

Usefulness of computed tomography venography in gynecologic cancer patients with lower extremity edema

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Abstract

Lower extremity (LEx) edema is a common complication in gynecologic cancer patients. There are 2 main causes of edema in these patients such as deep vein thrombosis (DVT) and lymphedema. Early diagnosis and treatment of DVT are certainly important, but it is often difficult to evaluate proximal DVT by using ultrasound. The aim of this study is to demonstrate the usefulness of computed tomography venography of the lower extremity (CTV LEx) for the diagnosis of the DVT and investigate predictive factor of DVT in gynecologic cancer patients with LEx edema.

The medical records of 415 gynecologic cancer patients who were referred to the department of rehabilitation medicine with LEx edema were retrospectively reviewed in this case-controlled study. We categorized CTV LEx findings as follows: DVT proximal to the inguinal ligament (inferior vena cava or iliac vein thrombosis) and DVT distal to the inguinal ligament (femoral, popliteal, or calf vein thrombosis). We also evaluated patient characteristics including D-dimer level. We analyzed the correlation of each factor with DVT frequency and used receiver operating characteristic curve analysis to determine the appropriate D-dimer threshold.

Sixty-six patients were diagnosed with DVT; of them, 35 (53%) had DVT proximal to the inguinal ligament. Twenty-two patients were diagnosed with pulmonary embolism, of whom 15 had proximal DVT. Patients with proximal DVT tended to have pulmonary embolism ($P < .001$). Distal organ metastasis (odds ratio [OR], 2.88; $P = .002$) and a high D-dimer level (OR, 1.13; $P = .001$) were correlated with DVT.

CTV LEx is a useful diagnostic tool for gynecologic cancer patients with LEx edema, particularly high-risk patients, that should be performed at the initial evaluation.

Abbreviations: BMI = body mass index, CDT = complex decongestive therapy, CT = computed tomography, CTV LEx = computed tomography venography of the lower extremity, DVT = deep vein thrombosis, IVC = inferior vena cava, LEx = lower extremity, LN = lymph node, PE = pulmonary embolism, ROC = receiver operating characteristic, US = ultrasonography, VTE = venous thromboembolism.

Keywords: computed tomography venography, deep vein thrombosis, edema, gynecologic cancer, lower extremity

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1. Introduction

Annually, >8000 patients in Korea are diagnosed with gynecologic cancer.^[1] Due to advances in diagnostic tools, and improved therapies, mortality rate of gynecologic cancer has decreased and the number of survivors is increasing. As this population increases, it is important to identify the long-term management of the effects of gynecologic cancer on and complications in survivors.^[2]

Lower extremity (LEx) edema is a common complication in gynecologic cancer patients.^[3–5] There are 2 main causes of edema in these patients such as deep vein thrombosis (DVT) and lymphedema. DVT, part of the venous thromboembolism (VTE) spectrum, results in many complications including pulmonary embolism (PE).^[6] In a recent study, the overall risk for venous thromboembolism was reportedly 7-fold higher in patients with malignancy^[7]; among patients who underwent chemotherapy, the annual rate of thromboembolic complication arising within the first 3 months was 11%.^[8]

LEx lymphedema is also a disabling side effect of surgical and radiotherapy treatment for gynecological cancer. In previous studies, an estimated 1% to 49% of gynecologic cancer patients were diagnosed with LEx lymphedema.^[9–11]

Complex decongestive therapy (CDT) is performed to treat lymphedema patients without DVT. In CDT, manual lymphatic drainage and low-stretch bandaging are performed. Intermittent pneumatic compression can also be used to treat lymphedema.^[12,13] However, some patients with LEx edema may have undetected DVT. Moreover, to manage DVT, the initiation of an anticoagulation is most important; massage should be avoided due to the risk of PE.^[14] Therefore, to ensure safe management, DVT must be ruled out before the start of treatment for LEx edema in patients with gynecologic cancer.

Ultrasonography (US) or computed tomography venography (CTV) can be used to differentiate between DVT and lymphedema. US is easy to perform and noninvasive, but the diagnostic accuracy of US for DVT depends on the technique used, and proximal veins are difficult to observe.^[15,16]

On the one hand, CTV, which is invasive, has a smaller anatomical blind spot than US, and thus, it can more extensively evaluate venous problems.^[17] However, CTV should be performed in appropriate patients because it is costly and carries a risk of contrast media reaction and post procedural phlebitis. In previous studies, estimates of severe reactions to contrast media such as pulmonary edema, cardiac arrhythmias, and cardiac arrest range from 0.04% to 0.2%.^[18,19] Therefore, this study aimed to identify patients at high risk of proximal DVT who required CTV and verify the usefulness of CTV.

Furthermore, the levels of D-dimer, which is used as a marker of possible DVT, are also elevated in cancer patients.^[14] Therefore, the usefulness of D-dimer as a predictive factor of DVT in cancer patients should be evaluated, but few reports have examined its sensitivity or specificity in this population. Thus, here we also evaluated the usefulness of D-dimer for predicting DVT in gynecologic cancer patients.

2. Methods

2.1. Subjects

In this retrospective study, we collected information from medical chart reviews of 619 gynecologic cancer patients who were referred to the department of rehabilitation medicine for LEx edema between January 2007 and December 2018. Patients were identified using International Classification of Disease, Tenth Revision, Clinical Modification codes that contained at least 1 diagnosis of gynecologic cancer. Among them, 415 who underwent CTV of the LEx (CTV LEx) were recruited; 271 underwent chest computed tomography (CT) as well. Patients who were previously diagnosed with DVT were excluded, as were those with other diseases that could cause edema, such as heart or kidney disease. The study protocol was approved by the Research Ethics Committee of Asan Medical Center (Study number: S2014-1448-0004).

We divided all patients into a DVT group, those diagnosed with DVT, and a non-DVT group, those without evidence of DVT, and compared their characteristics.

2.2. Evaluation

The diagnosis of DVT was based on CTV LEx findings by a radiological specialist. We checked the CT findings of all patients and classified the DVT into being within a proximal vein (inferior vena cava [IVC], common or external iliac) or a distal vein (femoral, popliteal, calf, peroneal, or muscular).

Moreover, the following evaluations were performed in all patients at the outpatient department of rehabilitation medicine; malignancy type; symptom onset timing (from the day of surgery to the day of evaluation for edema); body mass index (BMI); LEx circumference; D-dimer level; comorbidities such as diabetes mellitus and hyperlipidemia; treatment method such as radiotherapy or chemotherapy. After being referred to the department of rehabilitation medicine for edema, CTV LEx was prescribed and the stage at initial diagnosis, regional lymph node (LN) involvement, and distant organ metastasis were examined.

Leg circumference was measured at 10cm above the upper margin of the patella (above 10cm) and 10cm below the lower margin of the patella (below 10cm) in the bilateral LEx. If the patient had bilateral edema, the circumferential results were not used.

Although lymphoscintigraphy was not performed in all patients, we checked all available lymphoscintigraphy findings. Patients were evaluated for the presence of dermal backflow and decreased LN uptake 2 hours after an intradermal ^{99m}Tc-phytate injection. The lymphoscintigraphy test results included normal or decreased LN uptake or the presence of dermal backflow. We suspected lymphedema if lymphoscintigraphy findings revealed dermal back flow or decreased LN uptake.

2.3. Cancer treatments

Patients previously received cancer treatment such as surgery, chemotherapy, or radiotherapy. Most patients underwent surgery such as radical hysterectomy, laparoscopic radical hysterectomy, total abdominal hysterectomy, or bilateral salpingo-oophorectomy. For the radical cure, LN dissection such as pelvic LN dissection or paraaortic LN dissection was performed simultaneously. Debulking surgery was used for staging and treatment in ovarian cancer patients.

For radiotherapy, external beam radiation therapy or intracavitary brachytherapy was administered to cervical cancer patients. Some cervical cancer patients received cisplatin-based chemotherapy consisting of cisplatin alone or in combination with other agents such as 5-FU, bleomycin, vincristine, or ifosfamide. Cisplatin, carboplatin, paclitaxel, epirubicin, or topotecan were also used in ovarian cancer patients. In some of the endometrial cancer patients, radiotherapy or chemotherapy was administered as well. Not all patients received transfusion of packed platelets or were treated with erythropoietin.

2.4. Statistical analysis

All statistical analyses were performed using SPSS 18.0 (IBM, NY). A *t* test was used to compare subject characteristics (age, height, body weight, BMI) and symptom onset timing between the 2 groups. To investigate the correlation between each categorical variable and occurrence of DVT, Chi-square test, and multivariate logistic regression analysis were used. The Chi-square test was used to determine the relationship between proximal DVT and PE. Values of *P* < .05 were considered statistically significant. Predictive factors on univariate analysis (*P* < .10) were entered into a multivariate logistic regression analysis.

In addition, receiver operating characteristic (ROC) curve analysis was used to identify an appropriate diagnostic threshold for D-dimer. The Youden index (*J*) was also calculated for each observed point on the scale.

Table 1
Patient characteristics by group.

	DVT group (n = 66)	Non-DVT group (n = 349)	P value
Age, y	56.3 ± 10.6	56.1 ± 10.6	.92
Height, cm	156.4 ± 6.3	156.6 ± 6.2	.83
Body weight, kg	59.2 ± 9.3	60.4 ± 9.9	.46
Body mass index, kg/m ²	24.2 ± 3.6	24.7 ± 3.8	.52
Malignancy type			.11
Cervical cancer	23 (34.8%)	159 (45.6%)	
Endometrial cancer	17 (25.8%)	98 (28.1%)	
Ovarian cancer	22 (33.3%)	84 (24.1%)	
Others	4 (6.1%)	8 (2.3%)	
Stage			<.001*
I-III	34 (51.5%)	290 (83.1%)	
IV	32 (48.5%)	59 (16.9%)	
Treatment type			
Chemotherapy	50 (75.8%)	213 (61.2%)	.03*
Radiotherapy	26 (39.4%)	140 (40.3%)	.89
Surgery	63 (95.5%)	342 (98.0%)	.22
Edema location			.82
Unilateral	41 (62.1%)	222 (63.6%)	
Bilateral	25 (37.9%)	127 (36.4%)	
Onset of symptoms, mo	35.5 ± 50.1	68.1 ± 294.5	.37

Values are shown as mean ± SD or number (%). DVT = deep vein thrombosis.
* P < .05. For the statistical analysis, the Chi-square test and t test were performed.

3. Results

3.1. Characteristics by group

Sixty-six patients belonged to the DVT group and 349 patients belonged to the non-DVT group. The clinical characteristics of the 415 patients are listed in Table 1. The average age was 56.3 years in the DVT group and 56.1 years in the non-DVT group. The DVT group had a lower mean BMI than the non-DVT group (24.2 ± 3.6 vs 24.7 ± 3.8 kg/m²; P = .52), but the difference was not significant. The DVT group consisted of 23 patients with cervical cancer, 17 with endometrial cancer, and 22 with ovarian cancer, while the non-DVT group consisted of 159 patients with

cervical cancer, 98 with endometrial cancer, and 84 with ovarian cancer. Thirty-two (48.5%) patients were diagnosed with stage IV cancer in the DVT group versus 59 (16.9%) in the non-DVT group. Mean symptom onset time was longer in the non-DVT group (35.5 ± 50.1 vs 68.1 ± 294.5 month; P = .37), but the difference was not significant. The DVT group included a higher proportion of patients with a history of chemotherapy (75.8% vs 61.2%, P = .03). The percentage of patients complaining of unilateral LEx edema did not differ between the 2 groups (P = .82).

3.2. DVT location

Figure 1 shows the DVT locations by group. If a patient had a DVT with a minimum of 2 veins, each DVT location was counted respectively. Nine patients had thrombosis in the IVC, 38 patients in the iliac vein (common or external), 32 in the femoral vein, 23 in the popliteal vein, and 30 in the calf, peroneal, or muscular vein. The iliac vein was the most common thrombosis site. A total of 35 patients had DVT proximal to the inguinal ligament, of them, 17 had distal DVT as well, and 18 had only supra-inguinal DVT, which was located above the inguinal ligament (IVC and iliac vein).

A total of 22 patients in the DVT group were diagnosed with PE. Of them, 15 (68.2%) had proximal DVT. The incidence of PE was significantly higher in these patients (P < .001), suggesting that proximal DVT was correlated with PE in our study.

3.3. Prediction of DVT and proximal DVT

In the univariate analysis, the predictors of DVT included regional LN metastasis, distant organ metastasis, history of chemotherapy, and higher D-dimer level. In the multivariate analysis, independent predictors were distant organ metastasis (odds ratio [OR], 2.88; P = .002) and, higher D-dimer level (OR, 1.13; P = .001) (Table 2). The remaining variables were not statistically significant.

When univariate analysis was applied to patients with proximal DVT, predictors of proximal DVT included regional

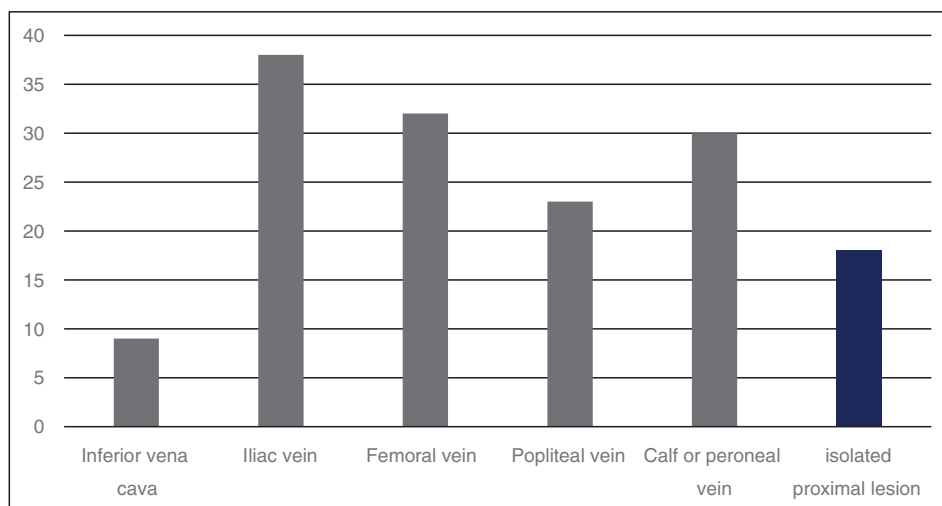


Figure 1. Location of thrombosis in the DVT group. Values shown are numbers of patients. Eighteen patients (27%) had only isolated supra-inguinal DVT lesions without distal lesions. DVT = deep vein thrombosis.

Table 2
Uni- and multivariate logistic regression analysis for the prediction of DVT and proximal DVT.

	DVT group (n=66)		Proximal DVT group (n=35)	
	P value	OR	P value	OR
Univariate analysis				
Regional LN metastasis	<.001*	3.56	<.001*	6.11
Distant organ metastasis	<.001*	4.63	<.001*	6.64
Treatment type				
Chemotherapy	.03*	1.98	.31	1.48
Radiotherapy	.89	0.96	.46	0.76
Surgery	.23	0.43	.20	0.36
Comorbidity				
Diabetes mellitus	.57	1.35	.51	1.53
Hyperlipidemia	.61	0.80	.46	0.63
Difference in lower extremity circumference				
Above 10 cm	.70	0.98	.34	0.93
Below 10 cm	.49	0.96	.35	0.93
D-dimer	<.001*	1.17	<.001*	1.13
Multivariate analysis				
Distant organ metastasis	.002*	2.88	.003*	4.15
D-dimer	.001*	1.13	<.001*	1.10

Values are shown as mean ± SD or number (%). Above 10 cm = circumference at 10 cm above the upper margin of the patella; below 10 cm = 10 cm below the lower margin of the patella; DVT = deep vein thrombosis, LN = lymph node.

* P < .05. For the statistical analysis, uni- and multivariable logistic regression analyses were performed. The difference in circumference was obtained by bilateral leg comparison only in patients with unilateral leg edema (DVT group, n = 34; Proximal DVT group, n = 21).

LN metastasis, distant organ metastasis, and higher D-dimer level. In the multivariate analysis, the independent predictors were distant organ metastasis (OR, 4.15; P = .003) and the higher D-dimer level (OR, 1.10; P < .001).

Table 3
D-dimer measurement in patients with suspected proximal DVT.

D-dimer cutoff, μg/mL	Sensitivity (%)	Specificity (%)	Youden index
0.3	96.9	24.3	.212
0.5	90.6	45.7	.363
1	81.3	65.8	.471
2	78.1	77.1	.552
3	62.5	82.2	.447
4	50.0	87.2	.372

Youden index (J) = sensitivity + specificity - 1. DVT = deep vein thrombosis.

3.4. Characteristics of D-dimer

Figure 2 shows the ROC curve obtained for various D-dimer cutoff values in this study. The D-dimer level would be considered “good” at predicting proximal DVT in gynecologic cancer patients because the area under the D-dimer ROC curve was 0.81. This curve shows that 0.5 μg/mL was a reasonable cutoff value for excluding proximal DVT, yielding high sensitivity (90.6%) and moderate (45.7%) specificity. Conversely, the specificity of a D-dimer plasma level at or above 4.0 μg/mL was 50.0%, while the sensitivity was 87.2% (Table 3). The highest combined sensitivity and specificity (J of 0.57) was for a D-dimer value of 2.32 μg/mL (sensitivity, 78.1%; specificity, 79.1%).

3.5. Lymphoscintigraphy findings

Of the 349 non-DVT group patients, 298 underwent lymphoscintigraphy. Among them, 63 (21.1%) patients had normal lymphoscintigraphy findings, whereas 235 (78.9%) had findings suggestive of lymphedema. Moreover, 35 patients were evaluated

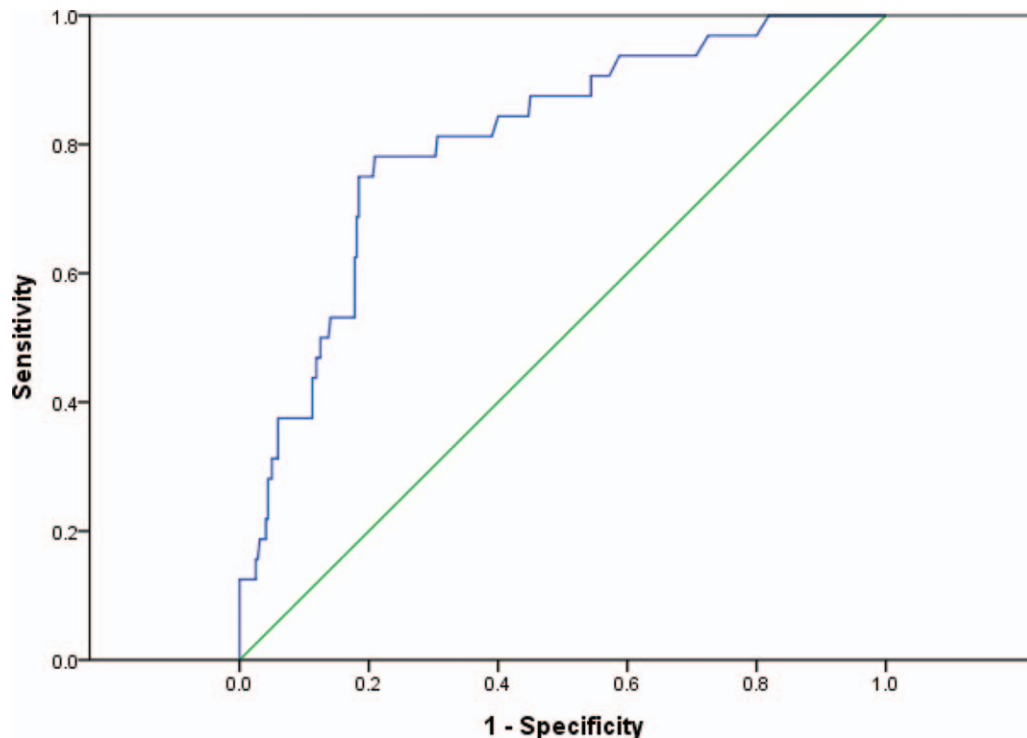


Figure 2. Receiver operating characteristic curve for plasma D-dimer level in the diagnosis of proximal deep vein thrombosis.

Table 4
Lymphoscintigraphy findings of patients.

	DVT group (n = 35)	Non-DVT group (n = 298)	P value
Normal	7 (20.0%)	63 (21.1%)	
Decreased uptake of LN	19 (54.3%)	86 (28.9%)	
Dermal back flow	9 (25.7%)	149 (50.0%)	.006*

Values are shown as number (%). DVT = deep vein thrombosis, LN = lymph node.

* $P < .05$. Patients with both dermal back flow and decreased uptake of LN findings are included in the dermal back flow column. For the statistical analysis, the Chi-square test was performed.

by lymphoscintigraphy in the DVT group (Table 4). Only 7 (20%) patients had normal lymphoscintigraphy findings, while 28 (80%) patients had findings compatible with lymphedema due to the presence of dermal backflow or decreased inguinal LN uptake. Dermal backflow findings were more common in the non-DVT group than in the DVT group (50.0% vs 25.7%; $P = .006$).

4. Discussion

In this retrospective study, we compared the differences in clinical characteristics between patients with DVT-associated edema and those with non-DVT-related edema as well as the features of DVT proximal to the inguinal ligament in gynecologic cancer patients. Our data showed that many of the patients diagnosed with DVT had only isolated supra-inguinal DVT lesions without distal lesions ($n = 18$; 27%). We also found a significant relationship between the incidence of PE and DVT proximal to the inguinal ligament ($P < .001$).

Similar results were demonstrated previously. Horii et al^[17] reported that PE was correlated with proximal DVT above the knee. Another study reported that distal DVT is less commonly associated with PE while the risk of proximal extension of calf vein clots in prospective studies employing repeat ultrasound at 1 week was reportedly low.^[20,21]

In gynecologic cancer patients, CTV LEX can be a useful tool for diagnosing proximal DVT. In our study, most patients who visited the hospital for edema underwent CTV LEX, while US was performed only in a few patients. Among DVT patients with only proximal lesions, only 4 underwent US. In 2 of the 4, US revealed DVT. If CTV LEX had not been performed, the proximal DVT would not have been detected; thus, treatment may have been delayed.

While US offers high accuracy for the detection of LEX DVT, the pelvic veins are often inadequately visualized due to its limited acoustic window. If US were used for these patients, the proximal DVT may have been missed. Conversely, CTV LEX can provide sufficient information about the proximal veins; thus, it is useful for diagnosing proximal DVT. Furthermore, among the patients with DVT, the risk of proximal DVT was significantly increased in the presence of active cancer.^[22] Therefore, CTV LEX can be more effective than US at identifying the presence of DVT in gynecologic cancer patients.

Of the 298 non-DVT group patients, 235 (78.9%) had lymphedema on lymphoscintigraphy. Similarly, 28 of 35 (80%) DVT group patients had lymphedema, suggesting that lymphedema findings on lymphoscintigraphy are commonly found in patients with DVT. If CTV LEX were not performed, these patients may have been treated with CDT under the diagnosis of lymphedema. Therefore, even if lymphoscintigraphy shows

lymphedema findings, these patients require additional CTV LEX to rule out DVT.

This study compared DVT and non-DVT groups to identify patients at high risk of DVT. A previous study reported that inpatients or advanced stage patients were at a higher risk of developing DVT.^[2,3] In our study, the presence of distant metastasis was correlated with DVT frequency since patients with distant metastasis have poor performance status; thus, their immobility may influence the occurrence of DVT.

Some of the results in this study differ from those of the previous study. The increased risk of venous thromboembolism with systemic chemotherapy and radiotherapy was well documented in prior studies.^[24–27] However, in our analysis, radiotherapy was not a significant risk factor for DVT since patient characteristics differed. In the DVT group, there were relatively more ovarian cancer patients, which may have contributed to this discrepancy since treatment options for ovarian cancer did not include radiotherapy.

Although there was no statistically significant difference, symptom onset time was longer in the non-DVT group. This demonstrates that DVT tends to occur at the acute disease stage. Perhaps lymphedema is a more common cause of LEX edema in patients with a long duration from the onset of malignancy to the development of edema.

We used ROC curve analysis to investigate D-dimer level as a potential biomarker for early diagnosis. In proximal DVT patients, the highest overall diagnostic accuracy ($J = 0.57$) was observed at a cutoff of 2.32 $\mu\text{g/mL}$ (sensitivity 78.1%, specificity 79.1%). In DVT patients, the highest overall diagnostic accuracy ($J = 0.54$) was observed at a cutoff of 2.12 $\mu\text{g/mL}$ (sensitivity 72.7%, specificity 81.1%). Patients with proximal DVT had a slightly higher D-dimer cutoff value because they tended to have extensive DVT lesions.

This study has several limitations. First, because of its retrospective nature, missing information could not be collected for some patients, for example, only 35 patients in the DVT group underwent lymphoscintigraphy and only 4 of the proximal DVT patients underwent US. Moreover, its retrospective nature may have led to unintentional selection bias. Second, the patient's performance status was not investigated in this study. In advanced cancer patients, poor performance results in immobility, which may be associated with DVT. Finally, our sample size was small for investigating D-dimer cutoff values. Further studies are needed to verify the D-dimer cutoff that correlates with proximal DVT.

5. Conclusions

Many patients with gynecologic cancer have isolated proximal DVT. It is possible that patients with DVT will also have findings of lymphedema on lymphoscintigraphy. If patients with proximal DVT were misdiagnosed with simple lymphedema and treated with CDT, risk of PE may increase and cause life-threatening complications. In addition, our study showed that distal organ metastasis and higher D-dimer level were associated with the presence of proximal DVT. Overall, CTV LEX is a useful diagnostic tool for gynecologic cancer patients with LEX edema, particularly high-risk patients, and should be used at the initial evaluation.

Author contributions

Jae Yong Jeon conceived the design of the study. Won Jun Kim and Dae Hwan Park collected the data. Won Jun Kim wrote the

manuscript. JaYoung Kim and Minsoo Kang reviewed the manuscript.

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