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A 5-year prospective assessment of risk factors for lower limb lymphedema after gynecologic cancer surgery

Kuniko Utsugi[1]✉, Naoki Ishizuka[2], Hidetaka Nomura[3], Atsushi Fusegi[3] & Hiroyuki Kanao[3]

Lower limb lymphedema is a distressing complication after lymphadenectomy. Currently, no definite intervention for reducing the incidence of lower limb lymphedema has been established. This study identified risk factors for lower limb lymphedema following a gynecologic surgery with a 5-year follow-up. A total of 190 patients who underwent surgery, including pelvic lymphadenectomy, between 2011 and 2012 were enrolled and followed up for 5 years. Lymphedema was defined as International Society of Lymphology stage I or higher. The patients' physical characteristics, surgical methods, and adjuvant therapies were investigated and hazard ratios and 95% confidence intervals were calculated. Kaplan–Meier analysis was performed to assess the 5-year cumulative risk of lower limb lymphedema. Multivariate analysis revealed that adjuvant chemotherapy with docetaxel or paclitaxel and the number of lymph nodes removed ≥ 60 were the risk factors. The 5-year cumulative incidence of total lower limb lymphedema was 39.6%, 51.6% with adjuvant chemotherapy using taxanes, 49.1% with the removal of ≥ 60 lymph nodes. The incidence of lower limb lymphedema was highest in the first year. Since taxane administration and lymphadenectomy remain essential for optimizing patient prognosis, close monitoring of lower limbs is crucial in the first year after lymphadenectomy for patients with these risk factors.

Keywords Adjuvant chemotherapy, Docetaxel, Gynecologic cancer, Lower limb lymphedema, Lymphadenectomy, Risk factors

The number of patients with gynecologic cancer is increasing worldwide[1]. Surgery is the main course of treatment for gynecologic cancer. The rate of lymph node metastases usually increases with the disease progression. Whether lymph node dissection affects prognosis is not known with certainty; however, one of the most important reasons for performing lymphadenectomy is to find out the exact stage of surgical progression and to determine the subsequent course of treatment[2–5]. Lower limb lymphedema (LLE) is one of the most worrisome sequelae after lymphadenectomy. LLE affects patients' quality of life, is not completely curable, and develops even after several years[6]. More than 20% of patients who undergo lymphadenectomy eventually develop LLE[7]. Many articles have evaluated the efficacy of sentinel lymph node (SLN) mapping as an alternative to lymphadenectomy for uterine cancer and SLN mapping may reduce the need for lymphadenectomy[8,9]. Nevertheless, lymphadenectomy is inevitable when SLN is not identified or lymph node (LN) metastases are identified after SLN mapping. In addition, SLN mapping is not feasible at some institutes because of either technical issues or insurance-related matters[10]. While many reports indicate that SLN mapping can prevent lymphedema[11,12], others suggest that lymphedema can still develop despite SLN mapping[13]. Therefore, it is crucial to devise solutions that include SLN mapping to decrease the incidence of LLE.

At present, no definite intervention for reducing the incidence of LLE has been established because the risk factors and incidence rate of LLE vary in each report[14,15]. Most reports are retrospective with relatively short follow-up periods. Although there are a few prospective studies, the risk factors for LLE vary depending on how it is defined (percentage of volume increase, BMI-corrected volume, clinical evaluation and patient self-report)[16–18]. In clinical practice, lymphedema is not always diagnosed based on volume alone, but also

[1]Cancer Screening Center, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan. [2]Center for Digital Transformation of Health, Kyoto University, 69 Yoshida-Konoe-Cho, Sakyo-ku, Kyoto City, Kyoto 606-8315, Japan. [3]Department of Gynecology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo 135-8550, Japan. ✉email: kuniko.utsugi@jfcr.or.jp

on factors such as firmness and skin condition. In this report, we adopted a clinical evaluation based on the International Society of Lymphology (ISL) classification[19]. We prospectively examined and followed up patients with gynecologic cancer who underwent lymphadenectomy preoperatively and for 5 years postoperatively. We investigated the risk factors for LLE and analyzed the 5-year cumulative incidence to determine a strategy for decreasing its incidence of LLE.

Methods

Study design and setting

This prospective case series was conducted at Cancer Institute Hospital of Japanese Foundation for Cancer Research. According to the inclusion and exclusion criteria mentioned below, patients were enrolled and followed for 5 years. All patients during these periods underwent open surgery, including lymphadenectomy, at our institute. This study was approved by the IRB of Cancer Institute Hospital of Japanese Foundation for Cancer Research (No. 2011 – 1027). All methods were carried out in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all participants.

Inclusion and exclusion criteria

Patients who were planned to undergo surgery including pelvic lymphadenectomy for gynecologic cancer between April 2011 and May 2012 were enrolled to analyze the risk factors for LLE after surgery. Patients who had deep vein thrombosis, aged ≥ 80 years, patients who declined to participate the study, and patients who were uncertain of malignancy before surgery were excluded.

Data collection

The recorded parameters included patient age, body weight, body mass index (BMI), waist–hip ratio (WHR), disease site, cancer stage, number of LNs removed, number of metastatic LNs, presence of para-aortic and inguinal lymphadenectomy, and information regarding adjuvant chemotherapy and adjuvant radiotherapy. The LLE evaluation was performed annually at the follow-up visits of the patients. Patients usually visited the hospital every 1–3 months for 3 years and every 3–6 months for 5 years for cancer follow-up. LLE evaluation was planned to be performed in the same month of the surgery. If an evaluation could not be conducted as scheduled, it was considered valid if performed within 6 months of the planned assessment. Otherwise, the LLE evaluation was deferred to the following year's follow-up.

Covariates

The following covariates were chosen from the patients' profiles: age; body weight; body mass index; number of lymph nodes removed (≥ 60); lymph node metastasis; number of metastatic lymph nodes; para-aortic lymphadenectomy; inguinal lymphadenectomy; adjuvant chemotherapy with docetaxel or paclitaxel; and adjuvant chemotherapy other than taxane. These covariates are usually analysed in other studies, but the results differ. Although many reports have been published on the effects of adjuvant radiation therapy, we mainly use adjuvant chemotherapy instead. There are few reports on adjuvant chemotherapy with individual agents; we added docetaxel and paclitaxel, as well as other agents. The cutoff value for lymph nodes removed was decided as 60 or more after examining the upper quartile points (75%), as described in the 'Statistical Analysis' section below.

LLE evaluation

The author (KU) checked the physical condition of the patient's lower limbs based on touch, measurement of the circumference of five points (dorsal aspect of the foot, ankle, 5 cm under the patella, 10 cm above the patella, and the upper part of the thigh), and the impedance of both lower limbs measured using In Body720; accordingly, the presence or absence of LLE was diagnosed and ISL staging was performed. LLE diagnosis was based on the size-up and depended on the condition of skin, hardness, and the pushing sign. Considerably, ISL staging was used for diagnosing of LLE in this study.

According to the consensus document of ISL staging[19], stage 0 refers to a latent or subclinical condition where swelling is not yet evident. Stage I entails the early assumption of fluid that is relatively high in protein content, which subsides with limb elevation. Stage II involves more changes in solid structures; limb elevation alone rarely reduces tissue swelling, and pitting is evident. In late Stage II, pitting of the limb may disappear as excess subcutaneous fat and fibrosis develop. Stage III encompasses lymphostatic elephantiasis where pitting can be absent, and trophic skin changes, such as acanthosis, changes in skin characteristics and thickness, further deposition of fat and fibrosis, and warty overgrowths have developed.

We defined lymphedema as a diagnosis of ISL stage I or higher.

Outcomes and definition

The primary outcome of this prospective study was the clarification of the risk factors for LLE. The secondary outcome was the analysis of the 5-year cumulative incidence of LLE with and without risk factors.

Statistical analysis

Background factors were analyzed descriptively with basic statistics (median, range) for continuous quantities and frequency (%) for categorical variables. Concerning the number of LNs removed, we assumed that there is a cutoff value somewhere, so we searched at the 25th, 50th, and 75th percentile points and settled on the 75th percentile, which was most strongly suggested to be associated. After examining the upper quartile points (75%), we presented the result that there was a risk at 60 or more. Candidate variables were screened by univariate analyses with P value less than 0.05. Subsequently screened variables were included in multivariate

Cox proportional hazards model since it is an analysis of time to event occurrence. Risks of developing LLE were estimated by calculating hazard ratio and 95% confidence intervals using Cox regression. Cumulative LLE incidence rates were estimated as 1-(Kaplan-Meier), and log-rank test was used to compare LLE incidence curves. All tests were performed at a significance level of $p = 0.05$, the significance level was set as two-sided and the CIs were calculated at a confidence level of 95%. SAS 9.4 (SAS Institute Inc. Cary, USA) was used for the analysis.

Results

A total of 224 patients were initially enrolled, among which 12 patients were excluded owing to the diagnosis of deep vein thrombosis, 8 for declining to participate, 4 patients for age ≥ 80 years, and 10 patients since they were uncertain of malignancy before surgery. A total of 190 patients were included in the final analysis (Fig. 1). In total, 190 patients were analyzed, including 64 with cervical cancer, 103 with endometrial cancer, 21 with ovarian cancer, and one with vulvar and vaginal cancer. The median age was 50 (21–77) years, median body weight was 53.3 kg (34.8–76.8), median BMI was 21.6 (14.1–32.9), and median WHR was 0.84 (0.71–0.98). The median number of LNs removed was 45 (14–154). Thirty-two patients had LN metastases. All patients underwent pelvic lymphadenectomy, para-aortic lymphadenectomy was performed in 50 patients, and 2 patients underwent inguinal lymphadenectomy. Adjuvant chemotherapy was administered to 97 patients, 85 with a taxane (58 docetaxel, 27 paclitaxel), and 12 with other chemotherapeutic agents (Table 1). Adjuvant radiation was performed in five patients.

The number of patients followed up each year for 5 years postoperatively was 169, 149, 97, 91, and 164 (Table 2). During the 5-year follow-up, 10 patients died of cancer and 2 died of other causes. Fourteen patients were lost to follow-up after 5 years. The reason for the decreasing number of patients, especially at 3 and 4 years postoperatively, was schedule conflicts between the author and the patients. The occurrence of LLE at each

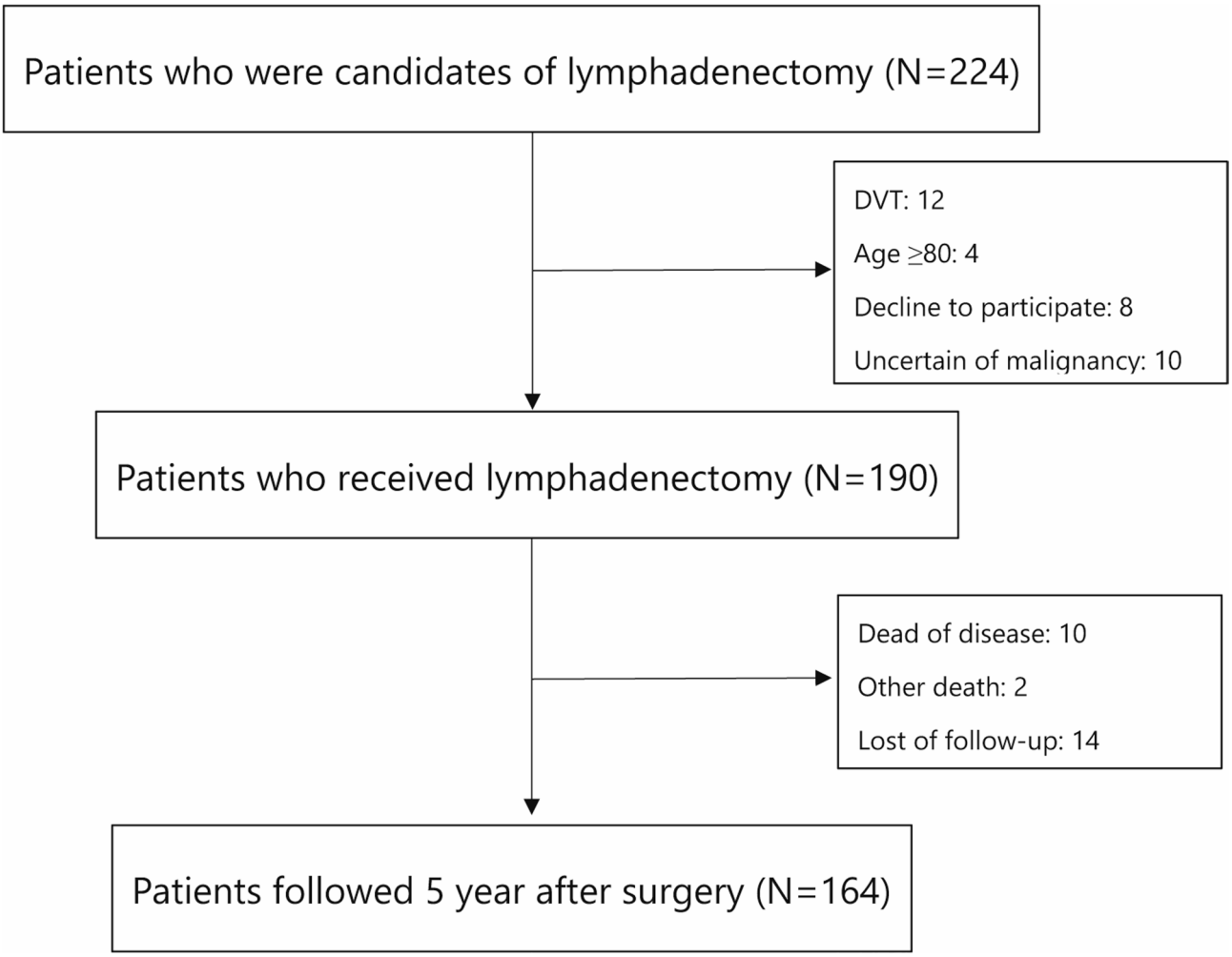

Fig. 1. Flowchart of data collection process. During the study period, 224 patients were candidates of pelvic lymphadenectomy. In accordance with exclusion criteria, 190 patients were included. We could follow 164 patients after 5 years.

All	*N* = 190
Age (y.o.)	50 (21–77)
Body weight (kg)	53.3 (34.8–76.8)
Body mass index	21.6 (14.1–32.9)
Waist–hip ratio	0.84 (0.71–0.98)
Disease	
Cervical cancer	64
Endometrial cancer	103
Ovarian cancer	21
Vulvar cancer	1
Vaginal cancer	1
Stage	
pT1N0M0	122
pT1N1M0	8
pT2N0M0	25
pT2N1M0	15
pT3N0M0	11
pT3N1M0	8
pT3N1M1	1
Number of LNs removed	45 (14–154)
14–19	11
20–39	58
40–59	74
60–79	20
80–99	12
≧100	15
Number of metastatic LNs	
0	158
1〜5	25
6〜10	4
11〜20	2
59	1
Pelvic lymphadenectomy	
no	0
yes	190
Para-aortic lymphadenectomy	
no	140
yes	50
Inguinal lymphadenectomy	
no	188
yes	2
Adjuvant chemotherapy	
no	93
Taxane	85
Docetaxel	58
Paclitaxel	27
others	12
Adjuvant radiotherapy	
no	185
yes	5

Table 1. Patient characteristics. Data are median (range) or n

year for 5 years postoperatively was 28.4% (48/169), 22.8% (34/149), 22.7% (22/97), 25.3% (23/91), and 25.0% (41/164). The incidence of severe LLE increased annually after surgery.

Univariate analysis showed that age (HR: 1.021; 95% CI: 1.002, 1.039; $p = 0.02$), number of LNs removed ≥ 60 (HR: 1.602; 95% CI: 1.038, 2.475; $p = 0.03$), and adjuvant chemotherapy with docetaxel (HR: 2.251; 95% CI: 1.314, 3.857; $p = 0.003$) or paclitaxel (HR: 2.221; 95% CI: 1.153, 4.278; $p = 0.017$) were significant risk factors

	n	Recurrence	DOD*	Other death	ISL**1–3	ISL1	ISL2	ISL3
Before	190	-	-	-	-	-	-	-
1 year	169	4	0	0	48 (28.4%)	42	6	0
2 year	149	3	3	Suicide 1	34 (22.8%)	33	1	0
3 year	97	2	2	0	22 (22.7%)	20	2	0
4 year	91	1	2	1	23 (25.3%)	20	2	1
5 year	164	6	3	0	41 (25.0%)	36	4	1

Table 2. Changes in patient status. *Dead on disease, **International Society of Lymphedema.

	Hazard Ratio	95% Confidence Interval	*p*
Age	1.021	1.002, 1.039	0.02
Body weight	1.002	0.975, 1.03	NS*
Body mass index	0.992	0.928, 1.06	NS
Number of lymph nodes removed ≥ 60	1.602	1.038, 2.475	0.03
Lymph node metastasis	1.457	0.864, 2.458	NS
Number of metastatic lymph nodes	1.024	0.992, 1.056	NS
Para-aortic lymphadenectomy	1.158	0.721, 1.862	NS
Inguinal lymphadenectomy	3.686	0.897, 15.141	NS
Adjuvant chemotherapy with docetaxel	2.251	1.314, 3.857	0.003
Adjuvant chemotherapy with paclitaxel	2.221	1.153, 4.278	0.017
Adjuvant chemotherapy other than taxane	1.66	0.635, 4.336	NS

Table 3. Univariate analysis of risk factors for lymphedema. *Not significant

	Hazard Ratio	95% Confidence Interval	*p*
Age	1.026	1.005, 1.047	0.01
Number of lymph nodes removed ≥ 60	1.636	1.015, 2.638	0.04
Adjuvant chemotherapy with docetaxel	2.224	1.285, 3.848	0.004
Adjuvant chemotherapy with paclitaxel	2.085	1.071, 4.059	0.03
Adjuvant chemotherapy other than taxane	2.079	0.783, 5.521	NS*

Table 4. Multivariate analysis of risk factors for lymphedema. *Not significant.

(Table 3). Multivariate analysis showed that age (HR: 1.026; 95% CI: 1.005, 1.047; $p = 0.01$), number of LNs removed ≥ 60 (HR: 1.636; CI: 1.015, 2.638; $p = 0.04$), and adjuvant chemotherapy with docetaxel (HR: 2.224; 95% CI: 1.285, 3.848; $p = 0.004$) or paclitaxel (HR: 2.085; 95% CI: 1.071, 4.059; $p = 0.03$) were risk factors for LLE (Table 4).

Univariate and multivariate analyses revealed that the number of LNs removed ≥ 60 was a risk factor for LLE. Even though ≥ 60 LNs being removed may image the effect of para-aortic lymphadenectomy, para-aortic lymphadenectomy was not a significant risk factor for LLE (HR: 1.158; 95% CI: 0.721, 1.862; p = NS) according to univariate analysis. To clarify the question, we checked the number of LNs removed and the occurrence of LLE at 1 year postoperatively in the pelvic lymphadenectomy-only group and the pelvic and para-aortic lymphadenectomy group (Table 5). In total, 128 patients underwent pelvic lymphadenectomy only, of whom 30 were diagnosed with ISL Stage I and 5 with ISL Stage II. The median number of LNs removed was 41 (14–110). Forty-one patients underwent pelvic lymphadenectomy and para-aortic lymphadenectomy 1 year postoperatively. In this group, the median number of pelvic LNs removed was 45 (21–83), whereas the number of para-aortic LNs removed was 33 (7–71). Twelve patients were diagnosed with ISL Stage I and 1 with ISL Stage II. The χ^2 test revealed no significant differences in LLE occurrence between the two groups. We found that the removal of ≥ 60 LNs is a risk factor for LLE, regardless of whether para-aortic lymphadenectomy is performed.

The Kaplan–Meier curve revealed a 5-year cumulative incidence of total LLE of 39.6% (Fig. 2). The 5-year cumulative incidence of LLE with adjuvant chemotherapy with taxane was 51.6%, whereas that of LLE with adjuvant chemotherapy other than taxane was 44.4% and that of LLE without adjuvant therapy was 27.9% (Fig. 3a). The 5-year cumulative incidence of LLE with LNs removed ≥ 60 was 49.1%, whereas that for LLE with LNs removed < 60 was 31.4% (Fig. 3b). As shown by the Kaplan–Meier curve, the rate of occurrence of LLE in the first year was significantly higher than that in the following years, especially in the groups with risk factors.

	Pelvic lymphadenectomy only	Pelvic and para-aortic lymphadenectomy	
	(*n* = 128)	(*n* = 41)	
No. of LNs removed	Pelvic LNs removed	Pelvic LNs removed	Para-aortic LNs removed
Median	41 (14–110)	45 (21–83)	33 (7–71)
< 10	0	0	1
10–19	9	0	5
20–39	52	16	21
40–59	54	17	12
60–79	8	6	2
80	5	2	0
No. of LLE after 1 year*	35 (27.3%)	13 (31.7%)	
ISL stage 1	30	12	
ISL stage 2	5	1	

Table 5. Comparison between pelvic lymphadenectomy with and without para-aortic lymphadenectomy. *Not significant

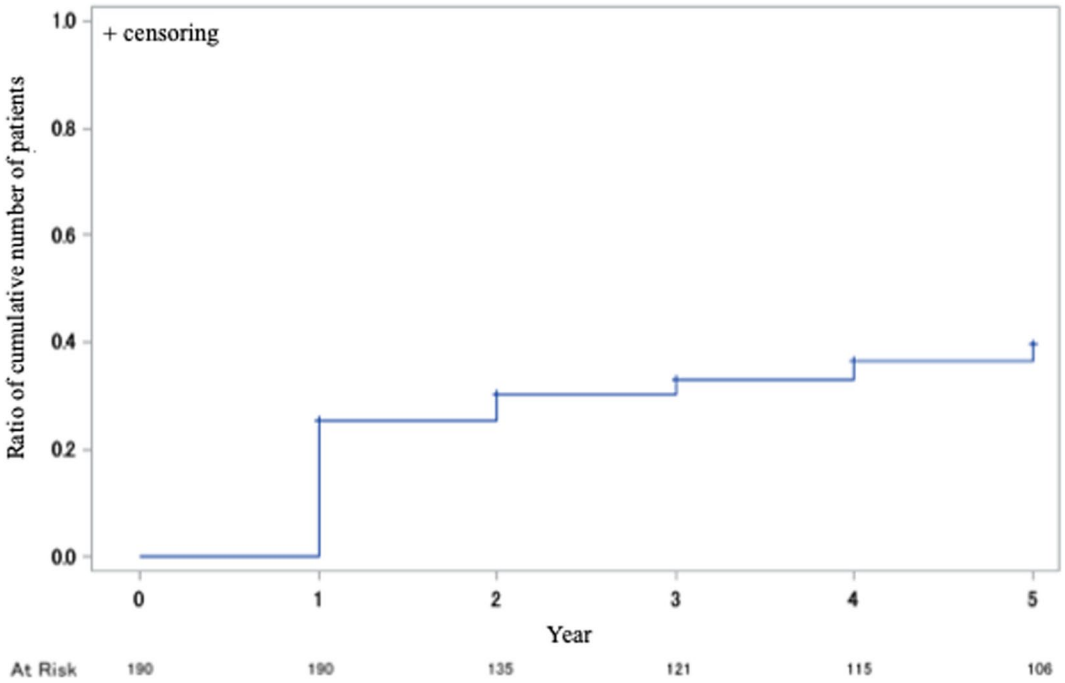

Fig. 2. The 5-year cumulative incidence of total lower limb lymphedema is 39.6%. The range of occurrence of LLE in the first year was significantly higher than that in the following years. LLE: Lower Limb Lymphedema.

Discussion

Our results demonstrated that adjuvant chemotherapy with taxanes, specifically docetaxel and paclitaxel as well as the removal of ≥ 60 LNs, were significant risk factors for LLE, regardless of the type of surgery (pelvic lymphadenectomy vs. pelvic lymphadenectomy with para-aortic lymphadenectomy). Age is a weak risk factor for LLE. This prospective study provided insights into the long-term occurrence of LLE by following up with patients who underwent lymphadenectomy for 5 years. Approximately 23–28% of patients who underwent lymphadenectomy suffered from lymphedema each year, and the cumulative incidence was 39.6%, which means that lymphedema progresses and regresses. The Kaplan–Meier curve indicates a high incidence in the first year, but the rate of new occurrence of LLE in each year diminishes from the second year. Reportedly, more than half of the LLEs develop within a year[20,21]. Hayes et al. also reported that 60% of LLE cases are persistent, whereas 40% of LLEs are transient, suggesting that some cases resolve with treatment[20].

In addition to the identified risk factors, previous studies have reported other contributors to LLE, including age, BMI, adjuvant radiotherapy, adjuvant chemoradiation, open surgery, prolonged operation time, cancer staging, and removal of circumflex iliac LNs. Even though the risk factor differed in each report, postoperative radiotherapy generally poses the highest risk[14,15,20,22–24]. However, because chemotherapy is the primary adjuvant

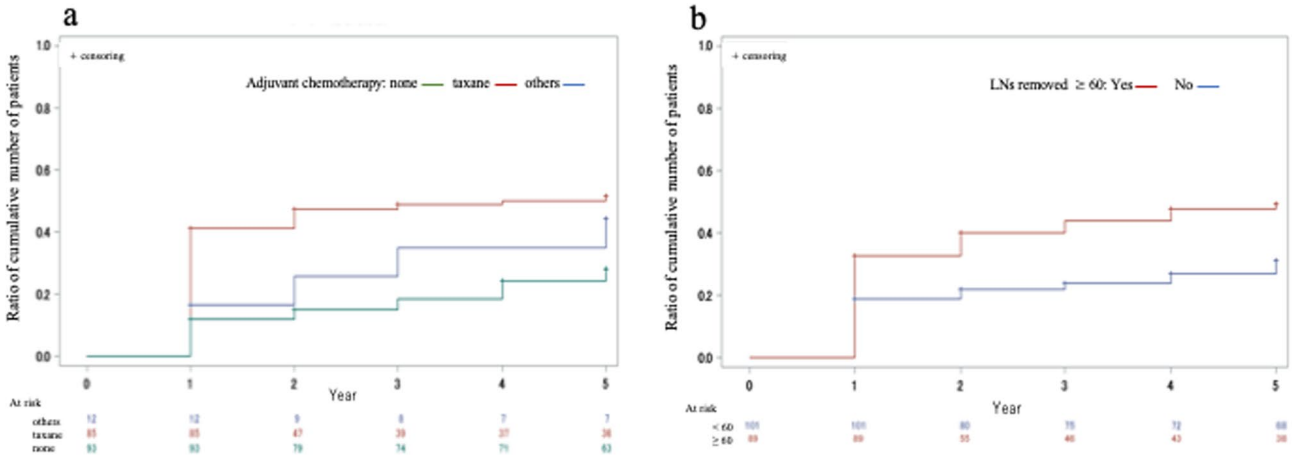

Fig. 3. a. The 5-year cumulative incidence of lower limb lymphedema with adjuvant chemotherapy with taxane was 51.6% that with adjuvant chemotherapy other than taxane was 44.4%, and that without adjuvant therapy was 27.9%. LLE: Lower Limb Lymphedema LN: lymph node b. The 5-year cumulative incidence of lower limb lymphedema with ≥60 LNs removed was 49.1%, and that with <60 LNs removed was 31.4%. LN: lymph node.

therapy at our institution[25], only five patients in our study cohort received radiotherapy, which was insufficient to evaluate its impact on LLE.

Our analysis showed that the risk of LLE increased slightly with age. Age as a risk factor for LLE is highly debated in the literature. Deura et al.[26] reported that age of ≥ 55 years is a risk factor for LLE in gynecologic cancer surgery, whereas most of the reports stated that age is not a risk factor for LLE[2,21,22,27,28]. Conversely, Carlson et al.[24] stated that the risk of LLE decreases with age ≥ 65 years. Thus, according to the abovementioned studies, age as a risk factor for LLE varies. This variability may be due to differences in the study populations and diseases, ethnicity, duration of observation, and definitions of LLE.

Most reports consider the number of LNs removed as a risk factor for LLE[14,21,24,28–30]. Meanwhile, Konno et al. recommended that resection of at least 20 LNs is required for endometrial cancer patients since resection of at least 20 pelvic nodes is one of the independent risk factors for prognosis (HR: 0.49; 95% CI: 0.24–0.99; $p = 0.04$)[31]. The number of LNs removed as a risk factor for LLE varies between reports, with the lowest being reported by Carlson et al.[29], at ≥ 8, and the highest being reported by Hareyama et al.[28], at ≥ 70. Conversely, Kim et al.[6] stated that the number of LNs removed is not a risk factor. There might be a difference in the diagnostic criteria for LLE or the difference in procedure for lymphadenectomy at each institute. As depicted in Table 3, the number of LNs removed was a risk factor, regardless of whether the LNs included para-aortic or not. The primary cause of LLE is lymphatic obstruction at the entrance to the retroperitoneum from the lower limb. The lymph flow from the lower limb goes through the inguinal LNs to the retroperitoneal pelvic LNs. Upper LNs, such as the para-aortic LNs, do not influence the occurrence of LLE; however, the pelvic LNs, especially those close to the inguinal LNs do. Hoffman et al.[32–34] found that the dissection of the circumflex iliac nodes (most caudal external iliac LNs) is a risk factor for LLE. In our study, we performed a complete pelvic lymphadenectomy, which included the circumflex iliac nodes. Hareyama et al.[28] also analyzed the association between the extent of lymphadenectomy and the occurrence of LLE and revealed that a dissection range below the inferior mesenteric artery or renal vein did not influence the occurrence of LLE. This finding indicates that the upper limit of lymphadenectomy is unrelated to the occurrence of LLE.

The highest risk factor for LLE is adjuvant chemotherapy with taxane. In their study on breast cancer-related lymphedema, Aoishi et al. identified adjuvant chemotherapy as a risk factor for lymphedema, especially docetaxel (HR: 3.790; 95% CI: 1.413–10.167; $p = 0.0081$)[35]. Taxane use is a risk factor for breast cancer-related lymphedema[36]. Even though gynecologic oncologists often experience LLE with the taxane-based adjuvant chemotherapy, especially with docetaxel, few studies have reported taxane as a risk factor of LLE. Recently, Lee et al. mentioned that docetaxel-based chemotherapy is a risk factor for the LLE and the HR is 1.77 (95% CI: 1.30–2.42; $p < 0.001$)[37]. Beesley et al.[21] considered adjuvant chemotherapy as a risk factor for LLE but did not mention the anticancer drug used. One of the side effects of taxane use includes edema, which occurs because of an induced increase in capillary transparency[38]. In breast cancer, if the edema appears only on the affected arm, it is considered lymphedema, whereas if the edema appears on the unaffected side, it is considered edema caused by a pharmacologic side effect. In gynecologic cancer, pelvic lymphadenectomy affects both the lower limbs. When we found LLE, we could not diagnose whether it was simple edema caused by pharmacologic side effects, lymphedema, or a combination of both. Our report clarified the influence of taxane on LLE.

These two main risk factors are inherent to preventive interventions against cancer recurrence. Docetaxel is preferable to paclitaxel in patients who are intolerant to alcohol because paclitaxel is dissolved in alcohol and causes numbness and pain of the hands and feet as side effects. More severe LLE under docetaxel chemotherapy may cause scleroderma-like skin. SLN dissection reduces the incidence of LLE; however, lymphadenectomy is

necessary if the SLN is not identified or metastases are detected. Currently, no definitive preventive intervention or treatment for LLE exists.

Reportedly, there is a lesser likelihood of the occurrence of lymphedema if the retroperitoneum is not closed; however, the evidence is limited to only these reports[28,39]. Some other studies such as Hareyama et al.'s suggest avoiding the resection of circumflex iliac nodes (most caudal LNs of external iliac nodes)[32–34]. However, because these LNs are the regional LNs of cervical, endometrial, and ovarian cancers, performing this method depends on the patients' status. Postoperative lymphedema education is also essential, as some reports indicate that it reduces the incidence of lymphedema, necessitating the provision of postoperative lymphedema education[40].

Preventing the progression of lymphedema is equally important to preventing its onset. Once lymphedema develops, combined decongestive therapy is the common choice of treatment[41–43]. Compression, in particular, is the most effective option and is performed by educated therapists[44–46]. Lymphaticovenular anastomosis (LVA) is commonly practiced due to advances in technology and equipment[47], and an increasing number of publications have reported positive results[48,49]. However, evidence-based, comparative studies are still scarce. Furthermore, there are a limited number of physicians with surgical skills. Vascularized LN transfer (VLNT) is another choice of treatment[37]; however, evaluation of VLNT is not consistent and includes the side effects of surgery, such as hematoma. Only case-control reports are currently available. Some cases remain refractory to these therapies[48–50].

Early detection and therapy remain the primary interventions for preventing LLE progression. Clinicians should closely monitor patients, particularly those with the primary risk factors identified, during follow-up. As most LLE cases manifest within the first year postoperatively and are generally not severe at this stage, a structured follow-up program at 1-year post-surgery is necessary to assess whether patients have developed LLE. If LLE is detected, immediate treatment or referral to a lymphedema clinic should be initiated.

The strengths of this study are its prospective design and relatively long postoperative follow-up of 5 years that included details on the annual occurrence of LLE. In this study, the diagnosis of LLE was performed by a well-experienced gynecologic oncologist who has the certificate of Dr. Vodder's Method of Manual Lymph Drainage and Combined Decongestive Therapy. We found that the removal of ≥ 60 LNs is a risk factor for LLE, regardless of whether para-aortic lymphadenectomy is performed, even though there are studies that have reported that para-aortic lymphadenectomy increased the incidence of LLE[37,51]. Since we followed 5 years, we can determine the cumulative 5-year incidence and each year incidence. We clarify that LLE progresses and regresses, perhaps in early stage LLE. We can demonstrate that the incidence of LLE at each point for 5 years following surgery is not the same as the 5-year cumulative incidence of LLE. It could be confusing if we do not talk about it in isolation because patients might fear the higher incidence compared with reality. Since the occurrence in the first year was the highest and most of the patients showed ISL stage I, it is clear that we need to check the patient's lower limbs at especially at one year after surgery, so that we can begin treatment for LLE at the early stage of LLE.

A key limitations of this study is the small sample size. Additionally, the number of patients available for follow-up at 3 and 4 years post-surgery declined significantly. For the purpose of eliminating measurement inter-personnel errors between inspectors, measurement and diagnoses were performed by the author alone (KU). Examining patients at a defined time of 5 years was not easy and accommodating patients and the author was difficult because the cancer follow-up interval was extended with time. Even though the LLE diagnosis was considered valid if performed within 6 months of the planned assessment, the schedules of patients and the author were difficult to match, particularly after 3–4 years of surgery. The other limitation was the method of the diagnosis of LLE, which according to the other reports, was usually performed considering the volume change, circumference of lower limb, and the impedance. However, the real diagnosis of LLE must be performed based on the size-up and hardness of lower limb and skin condition. Although the author made the diagnosis by ISL staging considering all of these aspects, it may not be perfect. Further, I should have looked into more risk factors. Although variables of risk factors that are of interest to the author are picked up in this study, there might be another risk factor for LLE hiding.

In conclusion, adjuvant therapy with a taxane, especially Docetaxel and LNs removed ≥ 60 are the risk factors for LLE. These risk factors are unavoidable in cancer treatment to prevent recurrence. Since most of the LLE appears already at one year after surgery with early stage, we should not miss the sign of LLE and begin the treatment. A structured follow-up program should be established to assess lower limb status at one year post-surgery. If LLE is detected, prompt treatment or referral to a lymphedema clinic is necessary. Particularly, patients with these risk factors require careful and continuous monitoring.

Data availability

Data will be made available on reasonable request. Correspondence and request should be addressed to K.U.

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Author contributions
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Declarations

Competing interests
The authors declare no competing interests.

Ethical approval
This study was approved by the IRB of Cancer Institute Hospital of the Japanese Foundation for Cancer Research (No. 2011 – 1027).

Informed consent
Written informed consent was obtained from all patients.

Additional information
Correspondence and requests for materials should be addressed to K.U.