Original Article

A detailed analysis of lymph node recurrence in endometrial carcinoma

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Background: The lymph node (LN) is one of the main sites of recurrence in patients with endometrial carcinoma (EC). Literature specifically analyzing LN recurrence (LNR) in EC remains limited in number.

Methods: Patients with EC undergoing surgery between 2006 and 2021 in Peking University People's Hospital was included, clinicopathological data of whom were collected and analyzed retrospectively by R 4.0.3.

Results: A total of 792 patients were included, with 73 patients having recurrence, among whom 21 patients had LNR. Median recurrence-free survival (RFS) in patients with LNR was 16 [4–39] months. LNR was extensive, with pelvic LNs most commonly involved (9/21). There are various patterns of LNR, with 33.3% (7/21) LN-only recurrence. Multivariable analysis suggested advanced stage, larger tumor diameter and poor histology were independent risk factors for LNR. Patients with LN metastasis (LNM) diagnosed at initial treatment accounted for 47.6% (10/21) of cases with LNR, 60.0% (6/10) of whom had recurrent LNs beyond the region of LNM, 90.0% (9/10) of whom had recurrence nodes overlapping with the range of lymphadenectomy. Uni- and multi-variable analysis suggested lymphadenectomy was not a protective factor for LNR, with both the range and number of LNs harvested considered.

Conclusions: LNR is common in patients with EC, with an extensive range and various patterns of recurrence. The International Federation of Gynecology and Obstetrics (FIGO) stage, tumor diameter and histology were independent risk factors for LNR, but lymphadenectomy seemed not a protective factor for LNR.

Keywords: Endometrial carcinoma (EC); lymph node recurrence (LNR); risk factor; lymphadenectomy

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Introduction

Uterine cancer, the second most common gynecological cancer in China, accounted for 2.18×10^4 death in 2015 (1). Endometrial carcinoma (EC), constituting the majority of uterine cancer, has a fairly low recurrence rate (2), and the lymph node (LN) is one of the main sites of recurrence (3-5). LN recurrence (LNR) was seldomly discussed as a separate topic, and was usually incorporated into the comparison between 'distant recurrence' and 'locoregional recurrence' (3). Studies discussing the risk or protective factors of LNR remain limited in number (5). Our study is designed to discuss the incidence, distribution and risk factors of LNR, including the potential protective effect of lymphadenectomy. We present the following article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2588/rc).

Methods

Study population and treatment

We retrospectively analyzed patients with EC in Peking University People's Hospital, who underwent surgery between 2006 to 2021. Clinicopathological data such as the International Federation of Gynecology and Obstetrics (FIGO) 2009 stage, tumor diameter, histology, lymphovascular space invasion (LVSI), peritoneal cytology, lymphadenectomy and adjuvant therapy, were collected from the medical record system. Histology was classified by invasiveness into 'endometrioid G1/2', 'endometrioid G3' and 'non-endometrioid'. Generally, patients with EC (I) <2 cm; (II) myometrial invasion (MI) <1/2; (III) endometrioid G1/2 would have a surgery without systemic lymphadenectomy, otherwise a staging surgery ± sentinel LN (SLN) biopsy would be adopted. Pelvic lymphadenectomy (PLND) involved external, internal and common iliac LNs, obturator LNs and deep inguinal LNs in our institution. Whether to perform para-aortic lymphadenectomy (PALND) depended on the range and pathological characteristics of the tumor, including intraoperative pathological findings of SLNs. Risk grouping for recurrence was in accordance with the guideline by the European Society of Gynaecological Oncology, the European Society for Radiotherapy and Oncology and the European Society of Pathology (ESGO/ESTRO/ESP) published in 2015 (6). Adjuvant therapy for EC included radiotherapy and chemotherapy, which were adopted generally according to patients' risk stratification, with age, health status and economic condition included in the practice as well. Patients with no less than intermediate risk generally received radiotherapy. The dose and range of radiotherapy depended on clinicopathological parameters, such as cervical involvement, LVSI, LN metastasis (LNM), residual foci, etc. Patients with no less than high-intermediate risk generally received chemotherapy ± radiotherapy, with platinum plus taxane being the most common regimen. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Peking University People's Hospital (No. 2020PHB013-01) and individual consent for this retrospective analysis was waived.

Follow-up and recurrence classification

Follow-up data were collected using medical record system, phone call and text message, including physical examination, ultrasonography, tumor marker, etc. CT and MRI scan were adopted if necessary. Follow-up was conducted every 3 months for the first 2 years, every 6 months for the next 3 years, and yearly since the fifth year. LNR was defined as recurrence in LN bearing area, e.g., pelvic sidewall, para-aortic area, consistent with the previous study (5), with/without recurrence of other patterns. Besides LNR, pelvic recurrence and peritoneal recurrence were adopted to refer to recurrence occurring in pelvic cavity and peritoneal cavity, e.g., recurrence in the vaginal cuff and on the surface of the liver. Distant recurrence referred to recurrence in distant organs or deep in the parenchyma of pelvic and abdominal organs, e.g., recurrence in the liver parenchyma. Recurrence-free survival (RFS) was defined as the time between surgery and the first recurrence, or death from any cause, whichever occurred first, or the last visit for patients alive without recurrence. Thus, for a cohort only composed of patients with LNR and patients without recurrence ('test-LNR') to explore risk factors of LNR, RFS is equivalent to LNR-free survival.

Statistical analysis

To explore possible risk/protective factors, univariable analysis and multivariable analysis were conducted by Kaplan-Meier analysis and Cox regression model. Mann-Whitney test was adopted to evaluate the distribution of continuous variables between groups while Chi-square test was adopted for categorized variables. All variables had an effective rate above 95% except for molecular subtype. Therefore, missing data were omitted from the analysis, while the molecular subtype was reported separately in Table S1. $P<0.05$ was considered statistically significant. Data were collected and analyzed by R 4.0.3.

Results

Overview of LNR in EC patients

A total of 792 patients with EC were included in this study, with a median follow-up of 47 [1–110] months. Clinicopathological data were presented in *Table 1*. Seventy-three (9.2%) patients experienced recurrence, with a 3-year RFS (3yRFS) of 98.2% and a 5yRFS of 97.2%. Excluding 14 patients with sites of recurrence unknown, 21 patients (35.6%) had LNR, and 38 (64.4%) had recurrence without LNR. Patients with LNR had a median RFS of 16 [4–39] months, with 76.2% (16/21) experiencing recurrence

Table 1 Clinicopathological characteristics of the EC patients, excluding recurrence with sites unknown

Clinicopathological characteristics	LNR[†] (n=21)	Recurrence without LNR (n=38)	No recurrence (n=733)
Age (years), median [range]	57.0 [46–76]	57.0 [23–77]	56.0 [28–83]
Tumor diameter (cm), median [range]	3.8 [0.8–11.0]	3.5 [0.1–10.0]	2.5 [0.1–16.0]
CA125 (U/mL), median [range]	38.0 [5.0–3,060.0]	23.4 [4.2–530.8]	20.5 [4.5–1,296.0]
Stage, n (%)			
I	6 (1.0)	16 (2.6)	602 (96.5)
II	1 (2.3)	2 (4.7)	40 (93.0)
III	8 (9.2)	9 (10.3)	70 (80.5)
IV	6 (25.0)	11 (45.8)	7 (29.2)
Histology, n (%)			
Endometrioid G1/2	6 (1.0)	17 (2.8)	574 (96.1)
Endometrioid G3	7 (8.2)	5 (5.9)	73 (85.9)
Non-endometrioid	8 (8.3)	16 (16.7)	72 (75.0)
LVSI, n (%)			
Negative	14 (2.1)	25 (3.8)	619 (94.1)
Positive	7 (5.8)	13 (10.8)	100 (83.3)
Peritoneal cytology, n (%)			
Negative	13 (1.8)	23 (3.2)	676 (94.9)
Positive	5 (9.4)	14 (26.4)	34 (64.2)
Chemotherapy, n (%)			
No	4 (0.9)	8 (1.8)	438 (97.3)
Yes	17 (5.2)	30 (9.2)	280 (85.6)
Radiotherapy, n (%)			
No	13 (2.6)	28 (5.7)	454 (91.7)
Yes	8 (5.7)	10 (7.1)	122 (87.1)
Lymphadenectomy, n (%)			
None	3 (2.5)	7 (5.7)	112 (91.8)
Biopsy only	0	3 (3.5)	82 (96.5)
PLND	5 (4.3)	8 (7.0)	102 (88.7)
PPALND	13 (2.9)	20 (4.4)	423 (92.8)
LNM, n (%)			
No	11 (1.5)	27 (3.8)	673 (94.7)
Yes	10 (14.9)	11 (16.4)	46 (68.7)

[†], with/without recurrence in sites beyond LNs. EC, endometrial carcinoma; CA125, carbohydrate antigen 125; LVSI, lymphovascular space invasion; PLND, pelvic lymphadenectomy; PPALND, pelvic and para-aortic lymphadenectomy; LNM, lymph node metastasis; LNR, lymph node recurrence; LNs, lymph nodes.

within 2 years (Table S1).

Distinct from LNM mainly involving pelvic and para-aortic LNs, LNR seemed more extensive, with a detailed description in Table S1. Common sites of LNR were as follows: pelvic LNs (9/21), retroperitoneal LNs (not specific) (5/21), inguinal LNs (4/21), para-aortic LNs (3/21), mediastinal LNs (2/21), supraclavicular LNs (2/21), the others.

Only 33.3% (7/21) of patients with LNR experienced LN-only recurrence, while the others experienced combined recurrence, with LN + distant ± others being the most common combination (7/21) (Figure S1).

Risk factors of LNR in EC patients

A cohort consisting of patients with LNR and patients with no recurrence was defined as 'test-LNR' (n=740), in order to discuss risk factors of LNR, excluding recurrent cases without LNR or with unknown sites of recurrence.

Advanced stage, poor histology, LVSI, tumor diameter ≥2 cm, LNM and adjuvant chemotherapy were significantly related to LNR by univariable analysis, among which only advanced stage [hazard ratio (HR): 6.8, 95% confidence interval (CI): 2.3–20.1], larger tumor diameter (HR: 1.2, 95% CI: 1.0–1.4) and poor histology (G3 *vs.* G1/2: HR: 6.9, 95% CI: 1.9–25.0; non-endometrioid *vs.* G1/2: HR: 10.6, 95% CI: 3.0–37.4) were independent risk factors of LNR by multivariable analysis (*Table 2*).

LNM and LNR

LNM was significantly associated with LNR in univariable analysis, and among patients with LNR, 47.6% (10/21) exhibited LNM at initial treatment, defined as 'LNMR'. In LNMR patients, 80.0% (8/10) had recurrent LNs related to metastatic LNs, e.g., left deep inguinal LNs metastasis → left inguinal LNs recurrence. However, 60.0% (6/10) of such LNMR patients had recurrent LNs beyond the regions of initial LNM, e.g., pelvic LNs metastasis → pelvic, para-aortic and inguinal LNs recurrence (Table S1).

Intriguingly, all of LNMR patients underwent systemic lymphadenectomy, with 80.0% (8/10) undergoing pelvic and para-aortic lymphadenectomy (PPALND) and 20.0% (2/10) undergoing PLND. However, 90.0% (9/10) of LNMR patients had recurrent LNs overlapping with the range of lymphadenectomy, suggesting possible failure of lymphadenectomy to eradicate tumor cells in the lymphatic system, even within the scope of this operation.

Effect of lymphadenectomy on LNR

Univariable analysis suggested lymphadenectomy was not a protective factor for LNR in EC patients (*Table 2*). Further multivariable analysis including lymphadenectomy and independent risk factors reached in *Table 2* didn't support the protective effect of lymphadenectomy for LNR (P=0.351), either. A Chi-square test stratified by LNM exhibited no correlation between lymphadenectomy and LNR for both LNM cases and non-LNM cases (P>0.999 and P=0.701, respectively, Fisher's exact test).

No association was suggested between the scope of lymphadenectomy and LNR by univariable analysis (*Figure 1*). Since no LNR occurred to patients undergoing LN biopsy only, they were merged with patients not undergoing lymphadenectomy into one group to conduct another univariable analysis, yet still failing to exhibit an association between systemic lymphadenectomy and a decrease in LNR (P=0.300).

Median number of LNs harvested in LNR cases was 20 [0–56], while that of cases without recurrence was 26 [0–78] (*Figure 2*). No significant difference was observed between the groups (P=0.254, Mann-Whitney test).

Discussion

As the majority of uterine cancer, EC has a relatively low rate of recurrence (2,7), but the incidence of recurrence still indicates a poor prognosis (8). Recurrence is often detected in vagina, pelvic cavity, peritoneal cavity, lung, liver, bone, LN (pelvic, para-aortic), etc. (4,7,9). LNR, as one of the main patterns of EC recurrence (3,4), is seldom documented specifically (5). LNR indicates failure in the lymphatic system, and there might exist unique characteristics. We discussed several interesting topics of LNR, including its incidence, common sites, risk factors, as well as relationship between LNR and LNM, between LNR and lymphadenectomy.

LNR existed in over 1/3 of recurrent EC cases, with a more extensive pattern involving lymphatic system around the whole body (4,10,11). Still, LNs mostly involved in recurrent EC were those in metastatic cases at initial treatment, i.e., retroperitoneal LNs, suggesting a possible mechanism of LNR from growth of potential metastatic lesions in the lymphatic system, which survived primary surgery and adjuvant therapy. This was consistent with the univariable analysis identifying LNM as a risk factor for LNR. Several studies demonstrated a similar correlation

Table 2 Survival analysis for risk factors of LNR in test-LNR

Clinicopathological features	Univariable analysis		Multivariable analysis	
	N	P value	HR (95% CI)	P value
FIGO stage		<0.001*		
I/II	649		Reference	
III/IV	91		6.8 (2.3–20.1)	0.001*
LVSI		0.004*		
Negative	633		–	–
Positive	107			
Tumor diameter (cm)†		0.004*		
<2 cm	289		1.2 (1.0–1.4)	0.032*
≥2 cm	447			
Histological subtype		<0.001*		
Endometrioid G1/2	580		Reference	
Endometrioid G3	80		6.9 (1.9–25.0)	0.003*
Non-endometrioid	80		10.6 (3.0–37.4)	<0.001*
Peritoneal cytology		<0.001*		
Negative	689		–	–
Positive	39			
LNM		<0.001*		
No	684		–	–
Yes	56			
Adjuvant radiotherapy		0.080		
No	467		–	–
Yes	130			
Adjuvant chemotherapy		<0.001*		
No	442		–	–
Yes	297			
Lymphadenectomy		0.421		
Yes	626		–	–
No	114			

†, adopted into multivariable analysis as a continuous variable; *, P<0.05. LNR, lymph node recurrence; FIGO, the International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; LNM, lymph node metastasis; HR, hazard ratio; CI, confidence interval.

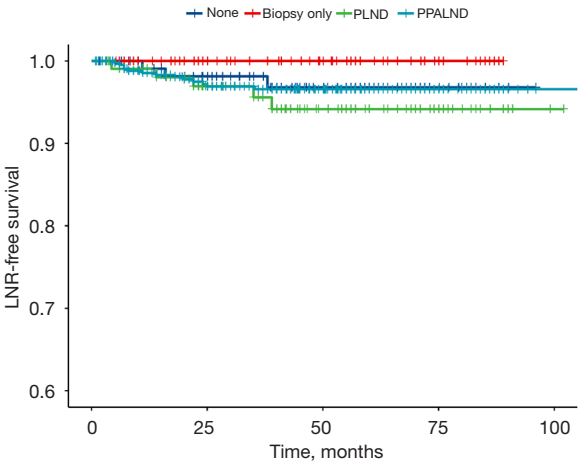

Figure 1 No association exhibited between range of lymphadenectomy and decrease of LNR in test-LNR. PLND, pelvic lymphadenectomy; PPALND, pelvic and para-aortic lymphadenectomy; LNR, lymph node recurrence.

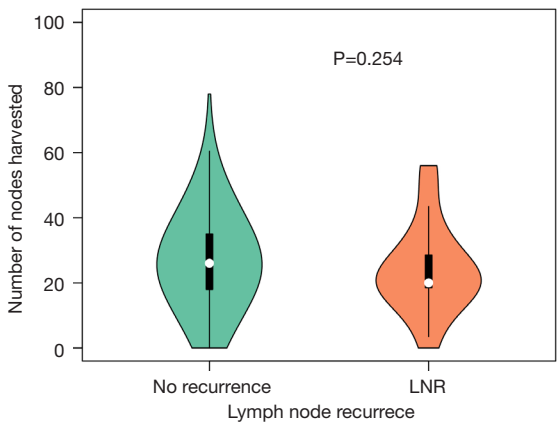

Figure 2 Distribution of LNs harvested between no-recurrence and LNR group in test-LNR. LNR, lymph node recurrence.

(5,11). However, 88.9% of LNMR patients had recurrent LNs exceeding the range of LNM at initial treatment, suggesting that LNM might have the ability to further disseminate in the lymphatic network, rather than simply be an exhibition of invasiveness of the primary lesion. This research seems the first to describe this phenomenon in EC.

The benefit of lymphadenectomy in EC patients has been a controversial topic for over a decade (12-14). The survival advantage associated with lymphadenectomy exists primarily in patients with a relatively high risk of recurrence (14-18), and improperly expanding the indication of lymphadenectomy might result in more adverse effects instead (19-25). Our research didn't support the role of lymphadenectomy in preventing LNR in terms of the scope and number of LNs harvest, with agreement with Mariani *et al.* (5). Lymphadenectomy removes LNs in certain node-bearing regions, instead of the whole lymphatic network. Considering the expanding property of the tumor in LNMR patients stated above, we propose chemotherapy agents with sufficient concentration and efficacy in lymphatic system might be crucial for prevention of LNR, rather than the attempt to eradicate LNs in drainage directions.

This study is the second study focused specifically on LNR in EC. In 2002, Mariani *et al.* firstly defined a similar concept, lymphatic failure, as a relapse occurring on node-bearing area as the primary site of failure. Different from our discussing risk factor in a cohort consisting of LNR and non-recurrence patients, Mariani *et al.* explored the difference between LNR and recurrence in other sites based upon a cohort of recurrent EC patients. Three predictors of lymphatic failure were LVSI, positive LNs, and cervical stromal invasion (5), two of which were also identified as risk factors of LNR in our research. Independent risk factors identified in our research, namely FIGO stage, tumor diameter and histology, were all related to malignant behavior of the tumor. Future research on the invasion, survival and proliferation of EC cells in the lymphatic system will help understand the formation of LNR and provide potential therapeutic targets.

Still there exist some limitations in our study. Over the span of 15 years, indications and practice of lymphadenectomy in EC have evolved in our institution, increasing the risk of confounding bias, e.g., random LN biopsy in the past *vs.* SLN biopsy nowadays. Also, due to relatively few cases of LNR, systematic comparison between LNR and recurrence in other sites as Mariani *et al.* was not conducted, and there was no separate discussion of cases with LN-only recurrence. Finally, a negative result might originate from a small sample size, rather than the objective lack of difference.

In summary, our study suggested LNR was common in patients with EC, with an extensive range and various patterns of recurrence. FIGO stage, tumor diameter and histology were independent risk factors of LNR, but lymphadenectomy seemed not protective for LNR.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2588/rc

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-21-2588/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Peking University People's Hospital (No. 2020PHB013-01) and individual consent for this retrospective analysis was waived.

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Supplementary

Table S1 Clinicopathological characteristics of the 21 patients with LNR

Patient	Risk group	Risk factors	Sites of recurrence	RFS (months)	Number of LNs removed	Range of lymphadenectomy
01	High-intermediate	≥65 years old; stage II; G3; ≥2 cm	Left iliac LNs	20	38	PPALND
02	High	≥65 years old; stage IIIC2; clear cell; LVSI; ≥2 cm; CA125 ≥35 U/mL	Retroperitoneal LNs	7	20	PPALND
03	High	≥65 years old; stage IIIB; CNH; serous; ≥2 cm; MI ≥1/2	Para-aortic LNs	5	22	PPALND
04	Low	None	Perirenal LNs	25	31	PPALND
05	High	Stage IIIC1; LVSI	Retroperitoneal LNs, bilateral inguinal LNs	39	23	PLND
06	High	Stage IIIC2; serous; LVSI; ≥2 cm; MI ≥1/2; CSI	Para-aortic LNs, pulmonary LNs	8	19	PPALND
07	High	Stage IIIC1; G3	Pelvic LNs, retroperitoneal LNs, left supraclavicular LNs	18	33	PPALND
08	High	≥65 years old; serous; ≥2 cm	Mediastinal and bilateral hilar LNs, right iliac LNs, para-aortic LNs	35	26	PPALND
09	High	Stage IIIA; cytology (+); ≥2 cm; CA125 ≥35 U/mL	Cardio-diaphragmatic angle LNs, hepatic hilar LNs; abdominal cavity (soft tissue mass between diaphragm and liver); liver	22	20	PLND
10	High	≥65 years old; stage IIIC1; G3; ≥2 cm, CA125 ≥35 U/mL, MI ≥1/2	Left inguinal LNs; vaginal cuff; lung	35	19	PLND
11	Metastatic	Stage IVB; G3; cytology (+); ≥2 cm; CA125 ≥35 U/mL; MI ≥1/2; LNM	Right iliac LNs; vaginal cuff	11	56	PPALND
12	Metastatic	Stage IVB; serous; LVSI; cytology (+); ≥2 cm, CA125 ≥35 U/mL; LNM; adnexal involvement	Intraperitoneal LNs; lung	6	51	PPALND
13	Metastatic	≥65 years old; stage IVB; serous; ≥2 cm; CA125 ≥35 U/mL; adnexal involvement	Bilateral iliac LNs; Mesenteric LNs, intraperitoneal LNs; vaginal cuff; peritoneal cytology (+)	11	0	None
14	Intermediate	Stage IB; ≥2 cm; CA125 ≥35 U/mL	Cervical LNs, axillary LNs; breast skin, lung, ilium, liver; mediastinal	14	6	PLND
15	Low	≥2 cm	Left iliac LNs; right ischium	22	18	PPALND
16	Intermediate	≥65 years old; G3; ≥2 cm	Retroperitoneum LNs, intraperitoneal LNs; peritoneal cavity, great omentum	38	0	None
17	High-intermediate	Stage IB; G3	Right iliac LNs; peritoneal cavity; lungs	4	17	PLND
18	Metastatic	Stage IVB; G3; ≥2 cm	Left inguinal LNs; pelvic cavity; peritoneal cavity	16	0	None
19	High	Stage IIIC2; clear cell; LVSI; ≥2 cm	Bilateral iliac and retroperitoneal LNs, bilateral inguinal LNs, mediastinal LNs; vaginal cuff, pelvic cavity; hilar area; lungs	7	24	PPALND
20	Metastatic	Stage IVB; serous; LVSI; cytology (+); ≥2 cm; CA125 ≥35 U/mL; MI ≥1/2; adnexal involvement; LNM	Pelvic and intraperitoneal LNs; pelvic intestinal space; peritoneum	14	15	PPALND
21	Metastatic	Stage IVB; LVSI; cytology (+); ≥2 cm; MI ≥1/2; adnexal involvement; LNM	Para-pancreatic LNs, right supraclavicular LNs, bilateral mandibular LNs; vaginal cuff; liver	24	19	PPALND

LVSI, lymphovascular space invasion; CA125, carbohydrate antigen 125; CNH, copy-number high; MI, myometrial invasion; CSI, cervical stroma invasion; LNM, lymph node metastasis; LNs, lymph nodes; RFS, recurrence-free survival; PPALND, pelvic and para-aortic lymphadenectomy; PLND, pelvic lymphadenectomy.

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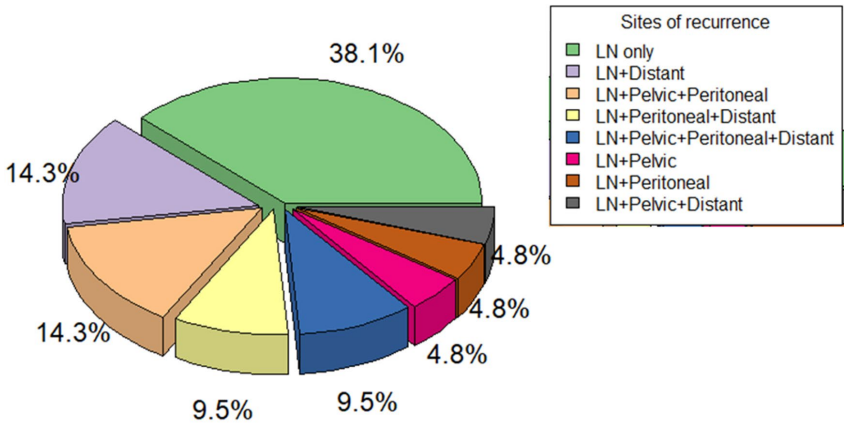

Figure S1 Multiple patterns of recurrence of LNR. LN, lymph node; LNR, lymph node recurrence.

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