

Original Article



Prognostic impact of the number of resected pelvic nodes in endometrial cancer: Japanese Gynecologic Oncology Group Study JGOG2043 post hoc analysis

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ABSTRACT

Objective: This study aimed to determine whether the number of resected pelvic lymph nodes (PLNs) affects the prognosis of endometrial cancer (EC) patients at post-operative risk of recurrence.

Methods: JGOG2043 was a randomized controlled trial to assess the efficacy of three chemotherapeutic regimens as adjuvant therapy in EC patients with post-operative recurrent risk. A retrospective analysis was conducted on 250 patients who underwent pelvic lymphadenectomy alone in JGOG2043. The number of resected and positive nodes and other clinicopathologic risk factors for survival were retrieved.

Results: There were 83 patients in the group with less than 20 PLNs removed (group A), while 167 patients had 20 or more PLNs removed (group B). There was no significant difference in patients' backgrounds between the two groups, and the rate of lymph node metastasis was not significantly different. There was a trend toward fewer pelvic recurrences in group B compared with group A (3.5% vs. 9.6%; $p=0.050$). Although Kaplan-Meier analysis showed no statistically significant difference in survival rates between the two groups (5-year overall survival [OS]=90.3% vs. 84.3%; $p=0.199$), multivariate analysis

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Presentation

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Y.K., K.T., Y.Y., J.S., N.S., S.N., T.N., K.Y. Data curation: H.N. Formal analysis: Y.K., M.M. Investigation: M.M. Methodology: Y.Y., K.H., W.Y. Project administration: H.W. Supervision: A.O., D.A. Writing - original draft: Y.K., H.W.

revealed that resection of 20 or more nodes is one of the independent prognostic factors (hazard ratio=0.49; 95% confidence interval=0.24–0.99; p=0.048), as well as surgical stage, high-risk histology, and advanced age for OS.

Conclusion: Resection of 20 or more PLNs was associated with improved pelvic control and better survival outcomes in EC patients at risk of recurrence who underwent pelvic lymphadenectomy alone and were treated with adjuvant chemotherapy.

Keywords: Endometrial Neoplasms; Cohort Studies; Lymph Node Excision; Multivariate Analysis

Synopsis

The therapeutic significance of thorough lymph node dissection remains controversial for high-risk endometrial cancer. We analyzed the JGOG2043 cohort who underwent pelvic lymphadenectomy alone and received adjuvant chemotherapy. Resection of ≥ 20 pelvic lymph nodes correlates with improved pelvic control and better survival outcome.

INTRODUCTION

The International Federation of Gynecology and Obstetrics (FIGO) has recommended surgical staging systems, including hysterectomy, bilateral salpingo-oophorectomy, and systematic lymphadenectomy for endometrial cancer (EC) since 1988 [1]. Because nodal involvement is one of the most significant prognostic factors for EC, the diagnostic significance of lymph node dissection (LND) has been established. It is beneficial to pathologically diagnose lymph node metastasis (LNM) to identify those who need post-operative adjuvant therapy. However, LND would lead to longer operation time, more blood loss, and complications such as lymphedema and lymph cyst formation [2], which would result in lowering the patient's quality of life. If a higher extent of LND would result in a better prognosis, LND can be strongly recommended for those with preoperative risk of LNM. Still, its survival benefit remains controversial so far.

Because nodal involvement rate has been reported to be increased by performing systematic LND [3], systematic LND is recommended in the staging procedure for EC patients at intermediate- or high-risk of recurrence. Regarding the thoroughness and anatomical extent of LND, gynecologic surgeons have different strategies for how thoroughly to perform pelvic LND and whether to perform para-aortic LND.

The Japanese Gynecologic Oncology Group (JGOG) previously conducted a phase III trial (JGOG2043) to determine the best adjuvant chemotherapeutic regimen for EC [4]. Patients indicated for adjuvant therapy were enrolled, and all of them received adjuvant chemotherapy, excluding those with a low risk of recurrence curable by surgery alone, extending beyond the abdominal cavity, and having 2 cm or greater residual tumor. In JGOG 2043, all patients underwent pelvic LND; almost half experienced para-aortic LND. We, therefore, used the cohort of the patients who underwent pelvic LND alone to analyze the prognostic impact of PLN count in EC in this post hoc study because para-aortic LND has been reported to affect the patient's survival under various clinical settings [5,6]. Although the JGOG2043 trial included pelvic LND as an eligibility criterion for enrollment, it did not specify the exact

technique or extent of LND. The number of lymph nodes removed was expected to vary because it was a randomized, multicenter trial with 118 enrolled centers. Additionally, in Western countries, adjuvant radiation therapy is generally applied for local control. However, in JGOG2043, adjuvant therapy was chemotherapy, which would allow us to more accurately evaluate the prognostic effect of pelvic LND as a local therapy. Therefore, we considered this population suitable to evaluate the prognostic value of the number of lymph nodes removed.

MATERIALS AND METHODS

The JGOG2043 recruited patients with pathologically confirmed EC who were considered to show a high risk of recurrence following surgery. A high risk of recurrence was defined as FIGO surgical stage I/II with myometrial invasion (MI) of more than half and histologic grade 2–3 (including serous, clear cell, and undifferentiated histology) or surgical stage III/IV without distant metastasis beyond the abdominal cavity. All patients underwent total hysterectomy, bilateral salpingo-oophorectomy, and at least pelvic LND, resulting in a maximum residual tumor diameter of less than 2cm. Para-aortic LND was optional and performed by the decision of investigators depending on the risk of recurrence and para-aortic LNM. The JGOG2043 was approved by the institutional review board at each participating institution, and written informed consent was obtained from all participants. A total of 788 eligible patients were enrolled and randomly assigned to the following treatment arms at a 1: 1: 1 ratio: doxorubicin+cisplatin (AP therapy, 263 patients), docetaxel+cisplatin (DP therapy, 263 patients), or paclitaxel+carboplatin (TC therapy, 262 patients). All participants essentially received six cycles of chemotherapy. After completion of initial treatments, follow-up continued until disease relapse or recurrence was noted without the addition of further anticancer therapy, including radiotherapy. The median follow-up period was seven years.

The following demographic pieces of information were retrieved: age at initiation of treatment, surgical stage (FIGO 1988), histologic grade, histologic type, MI, cervical invasion, lymph vascular space invasion (LVSI), pelvic LNM, ascitic cytology, and regimen of adjuvant chemotherapy. Regarding LNM, information on the number of resected and positive nodes in the pelvic region was retrieved. Additionally, we initiated our analysis following a predefined protocol, where patients were categorized into two groups: one with fewer than 20 nodes removed and another with 20 or more nodes removed. This categorization was based on previous reports showed that resection of over 22 nodes is adequate pelvic LND [7], and in the patients with intermediate or high-risk disease, a more extensive LND (1, 2–5, 6–10, 11–20, and >20) was associated with improved 5-year disease-specific survivals across all five groups respectively [8] and on past clinical trials where removing 20 or more nodes was deemed adequate for pelvic LND [9]. For statistical analysis, the χ^2 test was used to assess independence. Correlations between survival and clinicopathological factors were analyzed by Cox proportional hazard analysis. Survival was estimated by the Kaplan-Meier method with stratification by various factors, and differences in survival between groups were analyzed by the log-rank test. Statistical analysis was performed using the JMP software program ver16.1 (SAS Institute Inc., Cary, NC, USA). The values of $p < 0.05$ were considered statistically significant. This study was approved by the Institutional Review Board of Hokkaido University Hospital (protocol code 021-0029; July 18, 2021). The requirement for obtaining informed consent was waived owing to the study's retrospective nature. Patient consent was obtained by opt-out.

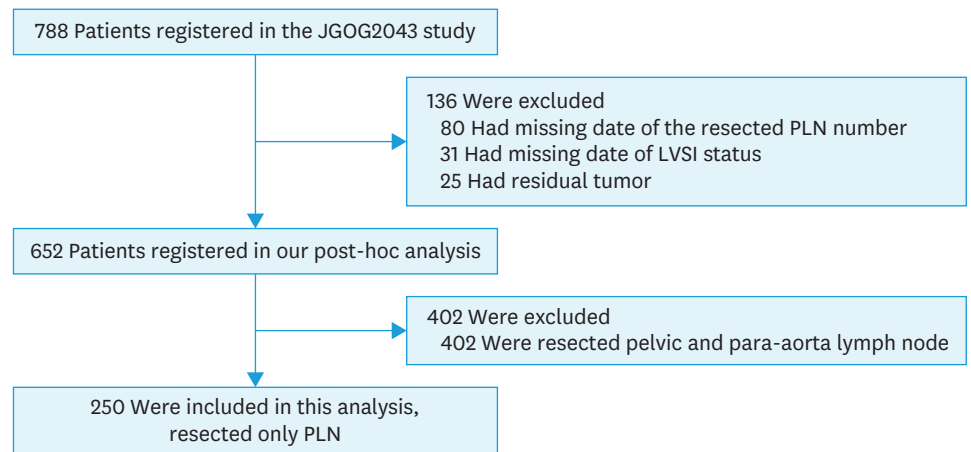


Fig. 1. Flow chart of patient's enrollment. LVSI, lymph vascular space invasion; PLN, pelvic lymph node.

RESULTS

The CONSORT flow diagram of this retrospective study is shown in **Fig. 1**. Among 788 patients registered, firstly, we excluded the patients who had the missing data of the resected PLN number (n=80), those with any residual tumors (n=25) and those with missing data on LVSI (n=31). The remaining 652 cases were subjected to another post-hoc analysis examining the significance of para-aortic LND. Secondly, we excluded those who underwent pelvic and para-aortic LND (n=402). Thus, a total of 250 patients were enrolled in this study.

The patient's characteristics are shown in **Table 1**. Sixty-seven patients (26.8%) showed positive pelvic nodes among 250 patients. The median number of resected nodes was 25 (interquartile range, 16–34) in the pelvic region (**Fig. 2**). We continued further analysis by dividing all patients into 2 groups (group A; less than 20 nodes, or group B; 20 or more nodes). Eighty-three patients (33.2%) are classified as group A, and 167 (66.8%) as group B.

Table 1. Characteristics of the patients

Variables	Group A (n=83)	Group B (n=167)	p-value
No. of the resected PLN	<20	≥20	
Age (yr)	59 (39–74)	59 (22–74)	0.782
High-risk histology*	25 (30.1)	50 (29.9)	0.977
Surgical stage (FIGO 1988)			0.646
IC	22 (26.5)	34 (20.4)	
II	7 (8.4)	14 (8.4)	
III	51 (61.5)	115 (68.9)	
IV	3 (3.6)	4 (2.4)	
Myometrial invasion ≥50%	49 (59.0)	103 (61.7)	0.688
LVSI positive	45 (54.2)	96 (57.5)	0.624
Ascitic cytology positive or suspicious [†]	36 (45.6)	81 (50.6)	0.462
Regimen of adjuvant chemotherapy			0.715
AP	25 (30.1)	46 (27.5)	
DP	26 (31.3)	61 (36.5)	
TC	32 (38.3)	60 (35.9)	
PLN metastasis	20 (24.1)	47 (28.1)	0.494

Values are presented as median (range) or number (%).

AP, doxorubicin plus cisplatin; DP, docetaxel plus cisplatin; LVSI, lymphovascular space invasion; PLN, pelvic lymph node; TC, paclitaxel plus carboplatin.

*Serous, clear cell, or grade 3 endometrioid; [†]Eleven had missing data.

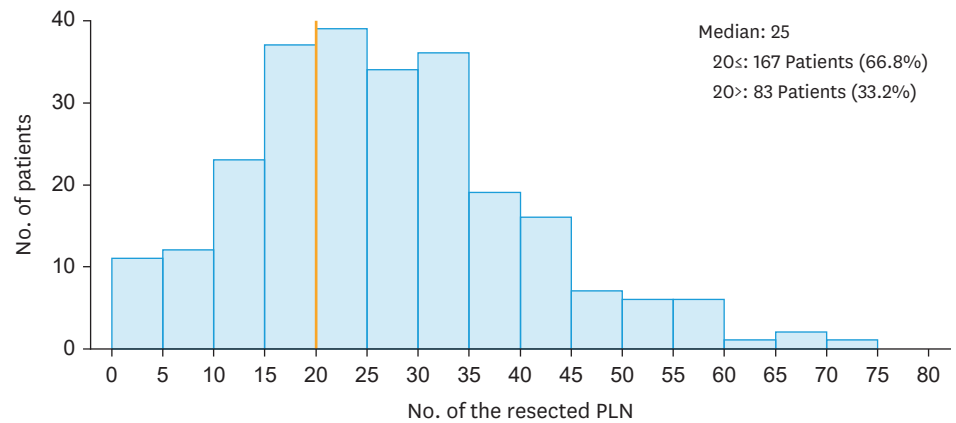


Fig. 2. Distribution of the number of resected PLN. PLN, pelvic lymph node.

There was no statistically significant difference in clinicopathologic variables between the 2 groups (**Table 1**). Notably, there was no statistically significant difference in the pelvic LNM frequency between the two groups (group A: 24.1% vs. group B: 28.1%).

1. Survival analysis

Five-year overall survival (OS) and 5-year disease-free survival (DFS) were 84.3% and 79.5% in group A, 90.4%, and 83.8% in group B, respectively. The survival curves showed that group B appeared to outperform group A, but the log-rank test showed no statistically significant difference (**Fig. 3**). Multivariate analysis demonstrated that resection of 20 or more PLNs was an independent prognostic factor for OS (hazard ratio [HR]=0.49; 95% confidence interval [CI]=0.24–0.99; p=0.048) as well as age (60 or more), high-risk histology (serous, clear cell, or grade 3 endometrioid), and stage III/IV (**Table 2**). About DFS, high-risk histology, more

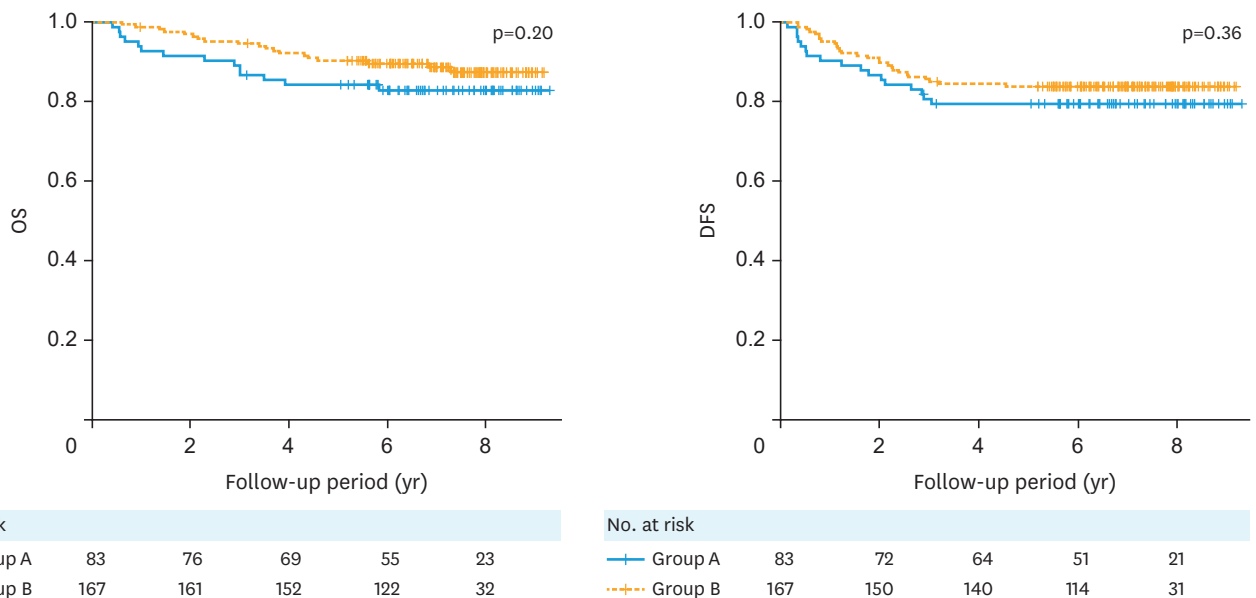


Fig. 3. OS and DFS among groups. DFS, disease-free survival; OS, overall survival.

Table 2. Cox proportional hazard model for OS and DFS

Variables	Hazard ratio	95% CI	p-value
OS			
No. of resected PLN \geq 20	0.49	0.24–0.99	0.048
Age \geq 60 yr	2.42	1.18–4.95	0.016
High-risk histology*	2.66	1.30–5.43	0.007
Stage III or IV	6.18	2.22–17.2	<0.001
Myometrial invasion \geq 50%	2.16	0.95–6.95	0.067
LVSI positive	1.07	0.49–2.35	0.867
DFS			
No. of resected PLN \geq 20	0.57	0.31–1.07	0.080
Age \geq 60 yr	1.59	0.86–2.95	0.142
High-risk histology*	2.91	1.58–5.36	<0.001
Stage III or IV	6.58	2.61–16.6	<0.001
Myometrial invasion \geq 50%	2.10	1.04–4.23	0.037
LVSI positive	1.32	0.67–2.60	0.428

CI, confidence interval; DFS, disease-free survival; LVSI, lymph vascular space invasion; OS, overall survival; PLN, pelvic lymph node.

*Serous, clear cell, or grade 3 endometrioid.

Table 3. χ^2 test on site of relapse and number of resected PLN

Variables	No. of resected PLN		p-value
	20 $>$ (n=83)	20 \leq (n=167)	
Site of relapse			
Intra pelvic	8 (9.6)	6 (3.5)	0.050
Extra pelvic	15 (18.1)	22 (13.2)	0.304
PLN	2 (2.4)	1 (0.6)	0.216

Values are presented as number (%).

PLN, pelvic lymph node.

than one-half myometrial invasion, and stage III/IV were independent prognostic factors, but 20 or more PLNs resection was associated with better DFS with marginally significant difference (HR=0.57; 95% CI=0.31–1.07; p=0.080) (**Table 2**).

2. Recurrence pattern

We next examined the correlation between the number of resected PLNs and the recurrence pattern. Intrapelvic failure, including PLN metastasis, was 9.6% in group A and 3.5% in group B, indicating that resection of 20 or more PLNs reduces intrapelvic failure with a marginally significant difference (p=0.050). Regarding the correlation between the number of resected nodes and extrapelvic failure or pelvic node failure, there was no significant difference between the two groups (**Table 3**).

DISCUSSION

This study revealed that the removal of 20 or more PLNs is an independent prognostic factor for OS along with other well-established prognostic factors such as advanced surgical stage, age, and high-risk histology in patients diagnosed with intermediate-high risk EC who underwent pelvic LND but not para-aortic LND.

Another result we obtained was that there was a trend towards fewer pelvic recurrences in the group with 20 or more PLNs removed than in the group with fewer than 20 lymph nodes removed. This trend may be one of the reasons why removing 20 or more PLNs was a significant prognostic factor for OS. In contrast, there was no significant difference in

extrapelvic recurrence and pelvic lymph node (PLN) recurrence. This result may be because there were only three PLN recurrences.

While our findings suggest the therapeutic value of pelvic LND in EC patients with intermediate-high risk of recurrence, the therapeutic significance of pelvic LND has not yet been fully established. Two European randomized controlled trials (RCTs), namely the ASTEC trial [10] and the Italian study [9], have assessed the life expectancy of patients who underwent pelvic LND compared to those who did not. Both studies reported no statistically significant difference in prognosis between the group undergoing pelvic LND and that without LND. Nevertheless, problems were noted in each trial: the ASTEC trial included a median of only 12 PLNs removed, and approximately 45% of enrolled patients had a low risk of recurrence and were considered to have a low risk of LNM. In the Italian study, 66.9% of the patients were considered not at high risk of recurrence and did not receive adjuvant therapy, suggesting many were at low risk of LNM. The study additionally highlighted non-uniformity in the administration of adjuvant treatment, with 20.8% of patients receiving radiotherapy, 7.2% undergoing chemotherapy, and 5.1% receiving a combination of radiotherapy and chemotherapy.

In addition to the previously mentioned study of improved prognosis with 20 or more nodes removed [8], several other studies have reported on the number of PLNs removed in EC patients. An analysis using the US Surveillance, Epidemiology, and End Results (SEER) database found that removal of up to 25 nodes detected positive lymph nodes in 85% of cases. The detection rate of metastatic lymph nodes was significantly higher in the 21–25 node group than in the 1–5 node group. Removing 20 or more lymph nodes may be desirable to demonstrate true lymph node negativity [3]. In a single-center retrospective analysis of stage I and II patients who did not have metastases in the lymph nodes removed, it was reported that the number of PLNs removed was not significantly correlated with better prognosis in EC grades 1 and 2. Still, in high-risk histology, the number of PLNs removed was an independent prognostic factor for OS and PFS. The study cited two reasons for the prognostic significance of removing more lymph nodes: first, the therapeutic benefit of removing occult LNM, and second, the impact of ‘stage migration,’ where removing fewer lymph nodes can result in missing metastases and classifying patients as lower stage. If more lymph nodes were removed, they would be classified as stage III with a poorer prognosis [11]. Our results are considered to be complex reason because it is difficult to determine which is the main factor, the effect of occult metastatic lymph node removal or the stage migration effect.

This post hoc study’s strengths are that it analyzes a cohort enrolled in an RCT with a high level of evidence and that the content of the adjuvant therapy (dosage, administration interval of chemotherapy) is strictly defined and consistent within the protocol. Another strength is that since all patients have received adjuvant chemotherapy, the survival effect of pelvic lymphadenectomy as a local treatment can be assessed more rigorously compared to those treated with adjuvant radiotherapy.

There are several limitations to this study. First, the staging classification was based on the outdated FIGO 1988 criteria. Therefore, we attempted to reclassify to FIGO 2008 but could not because stage IIIA included cases with one or more of the following: serosal invasion, adnexal metastases, and positive ascitic cytology, the details of which were not registered in JGOG2043. The present cohort included one hundred (40%) stage IIIA cases, and it is undeniable that the FIGO 2008 criteria could classify a certain number of these cases as

stage I or II. This may have influenced the results. In addition, the new FIGO 2023 criteria introduced a new molecular classification [12], and this study did not conduct molecular analysis, so whether the therapeutic significance of the extent of lymphadenectomy differs according to molecular classification was not examined.

Secondly, the number of cases in group B was twice that of group A (Group A:83, Group B: 167), because the standard threshold for the number of lymph nodes removed was predetermined to be 20, based on previous reports. Furthermore, Group B, with 20 or more PLNs removed, had slightly poorer background factors, with a slightly higher proportion of LVSI, invasion into the deep muscle layer, positive ascitic cytology, and stage III disease, although these are not statistically significant. It is possible that differences in the number of cases between the two groups and differences in patients' backgrounds may have influenced the results. Therefore, we suspect that this may have prevented a significant difference in the analysis of survival curves.

Finally, since JGOG2043 was a trial comparing adjuvant chemotherapy, it did not gather data regarding perioperative, early postoperative, or late complications. Therefore, it remains unclear from this study whether complications increase as the number of PLNs removed rises. Recently, a study evaluated lymphatic complications between sentinel node biopsy (SNB) and pelvic LND for EC. The mean number of removed lymph nodes was 3.0 in the SNB group and 33.8 in the pelvic LND group, respectively. The occurrence rates of lower-extremity lymphedema and pelvic lymphocele were significantly lower in patients who underwent SNB than those who underwent pelvic LND [13].

Regarding these limitations mentioned above, RCTs with a certain number of PLNs removed are essential for more accurate validation of the therapeutic significance of LND. There are currently two RCTs examining the therapeutic significance of LND. One is the JCOG1412 trial [14], which examines the therapeutic importance of para-aortic LND among EC patients with a high risk of recurrence by comparing a pelvic LND-only group with a pelvic plus para-aortic LND group. The other is the ECLAT trial [15], which compares a no LND group with a pelvic plus para-aortic LND group among EC patients with a high risk of recurrence. In the mid-stage report of the JCOG1412 trial, the median number of PLNs removed in both groups was 45 in the pelvic LND alone group and 43 in the pelvic plus para-aortic LND group, which was adequate and did not differ between the two groups [16]. The ECLAT study has been conducted mainly by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) study group that conducted the LION study, which examined the therapeutic significance of LND in ovarian cancer, and the lymph node removal technique was defined in the protocol as in the LION study. In the LION study, the median number of removed lymph nodes was 57 (22 in the para-aortic region and 35 in the pelvic region) [17]. Therefore, it can be inferred that a similar number of lymph nodes were also removed in the ECLAT study. The number of lymph nodes removed in both studies should be sufficient to validate the more precise therapeutic significance of LND. We eagerly anticipate the results of these trials.

In conclusion, among a group of patients diagnosed with intermediate- and high-risk EC who underwent pelvic LND only and received adjuvant chemotherapy, removing 20 or more PLNs correlated with an improved prognosis and a reduced risk of pelvic recurrence.

It was suggested that thorough PLN dissection may lead to a good prognosis in high-risk endometrial cancer. RCTs, with an adequate number of removed lymph nodes, are crucial to demonstrate the therapeutic significance of LND.

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