Thai Journal of Obstetrics and Gynaecology
September 2024, Vol. 32, No. 5, pp. 340-357.

GYNAECOLOGY

Benefit of Paraaortic Lymph Node Evaluation in Endometrioid Endometrial Carcinoma; A 10-year retrospective study in Thailand

Atthapon Jaishuen, M.D.*,
Pattra Wisarnsirirak, M.D.**,
Janjira Petsuksiri, M.D.***,
Perapong Inthasorn, M.D.*,
Sompop Kuljarusnont, M.D.*,
Khemanat Khemworapong, M.D.*,
Vitcha Poonyakanok, M.D.*

** Division of Gynaecology Oncology, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*
*** Division of Gynaecology Oncology, Department of Obstetrics and Gynaecology, Faculty of Medicine, Thammasat University, Bangkok, Thailand*
**** Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

ABSTRACT

Objectives: To evaluate 5-year survival in patients with endometrioid endometrial carcinoma, who underwent evaluation of retroperitoneal pelvic lymph nodes alone, compared to evaluation of pelvic with paraaortic lymph nodes.

Materials and Methods: This retrospective cohort study enrolled 636 women who were diagnosed with endometrioid endometrial carcinoma and underwent surgical staging at Faculty of Medicine Siriraj Hospital, Mahidol University between January 2006 and December 2015. Patients who underwent pelvic lymph node evaluation (n = 257) and pelvic with paraaortic lymph node evaluation (n = 379) were included.

Results: The median follow-up time was 60 months. The 5-year overall survival rate (OS) in the pelvic lymph node (PLN) and pelvic with paraaortic lymph node (PPALN) groups was 81.6% and 87.7%, respectively (p = 0.073). However, the PPALN group had significantly longer survival than the PLN group after adjustment for other prognostic factors (adjusted hazard ratio (HR)) 1.63 (1.06-2.52, p = 0.028)). There was a trend to improve 5-year disease-specific survival (DSS) for the European Society of Gynaecological Oncology (ESGO)/ European Society for Radiotherapy and Oncology (ESTRO)/ European Society of Pathology (ESP) high risk patients, who underwent PPALN evaluation (85.6%) compared with PLN evaluation (70.8%), p = 0.061.

Conclusion: In endometrioid endometrial carcinoma patients, the evaluation of pelvic and paraaortic lymph nodes is independently associated with enhanced survival outcomes.

Therefore, in situations when a sentinel lymph node biopsy is not feasible, we suggest evaluating the pelvic and paraaortic lymph nodes for all patients diagnosed with endometrioid endometrial cancer.

Keywords: cancer of the endometrium, lymphadenectomy.

Correspondence to: *Vitcha Poonyakanok, M.D., Division of Gynaecology Oncology, Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand*
E-mail: vpoonyakanok@gmail.com

ประโยชน์ของการเลาะประเมินต่อมน้ำเหลืองรอบหลอดเลือดเอออร์ตา ในมะเร็งเยื่อบุมดลูกชนิด endometrioid; การศึกษาแบบย้อนหลัง 10 ปีในประเทศไทย

อรรถพล ใจชื่น, ภัทรา วิศาลศิริรักษ์, จันจิรา เพชรสุขศิริ, พีรพงศ์ อินทศร, สมภพ กุลจรัสนนท์, เขมณัฏฐ์ เขมวรพงศ์, วิชชา ปุณยกนก

บทคัดย่อ

วัตถุประสงค์*: เพื่อประเมินอัตราการรอดชีวิต 5 ปีในผู้ป่วยมะเร็งเยื่อบุมดลูกชนิด endometrioid ที่ได้รับการเลาะประเมินต่อมน้ำเหลืองเฉพาะในอุ้งเชิงกรานเทียบกับการเลาะประเมินทั้งต่อมน้ำเหลืองในอุ้งเชิงกรานและรอบหลอดเลือดเอออร์ตา*
วัสดุและวิธีการ*: การศึกษาแบบย้อนหลังนี้ได้รวบรวมผู้ป่วยจำนวน 636 คน ที่ได้รับการวินิจฉัยว่าเป็นมะเร็งเยื่อบุมดลูกชนิด endometrioid และได้รับการผ่าตัดกำหนดระยะโรคที่คณะแพทยศาสตร์ศิริราชพยาบาล มหาวิทยาลัยมหิดล ระหว่างเดือนมกราคม 2549 ถึงธันวาคม 2558 โดยมีผู้ป่วยที่ได้รับการเลาะประเมินต่อมน้ำเหลืองเฉพาะในอุ้งเชิงกราน (n = 257) และการเลาะประเมินต่อมน้ำเหลืองในอุ้งเชิงกรานและรอบหลอดเลือดเอออร์ตา (n = 379) รวมอยู่ในการศึกษานี้*
ผลการศึกษา*: ผู้ป่วยได้รับการตรวจติดตามเฉลี่ยอยู่ที่ 60 เดือน พบว่าผู้ป่วย ในกลุ่มที่ได้รับการเลาะประเมินต่อมน้ำเหลืองในอุ้งเชิงกราน และกลุ่มที่ได้รับการเลาะประเมินต่อมน้ำเหลืองทั้งในอุ้งเชิงกรานและรอบหลอดเลือดเอออร์ตาอั ตราการรอดชีวิตที่ 5 ปี เท่ากับร้อยละ 81.6 และร้อยละ 87.7 ตามลำดับ (p = 0.073) อย่างไรก็ตามจากการวิเคราะห์พหุตัวแปร กลุ่มที่ได้รับการเลาะประเมินต่อมน้ำเหลืองทั้งในอุ้งเชิงกรานและรอบหลอดเลือดเอออร์ตามีอัตราการรอดชีวิตที่นานกว่าอีกกลุ่มอย่างมีนัยสำคัญ (adjusted HR 1.63 (1.06-2.52, p=0.028)) และ ผู้ป่วยที่มีความเสี่ยงสูงตามเกณฑ์ของ ESGO/ESTRO/ESP ที่ได้รับการเลาะประเมินต่อมน้ำเหลืองในอุ้งเชิงกรานและรอบหลอดเลือดเอออร์ตา มีแนวโน้มที่จะมีอัตราการรอดชีวิตเฉพาะโรคที่มากกว่าเมื่อเทียบกับอีกกลุ่ม (ร้อยละ 85.6 และร้อยละ 70.8, p=0.06)*
สรุป*: ในผู้ป่วยมะเร็งเยื่อบุมดลูกชนิด endometrioid การเลาะประเมินต่อมน้ำเหลืองในอุ้งเชิงกรานและรอบหลอดเลือดเอออร์ตา มีความสัมพันธ์กับอัตราการรอดชีวิตที่ดีขึ้น ดังนั้นคำแนะนำสำหรับการผ่าตัดรักษาผู้ป่วยมะเร็งเยื่อบุมดลูกชนิด endometrioid ในโรงพยาบาลที่ไม่สามารถตรวจประเมินต่อมน้ำเหลืองด้วยวิธี sentinel ได้ คือให้ทำการผ่าตัดเลาะประเมิน*

ต่อมน้ำเหลืองในอุ้งเชิงกรานและรอบหลอดเลือดเอออร์ตาร่วมด้วย

***คำสำคัญ**: มะเร็งเยื่อบุมดลูก, ต่อมน้ำเหลืองรอบหลอดเลือดเอออร์ตา*

Introduction

Endometrial carcinoma is the most common gynecologic cancer in developed countries[1, 2] and the third most common cancer in Thailand[3]. There are two types of endometrial carcinoma; endometrioid and non-endometrioid according to the Bokhman classification[4]. The endometrioid type accounts for 80% of endometrial carcinoma. In 1987, Gynecologic Oncology Group (GOG) 33 described the usefulness of surgical staging in patients with stage I clinical endometrial carcinoma[5]. In 1988, the International Federation of Gynecology and Obstetrics (FIGO) developed surgical staging for endometrial cancer instead of clinical staging. The surgical staging procedures include total hysterectomy, bilateral salpingo-oophorectomy, retroperitoneal pelvic, and paraaortic lymphadenectomy[6]. Although systematic lymphadenectomy is part of the surgical staging of endometrioid endometrial carcinoma, it is not performed universally. Patients with endometrial carcinoma are usually old, obese and have multiple comorbidities, for example, diabetes mellitus and hypertension. Furthermore, several studies report an increase in perioperative morbidity in lymphadenectomy patients, including increased blood loss, an increased risk of blood or blood component transfusion, an increased operative time, a longer hospital stay, surgical wound infection, lymphedema, and lymphocyst formation[7-10]. The survival benefits of lymphadenectomy are controversial. Two prospective randomized trials in patients with early endometrial carcinoma did not find therapeutic benefits for pelvic lymphadenectomy[11, 12]. However, several retrospective studies showed a survival benefit in patients with intermediate or high-risk endometrial carcinoma who underwent systematic pelvic and paraaortic lymphadenectomy[13-15]. This study was designed to compare the survival benefit of pelvic lymph node evaluation with pelvic and paraaortic lymph node evaluation.

Materials and Methods

Study population

This retrospective cohort study was carried out at the Department of Obstetrics and Gynaecology, Faculty of Medicine Siriraj Hospital, Mahidol University. After institutional ethics board approval was obtained (CoA no.SI 025/2018 and 178/2023, the presence of two separate CoA numbers is attributed to our extended and more comprehensive review of the data), medical records were reviewed from January 2006 to December 2015. Inclusion criteria were patients who were diagnosed with endometrioid endometrial carcinoma and underwent surgical staging at Siriraj Hospital between January 2006 and December 2015. All patients must undergo evaluation of the pelvic lymph node with or without paraaortic lymph node. Patients with a history of other cancers within the previous 5 years or who had previously received chemotherapy or radiation therapy were excluded. Informed consent was not applicable due to retrospective design study.

Dissection, sampling or debulking of enlarged lymph nodes in internal iliac nodes, external iliac nodes, obturator nodes and common iliac nodes was defined as evaluation of pelvic lymph nodes. Evaluation of paraaortic lymph nodes was defined as dissecting, sampling or debulking of enlarged lymph nodes in the precaval, laterocaval, interaortocaval, preaortic, and lateroaortic areas up to the renal veins. Patients with high-risk features as MAYO criteria[16] underwent pelvic lymphadenectomy. Systematic/para-aortic

lymphadenectomy was performed at surgeon's discretion due to patients' characteristics. When a patient underwent an evaluation of the lymph nodes in both areas, we defined it as an evaluation of the pelvic and paraaortic lymph nodes. At our institution, preoperative imaging was not routinely performed as a guide for lymphadenectomy.

Adjuvant treatment is determined by the stage of the disease. In the early stage, patients undergo observation, brachytherapy, or whole pelvic radiation, depending on uterine risk factors. In advanced stages, patients receive six cycles or more of chemotherapy alone or in combination with whole pelvic radiation. For patients with paraaortic lymph node metastasis, extended field paraaortic radiation is administered.

Patient data were reviewed, including age, weight, height, body mass index, complete blood count, surgical approach, operative time, blood loss, tumor size, myometrial invasion, cervical involvement, ovarian or adnexal involvement, peritoneal washing for cytology, pelvic and paraaortic lymph node involvement, lymphovascular space invasion (LVSI), adjuvant postoperative treatment, and follow-up status. Patients were also divided into subgroup according to the European Society of Gynaecological Oncology (ESGO)/ European Society for Radiotherapy and Oncology (ESTRO)/ European Society of Pathology (ESP) guidelines[17] classified as low, intermediate, high-intermediate and high-risk groups.

"Recurrence-free survival" (RFS) was defined as the time from the diagnosis until the detection of recurrence or the latest follow-up. "Disease-specific survival" was defined as the time from diagnosis to death caused by endometrial carcinoma or the latest follow-up. "Overall survival" was defined as the time from the diagnosis to death of any causes or the last follow-up.

The primary outcome was to compare overall survival (OS) between patients in the pelvic lymph node (PLN) evaluation group and the pelvic with paraaortic lymph node (PPALN) evaluation group. Secondary outcomes were to evaluate recurrence-free survival (RFS) between the two groups.

Statistical analysis

The sample size was calculated to compare 5-year OS according to the SEPAL study[15]. The 5-year OS in the pelvic lymph node evaluation groups and in the pelvic and paraaortic lymph nodes was 74.5% and 85.8%, respectively. We defined type I error rate (α) of 5% and power of test of 80%, the sample size by using nQuery Advisor was at least 199 patients in each group, which required 74 events of death. For the multivariable Cox regression model with 10 prognostic factors, the sample size was calculated according to the general rule of thumb. We defined events per variable (EPV) as 50 and then the required sample size was at least 100+50(10) = 600 patients.

Statistical analysis was performed using PASW (SPSS) version 18 (SPSS Inc., Chicago, IL, USA). Categorical data were reported as numbers and percentage, while mean and standard deviation (SD) or median and range (minimum, maximum) were used for continuous data, as appropriate. Independent t-test or Mann-Whitney U test was performed to compare mean or median between groups for continuous data. The Pearson chi-square test was used to compare the proportion between groups for categorical data. The Kaplan-Meier method was used to estimate survival time and survival rate, and the log-rank test was used to compare survival time between groups for the overall analysis and the subgroup analysis, classified as low, intermediate, high-intermediate and high-risk groups according to the ESGO / ESTRO / ESP guidelines[17]. Simple and multiple Cox regression analysis was performed to identify prognostic factors of survival and recurrence. The hazard ratio (HR) with the corresponding 95% confidence interval (95%CI) was used to determine the strength and direction of their association. The p value < 0.05 was considered statistically significant.

Results

Patient Characteristics

From January 2006 to December 2015, 1,300 medical records were reviewed, and 636 patients were included in this study. Two hundred and fifty-seven patients underwent only pelvic lymph node

evaluation, while 379 patients underwent pelvic with paraaortic lymph node evaluation. A comparison of clinical and pathological characteristics is shown in Table 1.

Table 1. Comparison of clinical and pathological characteristics by extension of lymph node evaluation in 636 patients with endometrioid endometrial cancer.

	PLN evaluation (n = 257)	PPALN evaluation (n = 379)	p value
Age (years), mean ± SD	56.9 ± 10.9	57.7 ± 10.0	0.352
Body mass index (kg/m^2), mean ± SD	28.1 ± 6.5	26.1 ± 4.9	< 0.001
FIGO 2009 staging, n (%)			0.004
IA	159 (61.9)	204 (53.8)	
IB	40 (15.6)	72 (19.0)	
II	16 (6.2)	43 (11.3)	
IIIA	13 (5.1)	16 (4.2)	
IIIB	1 (0.4)	4 (1.1)	
IIIC1	23 (8.9)	21 (5.6)	
IIIC2	0 (0)	14 (3.7)	
IVB	5 (1.9)	5 (1.3)	
Histological grade, n (%)			0.005
Grade 1	134 (52.1)	151 (39.9)	
Grade 2	101 (39.3)	176 (46.4)	
Grade 3	22 (8.6)	52 (13.7)	
Risk groups			0.142
Low risk (LR)	144 (56.0)	179 (47.2)	
Intermediate risk (IR)	31 (12.1)	57 (15.1)	
High intermediate risk (HIR)	40 (15.6)	83 (21.9)	
High risk (HR)	37 (14.4)	55 (14.5)	
Advanced/metastatic	5 (1.9)	5 (1.3)	
Surgical operation, n (%)			0.161
Laparotomy	234 (92.9)	335 (89.6)	
Laparoscopy	18 (7.1)	39 (10.4)	
Number of lymph nodes, median (min-max)			
Pelvic nodes	12 (2-61)	17 (2-72)	< 0.001
Paraaortic nodes	N/A	3 (1-21)	N/A
Operative time (minutes), median (min-max)	165 (60-355)	185 (60-400)	< 0.001
Estimate blood loss (mL), median (min-max)	200 (5-2000)	250 (10-2100)	0.599
Adjuvant treatment, n (%)		(n=378)†	0.006
None	133 (51.8)	143 (37.8)	
Chemotherapy	18 (7.0)	35 (9.3)	
Radiation	91 (35.4)	177 (46.8)	
Chemotherapy and radiation	15 (5.8)	23 (6.1)	

PPALN: Pelvic and paraaortic lymph node, PLN: Pelvic lymph node, FIGO: International Federation of Obstetricians and Gynecologists, SD: standard deviation

† No information of one patient who had adjuvant treatment at the other hospital

The median number of pelvic lymph node was 12 (2-61) in the PLN group and 17 (2-72) in the PPALN group. The median number of paraaortic lymph nodes was 3 (1-21). In the PLN group, pelvic lymph nodes were positive in 27 of 257 cases (10.5%). In the PPALN group, the isolated positive paraaortic lymph node was 1.3% (5/379), while 2.4% (9/379) had positivity for both the pelvic lymph node and the paraaortic lymph node and 8.2% (31/379) had positivity for the pelvic lymph node, as shown in Fig. 1. There were 57 cases (9%) that underwent laparoscopic surgery (18 in the PLN group and 39 in the PPALN group). The median number of pelvic lymph nodes and paraaortic lymph nodes in laparoscopic surgery was not different from that in laparotomy. In the PPALN group, operative time was significantly longer than in the PLN group ($p < 0.001$) but estimated blood loss was not different in both groups.

Treatment outcomes: OS, DSS, RFS

Overall survival (OS)

The median follow-up time was 60 months (1.3-60.0). Forty-one patients (16%) died in the PLN group and 41 patients (10.8%) died in the PPALN group. The 5-year OS rate in the PLN and the PPALN groups were 81.6% and 87.7%, respectively ($p = 0.073$) as shown in Fig. 2A. However, the PLN group had increased risk of 5-year death comparing to the PPALN group after adjustment for other prognostic factors (adjusted HR 1.63 (1.06-2.52, $p = 0.028$)) as shown in Table 2.

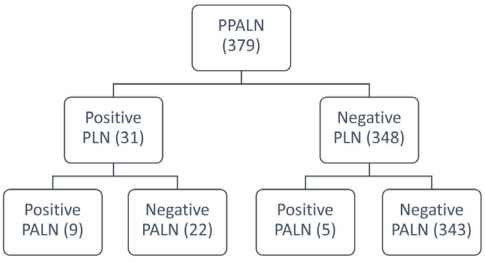

Fig. 1. Results from the pelvic and paraaortic lymph node evaluation groups.

** PPALN: pelvic and paraaortic lymph node, PLN: pelvic lymph node, PALN: paraaortic lymph node*

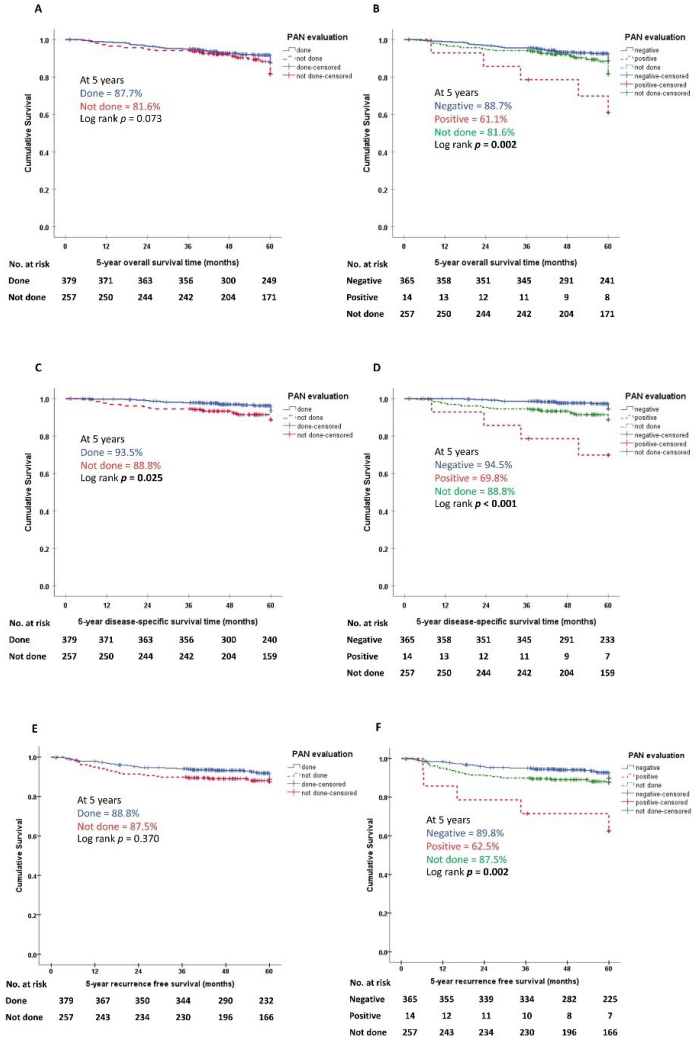

Fig. 2. Kaplan-Meier analysis of (A) 5-year OS of PLN and PPALN evaluation, (B) 5-year OS of PLN evaluation, PPALN evaluation with negative and positive PALN, (C) 5-year DSS of PLN and PPALN evaluation, (D) 5-year DSS of PLN evaluation, PPALN evaluation with negative and positive PALN, (E) 5-year RFS of PLN and PPALN evaluation, (F) 5-year RFS of PLN evaluation, PPALN evaluation with negative and positive PALN.

** PPALN: pelvic and paraaortic lymph node, PLN: pelvic lymph node, PALN: paraaortic lymph node*

Table 2. Prognostic factors for 5-year overall survival (OS) in 636 patients with endometrioid endometrial cancer patients.

Prognostic factors	5-year overall survival (OS)			
	Univariable		Multivariable	
	Unadjusted HR (95%CI)	p value	Adjusted HR† (95%CI)	p value
Age		0.002		0.003
< 55 years	Reference		Reference	
≥ 55 years	2.19 (1.32-3.62)		2.21 (1.32-3.70)	
Body mass index	0.99 (0.96-1.04)	0.970	-	-
Hemoglobin		0.053		0.042
≥ 13 g/dL	Reference		Reference	
< 13 g/dL	1.60 (0.99-2.57)		1.64 (1.02-2.65)	
Platelet	1.00 (1.00-1.00)	0.113	-	-
Tumor size		0.012		0.422
< 3 cm	Reference		Reference	
≥ 3 cm	2.09 (1.18-3.71)		1.30 (0.69-2.44)	
Risk groups		< 0.001		< 0.001
Low risk (LR)	Reference		Reference	
Intermediate risk (IR)	3.54 (1.81-6.94)	0.001	3.21 (1.63-6.32)	0.001
High intermediate risk (HIR)	3.51 (1.88-6.55)	< 0.001	3.26 (1.74-6.10)	< 0.001
High risk (HR)	4.79 (2.57-8.93)	< 0.001	4.89 (2.62-9.14)	< 0.001
Advanced/metastatic	9.25 (3.13-27.38)	< 0.001	10.35 (3.47-30.90)	< 0.001
Peritoneal washing for cytology		0.014		0.113
Negative	Reference		Reference	
Positive	2.29 (1.18-4.44)		1.73 (0.88-3.39)	
Number of pelvic lymph nodes	1.00 (0.97-1.02)	0.733	-	-
Lymph node evaluation		0.077		0.028
Pelvic and paraaortic lymph node (PPALN)	Reference		Reference	
Pelvic lymph node (PLN)	1.48 (0.96-2.28)		1.63 (1.06-2.52)	
Adjuvant treatment		0.001		0.387
No	Reference		Reference	
Yes	2.23 (1.37-3.64)		0.75 (0.39-1.44)	

† Analysis adjusted for all prognostic factors with p-value < 0.10 in univariable analysis with the main factor

HR: hazard ratio, CI: confidence interval

In the PPALN group, 365 patients had a negative paraaortic lymph node (36 deaths), and 14 patients had a positive paraaortic lymph node (5 deaths). As shown in Fig. 2B, the 5-year OS rate in the PLN group, the negative paraaortic lymph node group and the positive paraaortic lymph node group were 81.6%, 88.7% and 61.1%, respectively (p = 0.002). Patients in the negative paraaortic lymph node group had statistically significantly longer survival than patients in the positive paraaortic lymph node group (p = 0.001) and the PLN group (p = 0.030).

Disease-specific survival (DSS)

DSS was better for patients who underwent evaluation of the pelvic and paraaortic lymph nodes compared to patients who received evaluation of only the pelvic lymph nodes. The 5-year DSS rate was 88.8% in the PLN group and 93.5% in the PPALN group (p = 0.025) as shown in Fig. 2C. The PLN group had increased risk of 5-year disease specific death comparing to the PPALN

group after adjustment for other prognostic factors (adjusted HR 2.11 (1.17-3.79, p = 0.0213)) as shown in Table 3. As shown in Fig. 2D, the 5-year DSS rate in the PLN group, the negative paraaortic lymph node group, and the positive paraaortic lymph node group were 88.8%, 94.5%, and 69.8%, respectively (p < 0.001). Patients with a negative paraaortic lymph node survived statistically significantly longer than patients with a positive paraaortic lymph node (p < 0.001) and the PLN group (p = 0.006).

Table 3. Prognostic factors for 5-year disease specific survival (DSS) in 636 patients with endometrioid endometrial cancer patients.

Prognostic factors	5-year disease specific survival (DSS)			
	Univariable		Multivariable	
	Unadjusted HR (95%CI)	p value	Adjusted HR† (95%CI)	p value
Age		0.079		0.047
< 55 years	Reference		Reference	
≥ 55 years	1.78 (0.94-3.38)		1.97 (1.01-3.83)	
Body mass index	1.00 (0.95-1.05)	0.889	-	-
Hemoglobin		0.194	-	-
≥ 13 g/dL	Reference			
< 13 g/dL	0.66 (0.35-1.24)			
Platelet	1.00 (1.00-1.00)	0.358	-	-
Tumor size		0.017		0.484
< 3 cm	Reference		Reference	
≥ 3 cm	2.85 (1.21-6.72)		1.39 (0.55-3.53)	
Risk groups		< 0.001		< 0.001
Low risk (LR)	Reference		Reference	
Intermediate risk (IR)	5.09 (1.89-13.66)	0.001	4.79 (1.77-12.91)	0.002
High intermediate risk (HIR)	3.69 (1.37-9.90)	0.010	3.46 (1.28-9.36)	0.014
High risk (HR)	9.45 (3.92-22.80)	< 0.001	9.37 (3.86-22.74)	< 0.001
Advanced/metastatic	22.94 (6.70-78.53)	< 0.001	23.56 (6.72-82.57)	< 0.001
Peritoneal washing for cytology		0.008		0.06
Negative	Reference		Reference	
Positive	2.95 (1.32-6.59)		2.19 (0.97-4.96)	
Number of pelvic lymph nodes	0.99 (0.96-1.02)	0.445	-	-
Lymph node evaluation		0.028		0.013
Pelvic and paraaortic lymph node (PPALN)	Reference		Reference	
Pelvic lymph node (PLN)	1.92 (1.07-3.44)		2.11 (1.17-3.79)	
Adjuvant treatment		0.001		0.810
No	Reference		Reference	
Yes	3.87 (1.80-8.23)		1.13 (0.42-3.07)	

† Analysis adjusted for all prognostic factors with p-value < 0.10 in univariable analysis with the main factor

HR: hazard ratio, CI: confidence interval

Recurrent free survival (RFS)

Thirty-one patients (12.1%) had recurrence in the PLN group, and 37 patients (9.8%) recurred in the PPALN group. The 5-year RFS rate in the PLN and PPALN groups was 87.5% and 88.8%, respectively (p = 0.370) as shown in Fig. 2E. The PPALN group had still no different in recurrent comparing to the PLN group after adjustment for

other prognostic factors (adjusted HR 1.39 (0.86-2.25, p = 0.183)) as shown in Table 4.

In the PPALN group, 365 patients had negative paraaortic lymph nodes (32 recurrences) and 14 patients had positive paraaortic lymph nodes (5 recurrences). As shown in Fig. 2F, the 5-year RFS rate in the PLN group, the negative paraaortic lymph node group and the positive paraaortic lymph node group were 87.5%, 89.8% and 62.5%, respectively (p = 0.002). Patients with a negative paraaortic lymph node had statistically significantly longer survival than patients with a positive paraaortic lymph node (p < 0.001) but similar to the PLN group (p = 0.187).

Table 4. Prognostic factors for 5-year recurrence free survival (RFS) in 636 patients with endometrioid endometrial cancer patients.

Prognostic factors	5-year recurrence-free survival (RFS)			
	Univariable		Multivariable	
	Unadjusted HR (95%CI)	p value	Adjusted HR† (95%CI)	p value
Age		0.098		0.065
< 55 years	Reference		Reference	
≥ 55 years	1.55 (0.92-2.59)		1.65 (0.97-2.79)	
Body mass index	1.00 (0.96-1.05)	0.920	-	-
Hemoglobin		0.616	-	-
≥ 13 g/dL	Reference			
< 13 g/dL	0.88 (0.54-1.44)			
Platelet	1.00 (1.00-1.00)	0.231	-	-
Tumor size		0.004		0.208
< 3 cm	Reference		Reference	
≥ 3 cm	2.78 (1.38-5.60)		1.62 (0.77-3.43)	
Risk groups		< 0.001		< 0.001
Low risk (LR)	Reference		Reference	
Intermediate risk (IR)	2.20 (0.97-4.97)	0.059	2.03 (0.89-4.61)	0.091
High intermediate risk (HIR)	2.85 (1.42-5.69)	0.003	2.66 (1.32-5.33)	0.006
High risk (HR)	5.48 (2.88-10.44)	< 0.001	5.55 (2.91-10.57)	< 0.001
Advanced/metastatic	13.43 (4.91-36.78)	< 0.001	15.34 (5.55-42.42)	< 0.001
Peritoneal washing for cytology		0.118	-	-
Negative	Reference			
Positive	1.87 (0.85-4.08)			
Number of pelvic lymph nodes	1.00 (0.98-1.03)	0.968		-
Lymph node evaluation		0.371		0.183
Pelvic and paraaortic lymph node (PPALN)	Reference		Reference	
Pelvic lymph node (PLN)	1.24 (0.77-2.00)		1.39 (0.86-2.25)	
Adjuvant treatment		0.003		0.382
No	Reference		Reference	
Yes	2.26 (1.32-3.88)		0.72 (0.34-1.51)	

† Analysis adjusted for all prognostic factors with p-value < 0.10 in univariable analysis with the main factor
HR: hazard ratio, CI: confidence interval

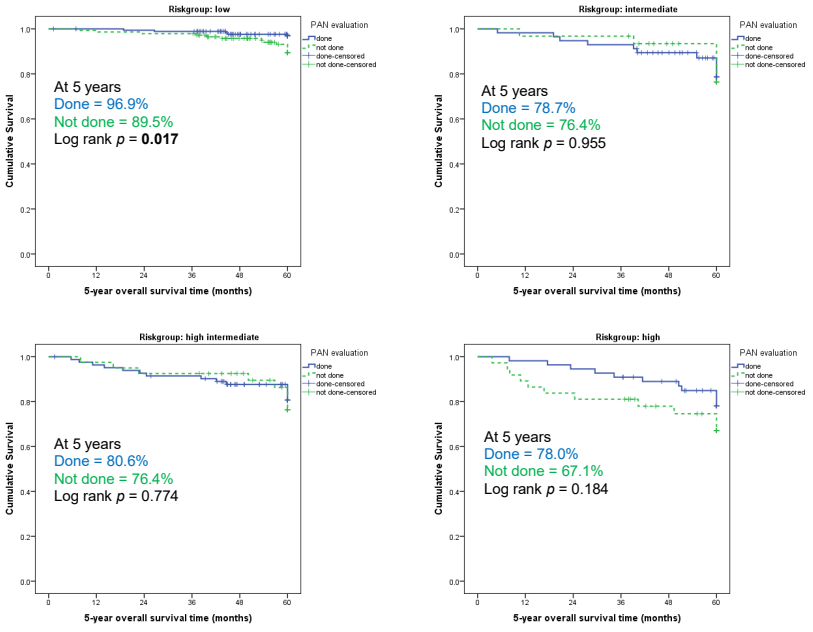

Fig. 3. Kaplan-Meier analysis of 5-year OS of PLN and PPALN evaluation stratified by ESGO/ESTRO/ESP risk groups (A) Low risk (B) Intermediate risk (C) High-intermediate risk (D) High risk

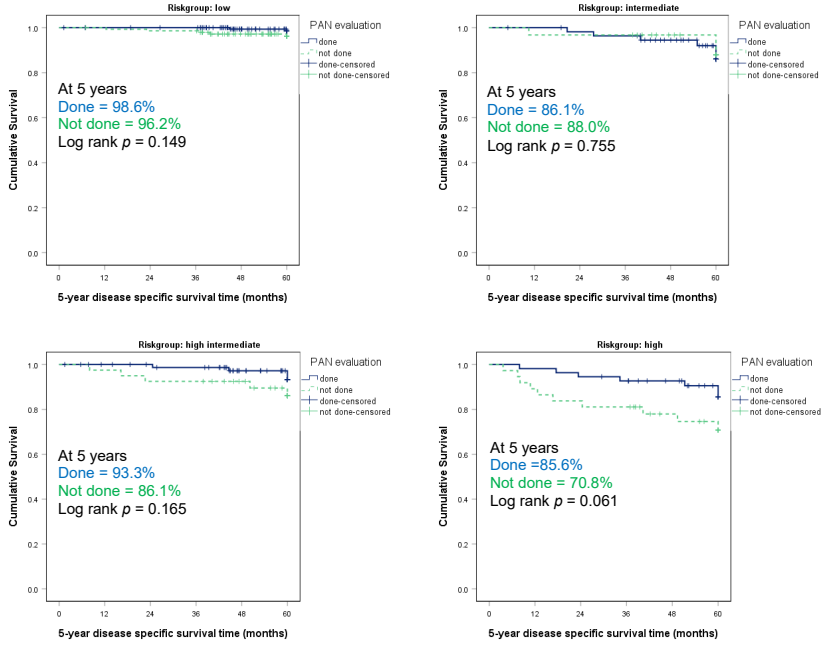

Fig. 4. Kaplan-Meier analysis of 5-year DSS of PLN and PPALN evaluation stratified by ESGO/ESTRO/ESP risk groups (A) Low risk (B) Intermediate risk (C) High-intermediate risk (D) High risk

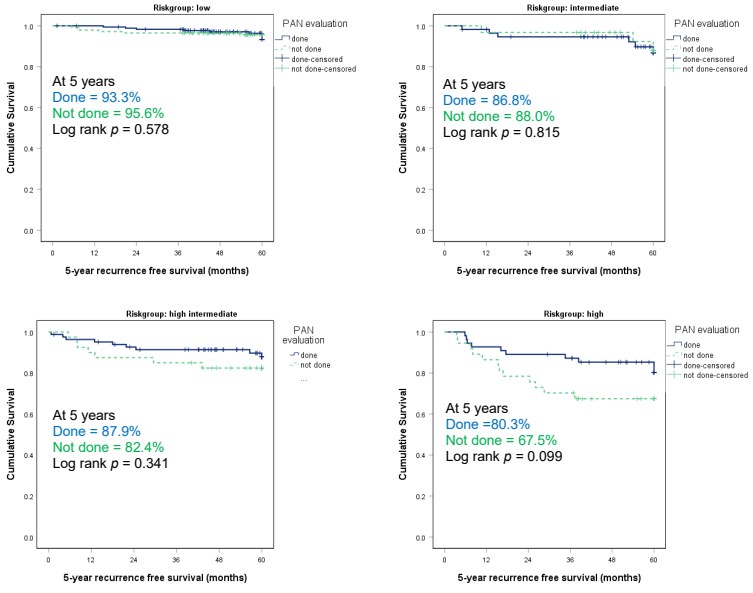

Fig. 5. Kaplan-Meier analysis of 5-year RFS of PLN and PPALN evaluation stratified by ESGO/ESTRO/ESP risk groups (A) Low risk (B) Intermediate risk (C) High-intermediate risk (D) High risk

Risk group analysis

We performed risk group analyses according to the ESGO / ESTRO / ESP guidelines[17]. For low-risk patients, the 5-year OS was higher for patients who received PPALN than the patients who received PLN evaluation (96.9% vs. 89.5%, p = 0.017). However, there was no benefit of PPALN evaluation for 5-year OS in other groups. (Fig. 3) There was no difference in 5-year DSS and 5-year RFS between PPALN and PLN evaluation for all risk groups. However, there was a trend to improve 5-year DSS (85.6% vs 70.8%, p = 0.061) and 5-year RFS (80.3% vs. 67.5%, p = 0.099) in high-risk patients who received PPALN evaluation as shown in supplementary Fig. S2D and S3D. All Kaplan-Meier graph of risk group analyses were provided in the supplementary materials (Fig. 4, 5).

Prognostic factors for 5-year OS, 5-year DSS and 5-year RFS

Table 2 shows the prognostic factors for 5-year OS of endometrial carcinoma by Cox regression analysis. The cutoff points for age, hemoglobin, and tumor size were calculated based on the largest area under the receiver operating characteristic curve (ROC) curve (not demonstrated). In the univariable analysis, age ≥ 55 years, tumor size ≥ 3 cm, risk groups, positive peritoneal washing, and adjuvant treatment were statistically significant prognostic factors for 5-year OS. In multivariable analysis, age ≥ 55 years (adjusted HR 2.21 (1.32-3.70, p = 0.003)), hemoglobin < 13 g/dL (adjusted HR 1.64 (1.02-2.65, p = 0.0422)), and risk groups (p < 0.001) were independent negative prognostic factors for 5-year OS.

For secondary outcomes, the univariable analysis of 5-year RFS revealed that tumor size ≥ 3 cm, risk groups, and adjuvant treatment were significant risk factors. Only risk group (p < 0.001) was significant risk factors for 5-year RFS in the multivariable analysis (Table 4). All cox regression analysis of 5-year OS, DSS, and RFS was provided in Table 2-4.

The data of Cox regression analysis for 5-year OS, DSS, and RFS using individual 15 risk factors were demonstrated in supplementary Table 5-7.

Table 5. Prognostic factors for 5-year overall survival (OS) in 636 patients with endometrioid endometrial cancer.

Prognostic factors	5-year overall survival (OS)			
	Univariable		Multivariable	
	Unadjusted HR (95%CI)	p value	Adjusted HR† (95%CI)	p value
Age		0.002		0.005
< 55 years	Reference		Reference	
≥ 55 years	2.19 (1.32-3.62)		2.10 (1.25-3.52)	
Body mass index	0.99 (0.96-1.04)	0.970	-	-
Hemoglobin		0.053		0.128
≥ 13 g/dL	Reference		Reference	
< 13 g/dL	1.60 (0.99-2.57)		1.45 (0.90-2.35)	
Platelet	1.00 (1.00-1.00)	0.113	-	-
Histological grade		< 0.001		0.001
Grades 1 and 2	Reference		Reference	
Grade 3	2.77 (1.67-4.58)		2.37 (1.41-3.96)	
Tumor size		0.012		0.06
< 3 cm	Reference		Reference	
≥ 3 cm	2.09 (1.18-3.71)		1.19 (0.62-2.30)	
Myometrial invasion		< 0.001		<0.001
< 50%	Reference		Reference	
≥ 50%	3.99 (2.55-6.24)		2.77 (1.71-4.46)	
Cervical involvement		< 0.001		0.019
Negative	Reference		Reference	
Positive	2.42 (1.51-3.90)		1.83 (1.11-3.02)	
Adnexal involvement		0.541	-	-
Negative	Reference			
Positive	1.30 (0.56-2.98)			
Peritoneal washing for cytology		0.014		0.214
Negative	Reference		Reference	
Positive	2.29 (1.18-4.44)		1.56 (0.78-3.13)	
Pelvic lymph node metastasis		< 0.001		0.005
Negative	Reference		Reference	
Positive	3.63 (2.17-6.06)		2.19 (1.27-3.76)	
Number of pelvic lymph nodes	1.00 (0.97-1.02)	0.733	-	-
Lymph node evaluation		0.077		0.004
Pelvic and paraaortic lymph node (PPALN)	Reference		Reference	
Pelvic lymph node (PLN)	1.48 (0.96-2.28)		1.94 (1.23-3.05)	
Adjuvant treatment		0.001		0.358
No	Reference		Reference	
Yes	2.23 (1.37-3.64)		0.75 (0.40-1.40)	
Lymphovascular space invasion (LVSI)		< 0.001		0.383
No	Reference		Reference	
Yes	2.56 (1.61-4.08)		1.25 (0.76-2.07)	

† Analysis adjusted for all prognostic factors with p-value < 0.10 in univariable analysis with the main factor
HR = hazard ratio

Table 6. Prognostic factors for 5-year disease specific survival (DSS) in 636 endometrioid endometrial cancer patients.

Prognostic factors	5-year disease specific survival (DSS)			
	Univariable		Multivariable	
	Unadjusted HR (95%CI)	p value	Adjusted HR† (95%CI)	p value
Age		0.079		0.109
< 55 years	Reference		Reference	
≥ 55 years	1.78 (0.94-3.38)		1.72 (0.89-3.34)	
Body mass index	1.00 (0.95-1.05)	0.889	-	-
Hemoglobin		0.194	-	-
≥ 13 g/dL	Reference			
< 13 g/dL	0.66 (0.35-1.24)			
Platelet	1.00 (1.00-1.00)	0.358	-	-
Histological grade		0.016		0.079
Grades 1 and 2	Reference		Reference	
Grade 3	2.36 (1.17-4.76)		1.90 (0.93-3.88)	
Tumor size		0.017		0.968
< 3 cm	Reference		Reference	
≥ 3 cm	2.85 (1,21-6.72)		1.02 (0.38-2.76)	
Myometrial invasion		<0.001		< 0.001
< 50%	Reference		Reference	
≥ 50%	7.66 (3.89-15.09)		5.03 (2.46-10.3)	
Cervical involvement		<0.001		0.007
Negative	Reference		Reference	
Positive	3.42 (1.88-6.22)		2.39 (1.26-4.54)	
Adnexal involvement		0.140	-	-
Negative	Reference			
Positive	2.01 (0.80-5.09)			
Peritoneal washing for cytology		0.008		0.318
Negative	Reference		Reference	
Positive	2.95 (1.32-6.59)		1.54 (0.66-3.59)	
Pelvic lymph node metastasis		<0.001		0.001
Negative	Reference		Reference	
Positive	6.33 (3.45-11.62)		3.08 (1.61-5.88)	
Number of pelvic lymph nodes	0.99 (0.96-1.02)	0.445	-	-
Lymph node evaluation		0.028		0.001
Pelvic and paraaortic lymph node (PPALN)	Reference		Reference	
Pelvic lymph node (PLN)	1.92 (1.07-3.44)		2.76 (1.49-5.10)	
Adjuvant treatment		0.001		0.889
No	Reference		Reference	
Yes	3.87 (1.80-8.23)		0.94 (0.37-2.36)	
Lymphovascular space invasion (LVSI)		0.001		0.566
No	Reference		Reference	
Yes	2.93 (1.60-5.38)		1.21 (0.63-2.30)	

† Analysis adjusted for all prognostic factors with p-value < 0.10 in univariable analysis with the main factor
HR = hazard ratio

Table 7. Prognostic factors for 5-year recurrence free survival (RFS) in 636 endometrioid endometrial cancer patients

Prognostic factors	5-year recurrence-free survival (RFS)			
	Univariable		Multivariable	
	Unadjusted HR (95%CI)	p value	Adjusted HR† (95%CI)	p value
Age		0.098		0.200
< 55 years	Reference		Reference	
≥ 55 years	1.55 (0.92-2.59)		1.41 (0.83-2.59)	
Body mass index	1.00 (0.96-1.05)	0.920	-	-
Hemoglobin		0.616	-	-
≥ 13 g/dL	Reference			
< 13 g/dL	0.88 (0.54-1.44)			
Platelet	1.00 (1.00-1.00)	0.231	-	-
Histological grade		0.026		0.153
Grades 1 and 2	Reference		Reference	
Grade 3	1.99 (1.09-3.64)		1.57 (0.85-2.92)	
Tumor size		0.004		0.232
< 3 cm	Reference		Reference	
≥ 3 cm	2.78 (1.38-5.60)		1.59 (0.74-3.40)	
Myometrial invasion		< 0.001		<0.001
< 50%	Reference		Reference	
≥ 50%	3.91 (2.40-6.38)		2.97 (1.76-5.00)	
Cervical involvement		< 0.001		0.028
Negative	Reference		Reference	
Positive	2.78 (1.68-4.63)		1.81 (1.07-3.08)	
Adnexal involvement		0.020		0.263
Negative	Reference		Reference	
Positive	2.40 (1.15-5.01)		1.55 (0.72-3.35)	
Peritoneal washing for cytology		0.118	-	-
Negative	Reference			
Positive	1.87 (0.85-4.08)			
Pelvic lymph node metastasis		< 0.001		0.08
Negative	Reference		Reference	
Positive	3.87 (2.23-6.70)		2.20 (1.23-3.95)	
Number of pelvic lymph nodes	1.00 (0.98-1.03)	0.968	-	-
Lymph node evaluation		0.371		0.103
Pelvic and paraaortic lymph node (PPALN)	Reference		Reference	
Pelvic lymph node (PLN)	1.24 (0.77-2.00)		1.50 (0.92-2.44)	
Adjuvant treatment		0.003		0.313
No	Reference		Reference	
Yes	2.26 (1.32-3.88)		0.70 (0.35-1.4)	
Lymphovascular space invasion (LVSI)		0.006		0.829
No	Reference		Reference	
Yes	2.09 (1.23-3.55)		0.94 (0.52-1.69)	

† Analysis adjusted for all prognostic factors with p-value < 0.10 in univariable analysis with the main factor
HR = hazard ratio

Discussion

Currently, the primary treatment for endometrial carcinoma is surgical staging, including lymphadenectomy. However, the extent and benefit of lymphadenectomy, especially in the paraaortic area, remains controversial. Our study showed that 5-year DSS was significantly better for patients who received evaluation of the pelvic with paraaortic lymph nodes compared to patients who underwent evaluation of only the pelvic lymph nodes. Additionally, PLN evaluation alone was also an independent risk factor for 5-year OS.

The characteristics of the patients were different due to the retrospective nature of the study. Patients in the PPALN group have a lower body mass index and higher grade of disease, suggesting a selection bias for surgeons to consider evaluation of pelvic with paraaortic lymph nodes which might impacts on outcomes.

The median number of pelvic lymph nodes was comparable to those in the other studies. Previous studies reported that the median number of evaluated pelvic lymph nodes was 10-19 lymph nodes[11-14, 18-20]. These numbers were comparable to our PLN group (12 lymph nodes). The median dissected pelvic lymph nodes of the PPALN groups in our study were higher than those of the other studies, at 17 lymph nodes. The median number of paraaortic lymph nodes has rarely been reported. The median number of paraaortic lymph node removals reported by May et al was 10 lymph nodes[19]. In our study, only 7.9% of the patients in the PPALN group had removed equal or more than 10 paraaortic lymph nodes. The median number of paraaortic lymph nodes removed in our study was 3 lymph nodes, since most patients received only a sampling of paraaortic lymph nodes. The SEPAL study demonstrated a survival benefit from pelvic and paraaortic lymph node dissection with a median removal of 23 paraaortic lymph nodes[15]. Although the median number of paraaortic lymph nodes in our study was less than the number in the SEPAL study, we measured a benefit from 5-year DSS and 5-year OS with the evaluation of both pelvic and paraaortic lymph nodes. We found an isolated paraaortic lymph node metastasis of 1.3% in our study. This was comparable to other investigators who reported a low rate of paraaortic lymph node metastasis (1.2-5%) with or without pelvic lymph node metastases[18, 19].

This study confirms the benefit of evaluation of both the pelvic and paraaortic lymph nodes. The positive paraaortic lymph node group showed the worst 5-year DSS outcomes compared to the other groups. Apparently, the negative paraaortic lymph node group had the best 5-year DSS among the groups. For overall survival, there was a significantly improved 5-year OS in patients who underwent pelvic with paraaortic lymph nodes compared to pelvic lymph nodes alone. Similarly, several studies found the survival benefit of paraaortic lymph node dissection[13-15]. This may be explained by more accurate staging and tumor debulking with paraaortic lymph node dissection. Consequently, the patient will receive more appropriate adjuvant treatments. In the secondary outcome, the RFS showed the same trend of nonsignificant improvement in the PPALN group. However, some studies showed that paraaortic lymph node dissection did not improve endometrial carcinoma survival[19, 21, 22]. This question will require future prospective studies to answer.

Improvement in 5-year OS and 5-year RFS may be confounded by many factors. Multivariable Cox regression analysis confirmed that extension of lymph node evaluation is an independent prognostic factor. This finding confirms another benefit of removal of paraaortic lymph nodes. Other factors, including age ≥ 55 years, hemoglobin < 13 g/dL, and risk groups ($p < 0.001$), are also independent factors in the multivariate analysis. Similarly, age ≥ 55 years, tumor size ≥ 3 cm, deep myometrial invasion, histological grade 3, and cervical involvement have been identified as prognostic factors for the survival of endometrial carcinoma[5, 23]. Risk groups are the only one prognostic factor for RFS. Chang et al also reported that the FIGO 2009 stage is an independent prognostic factor. They also reported that age and

extension of lymph node evaluation were prognostic factors for recurrence[18]. Different prognostic factors can be caused by different histological types. They included all histological subtypes, including endometrioid adenocarcinoma, papillary serous, and clear cell carcinoma.

We also performed a risk group analysis as the latest recommendation from ESGO / ESTRO / ESP guidelines[17]. There was no statistically significant difference in 5-year RFS between PPALN and the PLN group in all subgroups, but the data revealed the most relative reduction in the high-risk. For 5-year OS, patients in the low-risk subgroup who received PPALN evaluation were significantly better compared to only the PLN evaluation. This result was different from previous knowledge, which lymph node evaluation should be done in the intermediate and high-risk patients.

There might be bias in selecting healthy patients to undergo PPALN evaluation, resulting in better survival for these patients. In contrast, patients with co-morbidities may not be suitable for PPALN evaluation. These may explain the lack of difference in 5-year RFS and 5-year DSS between the PPALN evaluation and PLN evaluation in low-risk patients.

Our data demonstrated the most benefit from PPALN evaluation in the high-risk group. Given the small number of high-risk patients, the results did not reach statistical significance. There was no evidence to support PPALN evaluation in our study for intermediate-risk and high-intermediate-risk patients.

Another essential point of the paraaortic lymphadenectomy was its complications. The complications from PPALN evaluation were usually higher than those from PLN evaluation. Volpi et al reported that the addition of paraaortic lymphadenectomy was an independent predictor for both lymphedema and lymphocele[24]. Given the retrospective study design, we were not able to collect the complications data. We reported a non-significant difference in blood losses between the two procedural groups.

The strength of this study was the large sample size and the long follow-up time. This study reported almost 400 cases of evaluation of pelvic and paraaortic lymph nodes. However, there were several limitations due to the retrospective nature of the study. First, there might be some selection bias because a PPALN evaluation group tended to have lower BMI and higher histologic grade than a PLN evaluation group. Second, the pathological lymph node count was low in only median removal of 3 paraaortic lymph nodes. Third, we had a small proportion—only 9%—of laparoscopic approaches, which might be unusual in developing countries. Fourth, there was missing data regarding patients' co-morbidities, which might affect patients' survival. Finally, immunotherapy treatment and molecular profile-based treatment, which have been anticipated in recent years, were not available to us.

In the scope of this study, the utilization of sentinel lymph node sampling was notably absent from our institutional practices during the specified research period. However, in the present landscape, sentinel lymph node mapping plays a pivotal role in the surgical management of endometrioid endometrial carcinoma. The FIRES trial, conducted by Rossi et al, demonstrated a high sensitivity of 97.2% and a high negative predictive value of 99.6%. The study was stopped early according to the efficacy of the procedure. Interestingly, the results showed 17% isolated positive lymph nodes outside the standard dissection area of lymph nodes (internal iliac, presacral area)[25]. The recommendation from ESGO / ESTRO / ESP guidelines advocate that sentinel lymph node biopsy is an acceptable alternative to systematic lymphadenectomy for lymph node staging in stage I/II[17]. We are in the process of preparing to present a study employing sentinel lymph node techniques at our institution in the near future. However, it is essential to acknowledge that in instances where sentinel lymph node mapping encounters challenges, the necessity for systematic lymphadenectomy remains. Consequently, the potential implications of our study's findings are

substantial, offering invaluable insights into the scope of lymphadenectomy. Subsequent prospective research that compares pelvic lymph node dissection with combined pelvic and paraaortic lymph node dissection in endometrial carcinoma will provide further substantiation for this hypothesis (as demonstrated in the prospective SEPAL-P3 study)[26].

Conclusion

Our analysis of patients with endometrioid endometrial carcinoma revealed that the pelvic with paraaortic lymph node (PPALN) group exhibited an independent association with significantly prolonged survival when compared to the pelvic lymph node (PLN) group. These findings suggested a potential association between PPALN and improved survival outcomes.

Based on our findings, we suggest that all patients with endometrioid endometrial cancer, especially those in low- to middle-class settings or for whom sentinel lymph node biopsy was not feasible, should have their pelvic and paraaortic lymph nodes evaluated.

Acknowledgments

The authors thank Sasima Tongsai, Ph.D., a statistician in the office for research and development, Faculty of Medicine at Siriraj Hospital, Mahidol University, for conducting the statistical analyses.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
3. Observatory TGC. Thailand Source:Globocan 2020 [Available from: https://gco.iarc.fr/today/data/factsheets/populations/764-thailand-fact-sheets.pdf.
4. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol 1983;15:10-7.
5. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer 1987;60(8 Suppl):2035-41.
6. Koskas M, Amant F, Mirza MR, Creutzberg CL. Cancer of the corpus uteri: 2021 update. Int J Gynaecol Obstet 2021;155 Suppl 1:45-60.
7. Coronado PJ, Rychlik A, Martinez-Maestre MA, Baquedano L, Fasero M, Garcia-Arreza A, et al. Role of lymphadenectomy in intermediate-risk endometrial cancer: a matched-pair study. J Gynecol Oncol 2018;29:e1.
8. Orr JW, Jr., Holloway RW, Orr PF, Holimon JL. Surgical staging of uterine cancer: an analysis of perioperative morbidity. Gynecol Oncol 1991;42: 209-16.
9. Larson DM, Johnson K, Olson KA. Pelvic and para-aortic lymphadenectomy for surgical staging of endometrial cancer: morbidity and mortality. Obstet Gynecol 1992;79:998-1001.
10. Hidaka T, Kato K, Yonezawa R, Shima T, Nakashima A, Nagira K, et al. Omission of lymphadenectomy is possible for low-risk corpus cancer. Eur J Surg Oncol 2007;33:86-90.
11. group As, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 2009;373: 125-36.
12. Benedetti Panici P, Basile S, Maneschi F, Alberto Lissoni A, Signorelli M, Scambia G, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 2008;100:1707-16.
13. Bassarak N, Blankenstein T, Bruning A, Dian D, Bergauer F, Friese K, et al. Is lymphadenectomy a prognostic marker in endometrioid adenocarcinoma of the human endometrium? BMC Cancer 2010;10:224.
14. Eggemann H, Ignatov T, Kaiser K, Burger E, Costa SD, Ignatov A. Survival advantage of lymphadenectomy in endometrial cancer. J Cancer Res Clin Oncol 2016;142:1051-60.
15. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 2010;375:1165-72.
16. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori

G, Podratz KC. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol 2000;182:1506-19.
17. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer 2021;31:12-39.
18. Chang SJ, Kim WY, Yoon JH, Yoo SC, Chang KH, Ryu HS. Para-aortic lymphadenectomy improves survival in patients with intermediate to high-risk endometrial carcinoma. Acta Obstet Gynecol Scand 2008;87: 1361-9.
19. May T, Shoni M, Vitonis AF, Quick CM, Growdon WB, Muto MG. The role of para-aortic lymphadenectomy in the surgical staging of women with intermediate and high-risk endometrial adenocarcinomas. Int J Surg Oncol 2013;2013:858916.
20. Lutman CV, Havrilesky LJ, Cragun JM, Secord AA, Calingaert B, Berchuck A, et al. Pelvic lymph node count is an important prognostic variable for FIGO stage I and II endometrial carcinoma with high-risk histology. Gynecol Oncol 2006;102:92-7.
21. Tong SY, Lee JM, Lee JK, Kim JW, Cho CH, Kim SM, et al. Efficacy of para-aortic lymphadenectomy in early-stage endometrioid uterine corpus cancer. Ann Surg Oncol 2011;18:1425-30.
22. Toptas T, Simsek T. Survival analysis of pelvic lymphadenectomy alone versus combined pelvic and para-aortic lymphadenectomy in patients exhibiting endometrioid type endometrial cancer. Oncol Lett 2015;9:355-64.
23. Luomaranta A, Leminen A, Loukovaara M. Prediction of lymph node and distant metastasis in patients with endometrial carcinoma: a new model based on demographics, biochemical factors, and tumor histology. Gynecol Oncol 2013;129:28-32.
24. Volpi L, Sozzi G, Capozzi VA, Ricco M, Merisio C, Di Serio M, et al. Long term complications following pelvic and para-aortic lymphadenectomy for endometrial cancer, incidence and potential risk factors: a single institution experience. Int J Gynecol Cancer 2019;29:312-9.
25. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol 2017;18: 384-92.
26. Watari H, Katayama H, Shibata T, Ushijima K, Satoh T, Onda T, et al. Phase III trial to confirm the superiority of pelvic and para-aortic lymphadenectomy to pelvic lymphadenectomy alone for endometrial cancer: Japan Clinical Oncology Group Study 1412 (SEPAL-P3). Jpn J Clin Oncol 2017;47:986-90.