1.783	5.9	4.4-8.0	<0.001
Pelvic LN dissection (+)	1.396	4.0	2.7-5.9	<0.001
Para-aortic LN dissection (+)	1.012	2.8	2.1-3.6	<0.001
Type of cancer (Cervical cancer)	0.467	1.6	1.3-2.1	<0.001

LN lymph node, FIGO international federation of gynecology and obstetrics, CI confidence interval