Exploring the Clinical Characteristics of the Lymph Nodal Metastatic Regions in Patients with Endometrial Cancer

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Research Article

Keywords: endometrial cancer, lymph node dissection, survival

Posted Date: November 29th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-944965/v1>

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Abstract

Objective

To evaluate clinical factors that can help determine the extent of lymphadenectomy required in endometrial cancer patients and confirm the differences of metastatic lymph node regions based on the risk factors for endometrial cancer patients.

Methods

The medical records of 468 endometrial cancer patients were retrospectively reviewed between January 2006 and December 2018. Patients were categorized into pelvic lymph node dissection (PLND) and pelvic plus para-aortic lymph nodes dissection (PPALND) groups. Demographics, recurrence-free survival, and 5-year overall survival rates were compared, and the clinical factors affecting survival were evaluated using Cox proportional hazards model.

Results

The median follow-up period was 55 months (range, 6–142 months). The mean age was higher in the PPALND group than in the PLND group (51.0 vs. 54.5 years; $P < 0.001$). The PPALND group had a higher International Federation of Gynecology and Obstetrics (FIGO) stage, lymphovascular invasion, endocervical invasion, and FIGO grade ($P = 0.001$) than the PLND group. The PPALND group had higher 5-year recurrence-free and overall survival rates than the PLND group. While comparing lymph node (LN) metastasis confirmed pathologically, the group with confirmed metastasis showed a higher number of high-risk group patients than lymph node-negative patients. However, no difference was observed in pelvic LN metastasis, pelvic plus para-aortic LN metastasis, and isolated para-aortic LN metastasis groups.

Conclusions

When treating patients with endometrial cancer, risk group evaluation is an important factor for determining LN dissection. Our study found no differences in clinical factors of metastatic LN regions.

Introduction

Endometrial cancer has the highest incidence among all gynecological cancers in Western countries [1], and a continuous increase in its incidence has been observed in Korea [2]. Endometrial cancer is diagnosed at a relatively early stage than other gynecological cancers, owing to patients presenting with symptoms such as vaginal bleeding or discharges, and can be easily diagnosed using endometrial biopsies, such as curettage, aspiration, or hysteroscopic biopsy. Regarding the treatment for endometrial

cancer, surgery is performed along with the administration of adjuvant treatment based on the clinical stage. The types of surgery include total hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy, and the stage is determined according to the pathology report.

The extent of lymph node (LN) resection in cases of endometrial cancer has remained controversial for decades [3–7]. In 2010, the Survival Effect of Para-aortic Lymphadenectomy in Endometrial Cancer (SEPAL) study [5] reported that performing para-aortic lymph node dissection (PALND) resulted in improved survival rates among intermediate- and high-risk groups. The risk group was classified according to FIGO stage, FIGO grade, histology and lymphovascular invasion. However, limitations of this study included its retrospective nature and various biases owing to a comparison of studies conducted by different institutions that participated in the study. Only pelvic lymph node dissection (PLND) was performed in one of the institutions, and the status of the para-aortic LN was not evaluated. In contrast, several recent studies related to sentinel lymph node dissection (LND) have shown accurate detection of metastatic LNs without performing unnecessary dissections [8, 9].

In endometrial cancer, there is an additional issue of isolated para-aortic LN metastasis, which is known to occur in approximately 2–5% [10] of cases and is virtually impossible to identify using sentinel biopsy. Kang et al. reported that preoperative risk stratification of LN metastasis in endometrioid endometrial cancer patients using preoperative serum cancer antigen 125 levels and magnetic resonance imaging could help predict LN metastasis.

The National Comprehensive Cancer Network guideline indicates that LND is necessary for accurate surgical staging; however, it does not set a range for LND. As the range for LND increases, morbidity increases, along with the operation time, and it subsequently affects the recovery rate. Therefore, it is important to determine the accurate range for LND. In addition, the indication of sentinel LND needs to be more accurate.

In this study, we analyzed the risk factors associated with LN metastasis. Exploring the clinical differences in metastatic lymph nodal regions, we aimed to evaluate clinical factors that can help determine the appropriate extent of LND required for patients with endometrial cancer.

Methods

In this study, we reviewed electronic medical records of patients newly diagnosed with endometrial cancer using endometrial biopsy and treated at the National Cancer Center in South Korea between January 2006 and December 2018. This retrospective study was approved by the Institutional Review Board of our institution (IRB No. NCC2019-0272), and the requirement of informed consent was waived owing to the retrospective nature of this study.

A total of 1,578 endometrial cancer patients visited our outpatient clinic; however, 497 of those visited only once for counseling or a second opinion, and 439 patients had recurrent disease. Therefore, 468 patients who were treated with LND were included in this study (Fig. 1). We classified the patients into

two groups: PLND and pelvic plus para-aortic lymph nodes dissection (PPALND). In our institution, no specific risk factor was identified before surgery; there are cases where only PLND was performed or LND was omitted. The distinction between the PLND group and the PALND group was classified retrospectively as this study was conducted. The clinical characteristics of the two groups are summarized in Table 1. We first compared the clinical characteristics of patients who underwent PLND or PPALND. Additionally, we analyzed the detailed risk factors for LN involvement and investigated the appropriate range for LND. In total, 56 patients had pathologically confirmed LN metastasis (+) and were compared with those without LN metastasis (-)

Table 1
Baseline characteristics of patients

		Group 1		Group 2		P-value*
Characteristic	Value	(N = 141)		(N = 327)		
		N	%	N	%	
Age		50.98		54.49		0.00
Risk groups	Low	100	70.92	126	38.53	0.00
	Intermediate	23	16.31	57	17.43	
	High	18	12.77	144	44.04	
Tumor size (cm)		2.1		3.3		0.00
Myometrial invasion(mm)		3.56		7.78		0.00
Pelvic washing cytology	Negative	68	48.23	223	68.20	0.00
	Atypical cells	20	14.18	50	15.29	
	Malignant cells	4	2.84	14	4.28	
	Missing data	49	34.75	40	12.23	
LVSI	Yes	20	14.18	100	30.58	0.00
	No	121	85.82	227	69.42	
Histology	Endometrioid	130	92.20	242	74.01	0.00
	Non-Endometrioid	11	7.80	85	25.99	
FIGO grade	1	86	60.99	118	36.09	0.00
	2	38	26.95	95	29.05	
	3	8	5.67	54	16.51	
	Unknown	9	6.38	60	18.35	
Endocervix invasion	Yes	14	9.93	40	12.23	0.58
	No	127	90.07	287	87.77	
Cervix invasion	Yes	8	5.67	47	14.37	0.01
	No	133	94.33	280	85.63	
FIGO stage	Stage I-II	134	95.04	259	79.20	0.00

		Group 1		Group 2		P-value*
	Stage III-IV	7	4.96	68	20.80	
Adjuvant chemotherapy	Yes	29	20.57	117	35.78	0.00
	No	112	79.43	210	64.22	
Adjuvant radiotherapy	Yes	23	16.31	111	33.94	0.00
	No	118	83.69	216	66.06	

We collected data on clinical factors including age at diagnosis, International Federation of Gynecology and Obstetrics (FIGO) stage, FIGO grade, histology of the surgically removed tissues, method of surgical approach, the radicality of hysterectomy, LND, lymphovascular invasion, adjuvant chemotherapy, and radiotherapy. Risk group sub-categorization was also performed. FIGO grade 1 or 2 endometrioid cancers confined to the endometrium or with < 50% myometrial invasion was defined as low risk. Stage 1A grade 3 and Stage 1B grade 1 were defined as intermediate risk. Stage 1B grade 3 disease or Stages II, III, or IV disease were defined as high risk. [11] These clinical risk factors were classified using the European Society for Medical Oncology guidelines [12].

We examined the relationships of clinical factors and risk groups with PLND/PPALND groups using the chi-square test, Fisher's exact test, or Student's *t*-test. Five-year overall survival and recurrence-free survival rates were estimated using the Kaplan–Meier analysis. Patients lost to follow-up were censored. The log-rank test was used for comparing survival curves between the two groups solely and jointly with the three risk groups and FIGO stages. Cox proportional hazards model was applied to identify the predictive factors for prognosis with hazard ratios. *P* values < 0.05 were considered statistically significant.

Results

Data of 468 patients were selected for analysis: 141 patients received PLND alone and 327 patients received PPALND. The baseline characteristics of each group are shown in Table 1. The number of low-risk patients was higher in the PLND group than in the PPALND group. Malignant peritoneal cytology, lymphovascular invasion, endocervical invasion, and the non-endometrioid histology ratio were higher in the PPALND group than in the PLND group; the patterns of these characteristics differed significantly between the two groups. Additionally, the FIGO stage ($P < 0.001$) was higher in the PPALND group than in the PLND group. The Kaplan–Meier survival curve showed no difference between the two groups ($p = 0.526$ for OS, (Fig. 1), higher survival rates in the PPALND group were observed than in the PLND group in intermediate and high-risk groups (88.8 % vs. 80.8 % in the high-risk group, 94.9 % vs. 89.1 % in the intermediate group) (Fig. 2). These results have been reported by the SEPAL study in 2010.

The proportion of high-risk patients was higher in the LN metastasis (+) group than in the LN metastasis (-) group. Lymphovascular invasion, cervix invasion, the FIGO grade, and the FIGO stage showed

significant differences between the LN metastasis (+) and LN metastasis (-) groups (Table 2).

Table 2
Comparison of clinical characteristics between lymph node (+) and lymph node (-) metastasis patients

		Group 3		Others		P-value*
Characteristic	Value	(N = 56)		(N = 412)		
		N	%	N	%	
Age		55.29		53.18		0.16
Risk groups	Low	6	10.71	226	54.85	0.00
	Intermediate	11	19.64	80	19.42	
	High	39	69.64	106	25.73	
Tumor sizes(cm)		4.87		2.65		0.00
Myometrial invasion depth(mm)		16.41		5.16		0.00
Pelvic washing cytology	Negative	37	66.07	254	61.65	0.02
	Atypical cells	7	12.50	63	15.29	
	Malignant cells	6	10.71	12	2.91	
	Missing data	6	10.71	83	20.15	
LVSI	Yes	39	69.64	81	19.66	0.00
	No	17	30.36	331	80.34	
Histology	Endometrioid	29	51.79	343	83.25	0.00
	Non-Endometrioid	27	48.21	69	16.75	
FIGO grade	1	5	8.93	199	48.30	0.00
	2	15	26.79	118	28.64	
	3	15	26.79	47	11.41	
	unknown	21	37.50	48	11.65	
Endocervix invasion	Yes	10	17.86	44	10.68	0.18
	No	46	82.14	368	89.32	
Cervix invasion	Yes	24	42.86	31	7.52	0.00
	No	32	57.14	381	92.48	

* Fisher' exact test for Pervic washing cytology, and X-square test for all the other variables

		Group 3		Others		P-value*
FIGO stage	I/II	0	0.00	393	95.39	0.00
	III/IV	56	100.00	19	4.61	
Adjuvant chemotherapy	Yes	47	83.93	99	24.03	0.00
	No	9	16.07	313	75.97	
Adjuvant radiotherapy	Yes	40	71.43	94	22.82	0.00
	No	16	28.57	318	77.18	
* Fisher' exact test for Pervic washing cytology, and X-square test for all the other variables						

We subcategorized patients in the LN metastasis (+) group into three distinct sub-groups: pelvic metastasis, para-aortic metastasis, and pelvic and para-aortic metastasis. Their clinical characteristics are summarized in Table 3. Clinical factors were not significantly different among the sub-groups. Kaplan–Meier analysis of recurrence-free survival and overall survival curves is shown in Fig. 3. Recurrence-free survival was significantly different between the groups, whereas overall survival was not significantly different. Myometrial invasion depth was the only clinical factor associated with recurrence-free and overall survival (Table 3).

Table 3
Comparison of clinical characteristics among statuses of lymph node metastasis

Characteristic	Value	Pelvic LN metastasis (N = 19)		Para-aortic LN metastasis (N = 29)		Pelvic & para-aortic LN metastasis (N = 8)		P-value
		N	%	N	%	N	%	
Age		51.63		57.17		57.12		0.16 ^{\$}
Risk groups	Low	2	10.53	4	13.79	0	0	0.18*
	Intermediate	7	36.84	3	10.34	1	12.5	
	High	10	52.63	22	75.86	7	87.5	
Tumor size		4.29		4.82		6.40		0.37 ^{\$}
Myometrial invasion		14.08		17.09		23.00		0.43 ^{\$}
Pelvic washing cytology	Negative	11	57.89	19	65.52	7	87.5	0.68*
	Atypical cells	2	10.53	4	13.79	1	12.5	
	Malignant cells	2	10.53	4	13.79	0	0	
	Missing data	4	21.05	2	6.90	0	0	
LVSI	Yes	10	52.63	24	82.76	5	62.5	0.07*
	No	9	47.37	5	17.24	3	37.5	
Histology	Endometrioid	12	63.16	13	44.83	4	50	0.47*
	Non-Endometrioid	7	36.84	16	55.17	4	50	
FIGO grade	1	4	21.05	1	3.45	0	0	0.45*
	2	6	31.58	7	24.14	2	25	
	3	3	15.79	9	31.03	3	37.5	
	unknown	6	31.58	12	41.38	3	37.5	
Endocervix invasion	Yes	3	15.79	6	20.69	1	12.5	1.00*
	No	16	84.21	23	79.31	7	87.5	

* Fisher' exact test

^{\$} ANOVA test

		Pelvic LN metastasis		Para-aortic LN metastasis		Pelvic & para-aortic LN metastasis		P-value
Characteristic	Value	(N = 19)		(N = 29)		(N = 8)		
Cervix invasion	Yes	11	57.89	12	41.38	1	12.5	0.10*
	No	8	42.11	17	58.62	7	87.5	
FIGO stage	III/IV	19	100.00	29	100.00	8	100.00	
* Fisher' exact test								
\$ ANOVA test								

Discussion

To the best of our knowledge, this is the first study to compare clinical factors by sub-dividing the site of LN metastasis. Our findings indicate that clinical differences among the metastatic position of pelvic and para-aortic LNs are non-significant, emphasizing the need for considering LN metastasis as an independent risk factor.

Regarding early endometrial cancer cases confined to the uterus, determining the range for LND remains challenging. In our study, we observed that though patients undergoing PPALND had a better survival rate than those undergoing PLND, it was known that survival was also good even when LND was not performed in the early-stage endometrial cancer [6, 13, 14].

Contrarily, LN metastasis (+) patients were mostly in Stage III, and the ratio of risk factors was clearly different from that of LN metastasis (-) patients with respect to LVSI, non-endometrioid histology, high FIGO grade, cervix invasion, deeper myometrial invasion, and large tumor size. In the presence of a risk factor, it appeared necessary to perform a full dissection for accurate staging.

In the case of endometrial cancer surgery, the extent of performing LND has been a long-standing debate. The SEPAL study concluded that a complete PALND resulted in improved survival in high-risk group patients; however, its effect in low-to-intermediate-risk patients remains unclear. Reducing unnecessary procedures, including LND, plays a very important role in improving the patients' quality of life following treatment and preventing various complications intraoperatively.

The results of this study support expanding the range for LND in the presence of a risk factor; however, when patients were confirmed as having LN metastasis, no significant difference was observed in the risk factors. In addition, no difference in risk group assessment was observed, which is used as a reference for determining the surgical scope. To the best of our knowledge, this study is the first to analyze the risk factors while considering the status of LN metastasis. The SEPAL study only compared the rate of

survival among the ranges for LND performed. However, in our study, we compared the locations of metastatic LN(s) and found no significant difference among them.

Recently, sentinel LND is often being implemented in low-risk groups. Sentinel LND, which has been widely practiced recently, performs sampling by investigating the first LN drained from the uterus to avoid full dissection. However, the exact mechanism of lymphatic drainage remains unknown in gynecological cancers [15–18].

Anxiety regarding isolated para-aortic LN metastasis has been persistent. In general, its occurrence is 2–5%; however, when LN metastasis was categorized into three groups in our study, the cases of isolated para-aortic LN metastasis did not show any remarkable risk factors.

In conclusion, in the absence of a risk factor, no LND is required, and in the presence of a risk factor, complete LND is required to eliminate issues regarding isolated para-aortic LN metastasis. Implementation of LND by classifying it as no LND at an early stage without risk factor(s) and as full LND at an early stage with risk factor(s) appears more beneficial than expanding the range for LND gradually from no LND to PLND and subsequently from PLND to PPALND, depending on the risk.

Declarations

Conflict of Interest Statement

The authors declare no competing interests.

Funding

This research was funded by National Cancer Center (NCC), South Korea (grant no. NCC-1910180)

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Figures

Figure 1. Overall survival and recurrence-free survival rates between pelvic lymphadenectomy and pelvic and para-aortic lymphadenectomy

Figure 1

Overall survival and recurrence-free survival rates between pelvic lymphadenectomy and pelvic and para-aortic lymphadenectomy

Figure 2. Overall survival and recurrence-free survival rates for sub-categorization by risk groups

Figure 2

Overall survival and recurrence-free survival rates for sub-categorization by risk groups

Figure 3. Overall survival and recurrence-free survival rates for sub-categorization by risk groups

Figure 3

Kaplan–Meier survival curve for sub-categorization of the status of lymph nodal metastatic regions.