Survival Rates between Early Stage Endometrial Carcinoma With or Without Para-Aortic Lymph Node Resection

Kanate Thanagumtorn MD*

** Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand*

Background: *In 1988, the International Federation of Gynecology and Obstetrics (FIGO) introduced the concept of surgical staging of endometrial cancer. Pelvic lymph node resection is a part of our routine procedure for all endometrial cancer patients while the use of para-aortic lymph node resection is at the discretion of the physician during surgery.*

Objective: *To compare the survival rates of endometrial cancer patients receiving pelvic lymph node resection with patients receiving pelvic and para-aortic lymph node resection.*

Material and Method: *This was a retrospective cohort study of early stage endometrial cancer patients that underwent surgical staging with or without para-aortic lymph node resection. Eighty patients were in the only pelvic lymph node resection group (PLN group), and 284 patients were in the combined pelvic and para-aortic lymph node resection group (PPALN group). The survival data were analyzed using the Kaplan-Meier method, and the log-rank test was employed to compare the survival curves of the two groups.*

Results: *The median follow-up period was 31.5 months. Median number of pelvic lymph nodes removed was 9 (1-33) for the PLN group and 14 (3-44) for the PPALN group. Median number of para-aortic nodes removed was 2 (0-12), and the rate of lymph node metastasis was 8.24%. In the PPALN group, 3.52% of patients had para-aortic lymph node metastasis. The overall 3- and 5-year survival rates were 90.9% and 87.4%, respectively for the PLN group as compared to 93.2% and 88.7% respectively for the PPALN group (p = 0.484).*

Conclusion: *The survival rate of early stage endometrial carcinoma patients that underwent surgical staging with or without para-aortic lymph node resection is comparable.*

Keywords: *Para-aortic nodes, Endometrial cancer, Lymphadenectomy*

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In 1988, the International Federation of Gynecology and Obstetrics (FIGO) introduced the concept of surgical staging of endometrial cancer[1]. In 2005, the American College of Obstetricians and Gynecologists (ACOG) recommended surgical staging as an important part of surgical management of endometrial cancer[2]. The survival benefits of pelvic and para-aortic lymph node resection in surgical staging of endometrial carcinoma is still a controversial issue, even though many studies have been designed to find the survival impact of lymph node resection for this disease[3-5]. This is because of the great varieties of patient factors, disease factors, and surgical factors render the studies inconclusive. The sites (pelvic lymph node resection only or combined pelvic and para-aortic lymph node resection) and intensity of lymph node resection (selective, randomized sampling or systematic lymphadenectomy) have shown major differences in each study. It is difficult to compare or to determine the survival impact from previous available research. Although combined pelvic and para-aortic lymph node resection is recommended in Rajavithi Hospital (RH), patient limitations and surgeon preference result in a variety of surgical outcomes. Pelvic lymph node resection is a part of our routine procedure for all endometrial cancer patients, while the use of para-aortic lymph node resection is at the discretion of the physician during surgery.

Considering the variety of surgical management techniques employed in RH, the author designed a retrospective cohort to compare survival rates of endometrial cancer patients receiving pelvic lymph node resection alone to those receiving combined pelvic and para-aortic lymph node resection.

Correspondence to:
Thanagumtorn K, Department of Obstetrics and Gynecology, Rajavithi Hospital, 2 Phaya Thai Road, Ratchathewi, Bangkok 10400, Thailand.
Phone: +66-2-3548165 ext. 3226, Fax: +66-2-3548084
E-mail: kanate845@hotmail.com

Material and Method

The present study was a retrospective study. The Ethics Committee of RH reviewed and approved

this study. Data were retrieved from the database of tumor registry records of the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, RH between 2004 and 2011. The author compared survival rate of patients receiving pelvic lymph node resection (PLN) alone to combined pelvic and para-aortic lymph node resection (PPALN) for clinically early-stage endometrial cancer. Inclusion criteria were preoperative clinical stage I or occult stage II disease of all histologic grade endometrial cancer in patients received surgical staging as initial treatment. Uterine papillary serous carcinoma, clear cell, sarcoma of uterus, more than one histologic cell type and co-existing second primary cancer patients were excluded from the present study. The site and extent of lymph node resection were decided by the surgeon at the time of hysterectomy, typically depending on the grade, depth of invasion and size of primary tumor, as well as individual patient's medical co-morbidities and surgeon preference. The site of lymph node resection was based on operative records that indicate presence or absence of lymph node in pathologic reports. Variables collected were site of lymph node resection, number of lymph nodes collected, age, body mass index (BMI), underlying disease, histological type, FIGO staging, pathologic results, date of surgery, and date of death or last date known to be alive. The date of death was collected from the tumor registry record and the population death registry of The Bureau of Registration Administration, Ministry of the Interior.

Overall survival was defined as the interval from the date of surgery to the date of death from any cause, or date when the patient was last known to be alive. All statistical data analyses were performed using SPSS 17.0 (SPSS, Chicago, IL). Data were presented as mean ± standard deviation (SD) or median (minimum-maximum) for continuous variables and number (%) for categorical variables. Student t-test and/Mann-Whitney U test were used for continuous variables, and Pearson Chi-square and Fisher's exact test for categorical variables. The Kaplan-Meier method was used to generate survival curves and calculate 3- and 5-year overall survival rates, and the log-rank test was used to test for differences in survival rates. Multivariate analysis was performed using the Cox proportional hazards model to assess the impact of para-aortic lymph node resection on survival rates while controlling for known prognostic factors. A p-value of less than 0.05 was set for statistic significant.

Results

Four hundred three clinically diagnosed as early-stage endometrial cancer patients met the eligible criteria. Thirty-nine patients were excluded because they had not undergone lymph node resection. Three hundred sixty four endometrial cancer patients were included and analyse. Eighty cases were in the PLN group and two hundred eighty four cases were in the PPALN group. Table 1 showed clinical and pathological characteristics of eligible patients. Mean (±SD) age of patients was 57.13±9.43 years old. No significant differences in the two groups were recorded in the distribution of the variables, except for BMI and rate of recurrence. BMI of PLN group was higher than that of the PPALN group (29.52±6.97 vs. 26.18±4.50 kg/m^2, p<0.001). There was no significant difference between the death rates in the two treatment groups. Median follow-up period of the PLN group was 27 months, and ten patients in this group (12.5%) died. Median follow-up period of the PPALN group was 32 months, and thirty-one of these patients (10.9%) died. Median number of pelvic lymph nodes removed was 9 (1-33) for the PLN group and 14 (3-44) for the PPALN group. Median number of para-aortic nodes removed for the PPALN group was 2 (0-12). There were 36/284 (12.7%) specimens labeled as para-aortic lymph node had no lymph node in the pathologic reports. No significant differences were recorded in operative times or postoperative morbidity (2.7% vs. 7.7%, p = 0.121). Median blood loss during surgery in the PPALN group was significantly higher than that of the PLN group [400 ml (50-2,600) vs. 300 ml (50-1,300), p = 0.001]. Of 133 (36.5%), patients receiving adjuvant therapy, 25 (31.2%) were from the PLN group and 108 (38.0%) were from the PPALN group, with no significant differences. Of the 364 patients, 30 (8.24%) had lymph node metastasis. With regard to the PPALN group, 3.52% had para-aortic lymph node metastasis and included 2.46% that had both pelvic and para-aortic lymph node metastasis and 1.06% that had exclusive para-aortic lymph node metastasis (Table 2).

Overall 3- and 5-year survival rates for endometrial cancer patients in the present study were 92.0% and 87.2% respectively. Overall 3- and 5-year survival rates were 90.9% and 87.4% respectively for the PLN group, compared to 93.2% and 88.7% respectively for the PPALN group (p = 0.484), as shown in Fig. 1. Univariate analysis (Table 3) demonstrated that the variables which had statistically significant effects on survival rates were myometrial invasion >1/2, grade 3 endometrioid adenocarcinoma, adnexal

metastasis, advanced FIGO stage, the need for adjuvant therapy, and presence of recurrence. The other clinical variables such as age, BMI, underlying disease, lymph-vascular space invasion (LVSI), and site of lymph node

Table 1. Baseline characteristics classified by para-arotic lymph node resection

Characteristics	Pelvic lymph node resection only	Pelvic and para-arotic lymph node resection	Total	*p*-value
Age (years)				0.674
≤60	52 (65.0)	189 (66.5)	241 (66.2)	
>60	28 (35.0)	95 (33.5)	123 (33.8)	
Mean ± SD	56.73±10.25	57.24±9.21	57.13±9.43	
BMI (kg/m^2)				<0.001*
≤25	19 (23.8)	118 (41.5)	137 (37.6)	
>25	61 (76.2)	166 (58.5)	227 (62.4)	
Mean ± SD	29.52±6.97	26.18±4.50	26.91±5.31	
Underlying disease				0.208
Yes	27 (33.8)	118 (41.5)	219 (60.2)	
No	53 (66.2)	166 (58.5)	145 (39.8)	
Myometrial invasion				0.738
No or <1/2	50 (68.5)	180 (66.4)	230 (66.9)	
≥1/2	23 (31.5)	91 (33.6)	114 (33.1)	
Lymph-vascular invasion				0.382
Negative	21 (26.9)	72 (25.7)	93 (26.0)	
Positive	17 (21.8)	44 (15.7)	61 (17.0)	
NA	40 (51.3)	166 (58.6)	204 (57.0)	
Tumor type				0.879
Endometrioid adenocarcinoma grade I	45 (62.5)	150 (57.7)	195 (58.7)	
Endometrioid adenocarcinoma grade II	17 (23.6)	77 (29.6)	94 (28.3)	
Endometrioid adenocarcinoma grade III	10 (13.9)	33 (12.7)	43 (13.0)	
Adnexal metastasis				0.862
Negative	72 (92.3)	261 (92.9)	333 (92.8)	
Positive	6 (7.7)	20 (7.1)	26 (7.2)	
Stage				0.171
Stage 1-2	71 (91.0)	238 (85.0)	309 (86.3)	
Stage 3-4	7 (9.0)	42 (15.0)	49 (13.5)	
Adjuvant therapy				0.472
No adjuvant therapy	45 (56.2)	149 (52.5)	194 (53.3)	
Adjuvant therapy	25 (31.2)	108 (38.0)	133 (36.5)	
Unknown	10 (12.5)	27 (9.5)	37 (10.2)	
Recurrence				0.017*
No recurrence	80 (100.0)	265 (93.3)	345 (94.8)	
Recurrence	0 (0.0)	19 (6.7)	19 (5.2)	

BMI = body mass index; NA = not applicable
Data presented as n (%), unless otherwise specified
* Number may not add up the total number due to missing data

Table 2. Pathologic results of lymph node resection

Characteristics	Pelvic lymph node resection (n = 80)	Pelvic and para-aortic lymph node resection (n = 284)	Total (n = 364)
Negative	76 (95.00%)	258 (90.85%)	334 (91.76%)
Pelvic node positive	4 (5.00%)	16 (5.63%)	20 (5.49%)
Paraortic node positive	0 (0.00%)	3 (1.06%)	3 (0.82%)
Both positive	0 (0.00%)	7 (2.46%)	7 (1.92%)

resection had no statistically significant impact on survival rates. Multivariate analysis (Table 4) confirmed the statistically significant effect on survival rates of the aforementioned variables with the exception of advanced FIGO stage and the need for adjuvant therapy. Both univariate and multivariate analysis showed that site of lymph node resection had no statistically significant effect on survival rates.

Discussion

The present study of clinically diagnosed early-stage endometrial cancer patients found no benefit in using combined pelvic and para-aortic lymph node resection compared to pelvic lymph node resection alone in terms of overall survival rates. The incidence of pelvic node and para-aortic node metastasis in the present study was 20/364 (5.5%) and

Table 3. Univariate analysis of overall survival by different prognostic factors

Characteristics	Crude HR (95% CI)	*p*-value
Age		
≤60 years	1	
>60 years	1.31 (0.70-2.45)	0.402
BMI		
<25 kg/m^2	1	
≥25 kg/m^2	0.72 (0.39-1.34)	0.298
Underlying disease		
No	1	
Yes	1.06 (0.56-19.8)	0.864
Myometrial invasion		
No or <1/2	1	
≥1/2	2.84 (1.63-4.94)	<0.001*
Lymph-vascular invasion		
Negative	1	
Positive	1.90 (0.75-4.81)	0.177
NA	1.03 (0.46-2.32)	0.949
Tumor type		
Endometrioid adenocarcinoma grade I + II	1	
Endometrioid adenocarcinoma grade III	3.24 (1.64-6.43)	0.001*
Adnexal metastasis		
No	1	
Yes	2.78 (1.23-6.28)	0.014*
Site of lymph node resection		
Pelvic only	1	
Pelvic and para-aortic	1.29 (0.63-2.64)	0.485
Stage		
Stage (1-2)	1	
Stage (3-4)	3.08 (1.62-5.89)	0.001*
Adjuvant therapy		
No adjuvant	1	
Adjuvant	2.58 (1.30-5.13)	0.007*
Unknown	2.48 (2.95-6.55)	0.065
Recurrence		
No	1	
Yes	11.44 (5.78-22.63)	0.001*

HR = hazard ratio

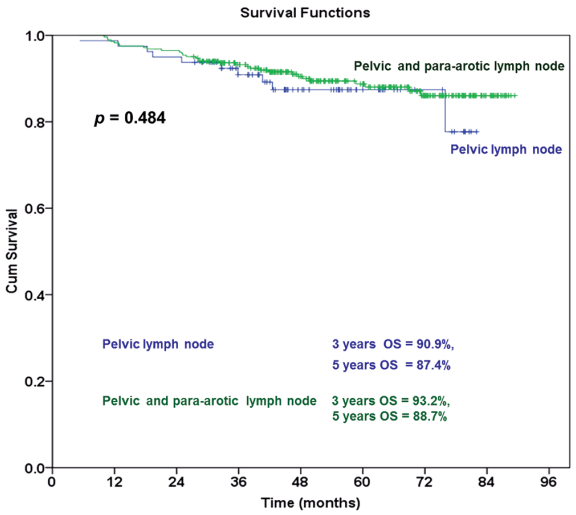

Fig. 1 Survival curves of both study groups.

Table 4. Multivariate analysis of overall survival by different prognostic factors

Characteristics	Adjusted HR (95% CI)	*p*-value
Site of lymph node resection		
Pelvic only	1	
Pelvic and para-arotic	2.20 (0.98-4.96)	0.056
Myometrial invasion		
No or <1/2	1	
≥1/2	2.13 (1.05-4.33)	0.037*
Tumor type		
Endometrioid adenocarcinoma grade I, II	1	
Endometrioid adenocarcinoma grade III	2.69 (1.27-5.67)	0.010*
Adnexal metastasis		
No	1	
Yes	2.13 (0.70-6.48)	0.183
Stage		
Stage (1-2)	1	
Stage (3-4)	1.12 (0.45-2.78)	0.803
Adjuvant therapy		
No adjuvant	1	
Adjuvant	0.86 (0.38-1.93)	0.709
Unknown	1.58 (0.52-4.80)	0.417
Recurrence		
No	1	
Yes	9.78 (4.22-22.68)	<0.001*

10/284 (3.5%) respectively. The incidence of isolated para-aortic node metastasis was only 3/284 (1.06%). This is lower than the 9% pelvic node metastasis, 5% para-aortic node metastasis, and 2% isolated para-aortic node metastasis reported in the large Gynecologic Oncology Group study among patients with clinical stage I cancers[6]. Lack of survival benefits of additional para-aortic node resection may be due to the small number of para-aortic nodes removed in the PPALN group (median = 2) resulting in a low incidence of para-aortic node metastasis; furthermore, a subset of patients who had both positive pelvic and para-aortic node may obscure the beneficial effects. At RH, para-aortic node resection usually entails removal of the precaval and lower aortic lymphatic tissue to the level of the inferior mesenteric artery. The extension of lymph node removed may not be adequate. From sentinel lymph node investigation[7], 47% of para-aortic sentinel nodes located above the inferior mesenteric artery. The rationale for the potential beneficial effect of more extensive lymph node resection is to identify patients with nodal metastasis who are potentially curable by adjuvant treatment. An interesting cohort study by May et al[8] suggested that a total number of fewer than 10 para-aortic lymph nodes was not adequate to represent the metastatic status of para-aortic node and contribute to less aggressive adjuvant therapy, which affect the disease-free survival (DFS). The limited extension and small number (median = 2) of para-aortic nodes removed in the present study was unable to represent the metastatic status. However, a meta-analysis from four randomized trials[9] and data from the ASTEC/EN.5 radiotherapy trial[10] have shown that adjuvant radiotherapy results in a small reduction in the risk of isolated pelvic recurrence, but not affects overall or disease-specific survival. Another factor that may contribute to the therapeutic benefit of more extensive lymph node resection is the removal of occult small-volume metastatic disease undiagnosed by the pathologist. Most studies have suggested that the survival benefit of para-aortic node resection requires the removal of a large number of nodes[3-5]. The median number of para-aortic nodes removed in the SEPAL study[3] was 23 (16-30), but even with that large number of nodes removed, para-aortic lymph node resection has survival benefits only for patients at intermediate or high risk of recurrence. Cragun et al[4] has shown that a cut-off at the median number of nodes removed of more than 11 pelvic nodes improved overall survival and progression-free survival for patients with poorly differentiated early-stage endometrial cancer. Again, the small number of para-aortic nodes removed in the present study (median = 2) cannot achieve the therapeutic benefit. In the other hand, some studies demonstrated no survival benefit of lymphadenectomy in endometrial cancer patients. Chan et al[11] carried out a retrospective analysis of data from the Surveillance, Epidemiology, and End Results program between 1988 and 2001. The outcomes of 39,396 endometrial cancer women were included in the analysis. It revealed that lymphadenectomy had no benefit for patients with stage I grade 1 and grade 2 disease, but was associated with an improved survival rates in stage I grade 3 and more advanced disease. The study from Hidaka et al[12] also found no survival benefit in low-risk disease. The randomized clinical trial by Benedetti et al[13] in which the median number of lymph nodes removed was 30 in the systematic lymphadenectomy group, showed similar 5-year disease-free and overall survival rates compared to the no-lymphadenectomy group. The same results were reported in the MRC ASTEC randomized trial[14]. The present study indicated no benefits of lymphadenectomy for early stage endometrial cancer patients, which is the same survival outcome as the above studies.

The generally accepted pathologic risk factors in endometrial cancers are related to depth of myometrial invasion, tumor grade, histological subtype, LVSI, FIGO stage, and lymph node metastasis[15,16]. Univariate and multivariate analysis in the present study demonstrated that the risk factors affecting survival rates were myometrial invasion >1/2, grade 3 endometrioid adenocarcinoma, adnexal metastasis, and FIGO stage. The present study was unable to demonstrate the significance of LVSI due to the lack of completeness of pathologic reports; LVSI was not reported in 57% of cases, which may reflect the pathologist's view that it was of no importance. Para-aortic lymph node resection usually requires a larger incision and more extensive dissection; therefore, the addition of para-aortic lymph node resection may lengthen operative times and increase peri-operative morbidity[12]. Fortunately, there were no serious complications in our patients. Although no significant differences were recorded in operative times or post-operative morbidity in the two groups in the present study, this may be due to the surgeon's decisions during operations to adjust treatment as appropriate for individual situations. Surgeons tend to omit para-aortic lymph node resection for patients with high BMI.

Limitations of the present study included the short duration of the median follow-up period, which

may not have been long enough to identify differences in overall survival rates. Another limitation includes the small number of cases in the study, and in particular, the missing or unavailable data. Because there were so few reported cases, node metastasis could not be incorporated for regression analysis.

In conclusion, the survival rate of early stage endometrial carcinoma patients that underwent surgical staging with or without para-aortic lymph node resection is comparable.

What is already known on this topic?

In 1988, the FIGO introduced the concept of surgical staging of endometrial cancer. The survival benefits of para-aortic lymph node resection in surgical staging of endometrial carcinoma is still a controversial issue. Although many studies have been designed to find the survival impact of lymph node resection of this disease, the great varieties of patient factors, disease factors, and surgical factors render the studies inconclusive.

What this study adds?

Para-aortic lymph node resection in the context of the present study (small number of para-aortic nodes removed) had no survival benefit for clinically early-stage endometrial cancer patients. Para-aortic lymph nodes resection should not be a routine procedure for clinically early-stage endometrial cancer patients.

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Potential conflicts of interest

None.

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การศึกษาเปรียบเทียบอัตราการรอดชีพระหว่างกลุ่มผู้ป่วยที่ได้รับและไม่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติกในมะเร็งเยื่อบุมดลูกระยะเริ่มต้น

คเณศร์ ธนกำธร

ภูมิหลัง: *พ.ศ. 2531, the International Federation of Gynecology and Obstetrics (FIGO) ประกาศคำแนะนำให้ทำการผ่าตัดเลาะต่อมน้ำเหลืองอุ้งเชิงกรานและต่อมน้ำเหลืองพาราเอออร์ติกในการผ่าตัดผู้ป่วยมะเร็งเยื่อบุมดลูก การผ่าตัดที่เกิดขึ้นจริงมีทั้งที่เลาะเฉพาะต่อมน้ำเหลืองบริเวณช่องเชิงกรานหรือเลาะทั้งต่อมน้ำเหลืองอุ้งเชิงกรานร่วมกับต่อมน้ำเหลืองพาราเอออร์ติกขึ้นอยู่กับข้อจำกัดของผู้ป่วยและดุลยพินิจของแพทย์ในขณะผ่าตัด*

วัตถุประสงค์: *เพื่อเปรียบเทียบอัตราการรอดชีพของผู้ป่วยมะเร็งเยื่อบุมดลูกระยะเริ่มต้นในกลุ่มที่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติก และกลุ่มที่ไม่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติก*

วัสดุและวิธีการ: *เป็นการศึกษา retrospective cohort โดยทบทวนเวชระเบียนของผู้ป่วยมะเร็งเยื่อบุมดลูกระยะเริ่มต้นที่ได้รับการผ่าตัดที่งานมะเร็งนรีเวช กลุ่มงานสูติ-นรีเวชศาสตร์ โรงพยาบาลราชวิถี ระหว่าง พ.ศ. 2547 ถึง พ.ศ. 2554 พบผู้ป่วย 284 ราย ที่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติก และผู้ป่วย 80 ราย ที่ไม่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติก*

ผลการศึกษา: *ค่ามัธยฐานของระยะเวลาในการติดตามผู้ป่วย 31.5 เดือน ค่ามัธยฐานของจำนวนต่อมน้ำเหลืองอุ้งเชิงกรานที่เลาะได้เท่ากับ 9 (1-33) ต่อม ในกลุ่มที่ไม่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติก และ 14 (3-44) ต่อม ในกลุ่มที่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติก ค่ามัธยฐานของต่อมน้ำเหลืองพาราเอออร์ติกที่เลาะได้ในผู้ป่วย 284 ราย เท่ากับ 2 (0-12) ต่อม อัตราการแพร่กระจายของมะเร็งไปต่อมน้ำเหลืองเท่ากับร้อยละ 8.24 และอัตราการแพร่กระจายของมะเร็งไปต่อมพาราเอออร์ติกในกลุ่มที่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติกเท่ากับร้อยละ 3.52 อัตราการรอดชีพที่ 3 และ 5 ปี ในกลุ่มที่ไม่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติก เท่ากับร้อยละ 90.9 และ 87.4 เทียบกับร้อยละ 93.2 และ 88.7 ในกลุ่มที่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติก (p = 0.484)*

สรุป: *การผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติกในกลุ่มผู้ป่วยมะเร็งเยื่อบุมดลูกระยะเริ่มต้นมีอัตราการรอดชีพไม่แตกต่างกับกลุ่มที่ไม่ได้รับการผ่าตัดเลาะต่อมน้ำเหลืองพาราเอออร์ติก*