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The 3 Years Overall Survival Rate in the Women with Stage III Endometrial Cancer across Different Sequences of Adjuvant Chemotherapy or Radiation Therapy

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ABSTRACT

Objectives: To analyze the three years overall survival (OS) and progression free survival (PFS) in women with stage III endometrial cancer across different sequences of chemotherapy (CT) and radiotherapy (RT).

Materials and Methods: A total of 110 stage III endometrial cancer (EC) patients treated with surgically staging and postoperatively received adjuvant therapy in the sandwich method were retrospectively analyzed. Treatment protocols were divided into three groups (Group A: 1-2 cycles of CT followed by RT and 4-5 cycles of CT, Group B: 3 cycles of CT before RT and 3 cycles of CT, and Group C: 4-5 cycles of CT before RT and 1-2 cycles of CT). Survival analysis was analyzed by log-rank test and Cox regression analysis.

Results: After 68 months of median follow-up time, the three years OS and PFS in all patients were 90.0% and 93.5%, respectively. There was no statistical difference in OS and PFS among the three groups. The three years OS was 100%, 86.8%, and 94.7% in groups A, B, and C. In addition, consecutively, the three years PFS was 100%, 91.88%, and 94.7% in groups A, B, and C.

Conclusion: Different adjuvant chemotherapy or radiation therapy sequences offer excellent clinical efficacy and no treatment-related mortality in stage III EC. Moreover, sequences of CT and RT in the sandwich method did not impact the three years OS and PFS.

Keywords: endometrial cancer, adjuvant therapy, sandwich method.

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อัตราการอยู่รอดโดยรวมที่ระยะเวลา 3 ปีของผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะที่ 3 ที่ได้รับการรักษาเพิ่มเติมหลังการผ่าตัด ที่แตกต่างกันในลำดับขั้นตอนการให้เคมีบำบัดและการฉายรังสี ในโรงพยาบาลราชวิถี

กมัยธร เทียนทอง, ฉัตรภัสร์ กล่ำนาค

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาอัตราการอยู่รอดโดยรวมและอัตราการปลอดโรคที่ระยะเวลา 3 ปี ของผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะที่ 3 ที่ได้รับการรักษาเพิ่มเติมหลังการผ่าตัด ที่แตกต่างกันในลำดับขั้นตอนการให้เคมีบำบัดและการฉายรังสี*

วัสดุและวิธีการ: *ผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะที่ 3 จำนวน 110 คน ซึ่งได้รับการรักษาโดยการผ่าตัดเพื่อกำหนดระยะของโรค ได้รับการรักษาเพิ่มเติมหลังการผ่าตัดแบบแซนวิชเทคนิค การรักษาเพิ่มเติมหลังการผ่าตัดแบบแซนวิชเทคนิค แบ่งเป็น 3 กลุ่ม ได้แก่ กลุ่ม A คือ ผู้ป่วยที่ได้รับยาเคมีบำบัด 1-2 ครั้ง ก่อนได้รับการฉายรังสี และตามด้วยยาเคมีบำบัด 4-5 ครั้ง, กลุ่ม B คือ ผู้ป่วยที่ได้รับยาเคมีบำบัด 3 ครั้ง ก่อนได้รับการฉายรังสี และตามด้วยยาเคมีบำบัด 3 ครั้ง และกลุ่ม C คือ ผู้ป่วยที่ได้รับยาเคมีบำบัด 4-5 ครั้ง ก่อนได้รับการฉายรังสี และตามด้วยยาเคมีบำบัด 1-2 ครั้ง วิเคราะห์อัตราการอยู่รอดด้วยวิธีการทางสถิติ*

ผลการศึกษา: *หลังจากการตรวจติดตามเป็นระยะเวลาเฉลี่ย 68 เดือน พบว่าอัตราการอยู่รอดโดยรวมและอัตราการปลอดโรคเฉลี่ย 3 ปี ของผู้ป่วยมะเร็งเยื่อบุโพรงมดลูกระยะที่ 3 คือ ร้อยละ 90.0 และ 93.5 ตามลำดับ โดยอัตราการอยู่รอดโดยรวมของผู้ป่วยกลุ่ม A, B, C คือร้อยละ 100, 86.8 และ 94.7 ตามลำดับ อัตราการปลอดโรคของผู้ป่วยกลุ่ม A, B, C คือร้อยละ 100, 91.9 และ 94.7 ตามลำดับ ทั้งนี้ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างทั้ง 3 กลุ่ม*

สรุป: *ลำดับของการให้ยาเคมีบำบัดและการฉายรังสีที่แตกต่างกันมีประสิทธิภาพที่ดีในการรักษา และไม่พบว่ามีอัตราเสียชีวิตที่เกิดจากการรักษา นอกจากนี้ลำดับการรักษาที่แตกต่างกันของแซนวิชเทคนิคไม่ส่งผลถึงอัตราการอยู่รอดและปลอดโรคที่ระยะเวลา 3 ปี*

คำสำคัญ: *มะเร็งเยื่อบุโพรงมดลูก, การรักษาเสริมหลังการผ่าตัด, ลำดับของการให้ยาเคมีบำบัดและการฉายรังสี*

Introduction

Endometrial cancer (EC) is one of the most common gynecologic malignancies. The incidence has continually increased due to aging, obesity, and metabolic syndrome[1]. Generally, EC is recognized as a disease related to a favorable prognosis since most patients are diagnosed at the early stage of the disease. Conversely, locally advanced EC patients tend to develop loco-regional and distant recurrence, subsequently lower survival[2]. Several adjuvant therapies are given to improve the outcome of these patients[3]. Adjuvant pelvic radiation (RT) is effective for loco-regional control, while adjuvant chemotherapy (CT) administration reduces distant metastatic risk[4]. Several studies in recent years have shown that the combination of these two treatment modalities may be the most promising option for patients with advanced disease[5]. The primary concern regarding the combination of RT and CT is the optimal timing of RT and CT. Patients receiving RT before CT may develop tumor progression outside the radiation field[6]. On the contrary, when CT is initially administered, patients may be suffering from the toxicity of CT, and the capacity to complete RT may be limited[7]. Many studies have been sequentially the timing of RT and CT to lessen toxicity and achieve optimal survival outcomes[8-11]. To date, the optimal sequence of administering RT and CT for locally advanced stage EC patients, either sequentially or sandwiched (adjuvant CT followed by RT and subsequent CT), remains controversial. The sandwich approach is one of the potential techniques with high efficacy and acceptable toxicity. Various studies supported the sandwich method for treating stage III EC and reported three years progression free survival (PFS) rates of 53%-80% and three years overall survival (OS) rates of 52%-91%[7, 12-15]. However, there is limited data about a sequence of CT and RT in the sandwich method. Therefore, we conducted a retrospective study to analyze the three years OS and PFS rates in women with stage III EC across different sequences of CT and RT in the sandwich method.

Materials and Methods

Patient selection

Electronic data of 110 FIGO stage III EC patients treated between January 2012 and June 2018 at the Department of Obstetrics and Gynecology, Rajavithi Hospital, Thailand, were retrospectively reviewed. Institutional review board (IRB) approval was obtained. All patients were surgically staged with total hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and paraaortic lymph node (LN) sampling or dissection. A sequence of CT and RT in the sandwich method was postoperatively administered. Exclusion criteria were women who had received neoadjuvant therapy (CT or RT) before hysterectomy and had not completed RT and six cycles of CT. Data regarding date of surgery, cytoreduction status, pathological factor, number of CT cycles received before and after RT, type of radiation therapy received, date of recurrence, and date of death was extracted. Optimal cytoreduction was total residual tumor less than or equal to one cm in diameter, and suboptimal debulking was defined as tumor more than one cm of disease.

Treatment protocol

Adjuvant CT was given within 2 weeks after surgery. The CT regimens composed of carboplatin (area under curve 5) plus paclitaxel (175 mg/m^2) and doxorubicin (60 mg/m^2) plus cisplatin (50 mg/m^2) every 21 days. Treatment toxicities-related death was assessed. At present, the optimal sequences of adjuvant therapy have yet to be determined. Therefore, there is no consensus guideline in our hospital. The treatment protocol is depended on the surgeon's preference. The adjuvant CT and RT were determined using the different sequences of the number of CT

cycles before and after RT initiation. Three sequence groups were identified.

- Group A: Patients received 1-2 cycles of CT followed by RT and additional 4-5 cycles of CT

- Group B: Patients received three cycles of CT followed by RT and additional 3 cycles of CT

- Group C: Patients received 4-5 cycles of CT followed by RT and additional 1-2 cycles of CT

External beam RT was provided to all patients, using a total dose of 50-50.4 Gy to the pelvis with a daily fraction of 1.8-2 Gy. In cases of para-aortic lymph node metastasis, para-aortic fields were routinely irradiated. Vaginal brachytherapy was provided when patients were considered at high risk of local recurrence or the discretion of the treating radiation oncologist, using two fractions of 6 Gy.

Statistical analysis

The sample size was estimated based on a previous study 15 that revealed 80% of the three years OS. The estimated single proportion with an alpha error of 5% and delta of 10% was tested with a dropout rate of 10%. Therefore, the number of participants was 107. All statistical analyses were evaluated using standard software (SPSS version 22; SPSS Inc., Chicago, IL, USA). The primary objective of this study was the three years OS in stage III EC across different sequences of adjuvant CT or RT. In addition, the secondary purposes were to evaluate the three years PFS and the optimal sequence of CT and RT in the sandwich method. Time to death or progression was calculated as the period from the date of surgery to the date of death or the first clinical or imaging evidence of disease recurrence. Clinicopathological data were summarized and presented as frequencies (number, percent) or means ± standard deviations. Both OS and PFS rates were estimated by the Kaplan-Meier method. The Pearson chi-square test was used to analyze the clinical and pathological factors differences among the groups. Univariate analysis was performed via the log-rank test. Multivariate analysis was done using the Cox proportional hazards model, using covariates with a p value less than 0.1 based on univariate analysis. All p values < 0.05 were statistically significant.

Results

This study enrolled 110 patients with stage III EC who underwent surgical staging and adjuvant CT and RT in the sandwich method. Table 1 shows the clinicopathological characteristics of the patients stratified by different sequences of CT and RT in the sandwich method. The patients were divided into three groups according to the number of CT cycles before and after RT. Of these, 15 (13.6%), 76 (69.1%), and 19 (17.3%) received adjuvant treatment in groups A, B, and C, respectively. The mean age at the time of surgery was 60.9 years old. The most common tumor histology was endometrioid adenocarcinoma (80.9%). On histologic examination, the majority of patients had deep myometrial invasion (84.5%), presence of LVSI (88.2%), and pelvic LN metastasis (63.6%). Approximately 27% of patients had paraaortic LN metastasis. Positive fluid for cytology was noted in 90% of patients. After surgical staging, optimal cytoreductive status was documented in 87.3% of patients. In group A, all patients had optimal cytoreductive status. Overall, there was no statistical significance of clinicopathological factors among the three groups. The most frequent chemotherapy regimen (108, 98.2%) was paclitaxel plus carboplatin. Doxorubicin plus cisplatin was only given to two patients (1.8%) in group B because of paclitaxel hypersensitivity in the first cycle of CT and a personal history of supraventricular tachycardia (SVT).

Table 1. Clinicopathological characteristics stratified by different sequences of CT and RT in the sandwich method.

Characteristics	All patients (n= 110)	Group A (n= 15)	Group B (n= 76)	Group C (n= 19)	p value
Age (years) at surgery (mean ± SD)	60.9 ± 8.5	60.2±9.6	62.1±8.5	56.6±6.6	0.970
Cytoreductive status					
Optimal	96 (87.3%)	15 (100%)	64 (84.2%)	17 (89.5%)	0.294*
Suboptimal	14 (12.7%)	0 (0%)	12 (15.8%)	2 (10.5%)	
Histology type					
Endometrioid	89 (80.9%)	14 (93.3%)	60 (79.0%)	15 (79.0%)	0.454*
Non-endometrioid	21 (19.1%)	1 (6.7%)	16 (21.0%)	4 (21.0%)	
Tumor size (cm) (mean ± SD)	5.9±2.5	6.3±2.1	5.9±2.5	5.3±2.5	0.610
Myometrial invasion					
< 50%	17 (15.5%)	2 (13.3%)	14 (18.4%)	1 (5.3%)	0.465*
≥ 50%	93 (84.5%)	13 (86.7%)	62 (81.6%)	18 (94.7%)	
LVSI					
Absent	13 (11.8%)	1 (6.7%)	10 (13.2%)	2 (10.5%)	0.904*
Present	97 (88.2%)	14 (93.3%)	66 (86.8%)	17 (89.5%)	
Isthmic involvement					
Absent	55 (50.0%)	7 (46.7%)	37 (48.7%)	11 (57.9%)	0.743+
Present	55 (50.0%)	8 (53.3%)	39(51.3%)	8 (41.2%)	
Cervical involvement					
Absent	72 (65.5%)	10 (66.7%)	49 (64.5%)	13 (68.4%)	0.944+
Present	38 (34.5%)	5 (33.3%)	27 (35.5%)	6 (31.6%)	
Uterine serosal involvement					
Absent	92 (83.6%)	11 (73.3%)	64 (84.2%)	17 (89.5%)	0.449+
Present	18 (16.4%)	4 (26.7%)	12 (15.8%)	2 (10.5%)	
Adnexal involvement					
Absent	67 (60.9%)	8 (53.3%)	45 (59.2%)	14 (73.7%)	0.416+
Present	43 (39.1%)	7 (46.7%)	31 (40.8%)	5 (26.3%)	
Pelvic LN metastasis					
Yes	70 (63.6%)	8 (53.3%)	45 (59.2%)	16 (84.2%)	0.094+
No	40 (36.4%)	7 (46.7%)	31 (40.8%)	3 (15.8%)	
Paraaortic LN metastasis					
Yes	30 (27.3%)	4 (16.7%)	21 (27.6%)	6 (31.6%)	0.934+
No	80 (72.7%)	11 (73.3%)	55 (72.4%)	13 (68.4%)	
Peritoneal cytology					
Positive	99 (90.0%)	14 (93.3%)	67 (88.2%)	18 (94.7%)	0.839*
Negative	7 (6.7%)	0 (0.0%)	6 (7.9%)	1(5.3%)	
Not done	4 (3.6%)	1 (6.7%)	3 (3.9%)	0 (0.0%)	

* Fisher's Exact Test, + Pearson chi-square test
Group A: 1-2 cycles of CT followed by RT and additional 4-5 cycles of CT
Group B: 3 cycles of CT followed by RT and additional 3 cycles of CT
Group C: 4-5 cycles of CT followed by RT and additional 1-2 cycles of CT
CT: chemotherapy, RT: radiotherapy, SD: standard deviation, LVSI: lymphovascular space invasion, LN: lymph node

Fig. 1. reveals Kaplan-Meier survival analysis in all patients. After 68 (8-113) months of median follow-up time, the three years OS and PFS were 90.0% and 93.5%, respectively. Fig. 2. demonstrates the Kaplan-Meier survival analysis by treatment group. Consecutively, the three-year OS was 100%, 86.8%, and 94.7% in groups A, B, and C. In addition, the three-year PFS was 100%, 91.88%, and 94.7% in groups A, B, and C.

Of 110 patients, 25 patients (22.7%) experienced the recurrent disease. Three patients (2.7%) had local recurrence, and 22 patients (20%) had distant metastasis. Disease recurrence was 6.7% (1 patient), 25% (19 patients), and 26.3% (5 patients) in groups A, B, and C, respectively. Furthermore, the death rate was highest in group B (11 patients, 14.5%), followed by one patient (5.3%) in group C. However, recurrence and survival did not statistically differ among the three groups. Ninety-eight patients (89.1%) remained alive at the analysis time. For the toxicities, there were no treatment-related deaths in this cohort.

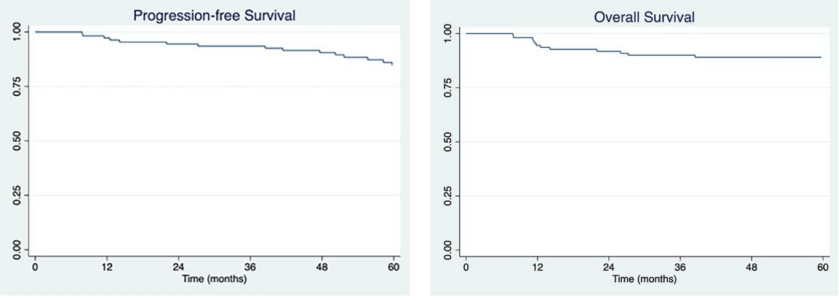

Fig. 1. Kaplan–Meier survival analysis in all patients (PFS analysis and OS analysis).

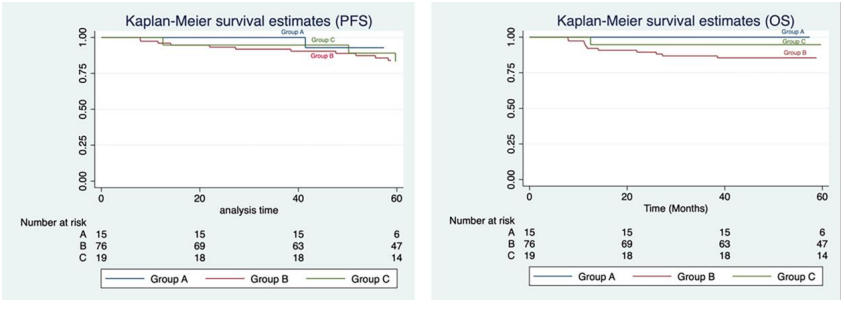

Fig. 2. Kaplan–Meier survival analysis by treatment group (PFS analysis and OS analysis).
Group A: 1-2 cycles of CT followed by RT and additional 4-5 cycles of CT
Group B: 3 cycles of CT followed by RT and additional 3 cycles of CT
Group C: 4-5 cycles of CT followed by RT and additional 1-2 cycles of CT

Table 2. establishes a univariate analysis of the prognostic factor of OS and PFS. The sequence of CT and RT in the sandwich method was not the predictive factor for OS and PFS. Paraaortic LN metastasis resulted in significantly worse survival, 2.70 times than no paraaortic LN metastasis. Moreover, the patients with an age of more than 60 years old, suboptimal cytoreductive status, non-endometrioid adenocarcinoma, and isthmic involvement had a statistical risk of disease recurrence compared to those under 60 years old, endometrioid adenocarcinoma, and non-isthmic

involvement for 2.17, 0.40, 2.40, and 2.36 times, respectively. As shown in table 3, no prognostic factor predicted both OS and PFS in a multivariable model.

Table 2. Univariate analysis of prognostic factors for OS and PFS.

Characteristics	PFS	HR (95% CI)	p value	OS	HR (95% CI)	p value
Adjuvant treatment						
B vs A	0.32	0.04, 2.40	0.267	0.00	0.00, ∞	1.000
B vs C	0.99	0.37, 2.70	0.996	0.35	0.04, 2.68	0.309
Age (yrs) (≤ 60 vs > 60)	2.17	0.89, 5.29	0.088	3.52	0.77, 16.08	0.104
BMI (kg/m²) (≤ 25 vs > 25)	0.95	0.42, 2.13	0.897	0.44	0.13, 1.46	0.178
Cytoreductive status (Optimal vs suboptimal)	0.40	0.16, 1.00	0.050	0.41	0.11, 1.50	0.178
Endometrioid Histology (yes vs no)	2.40	1.02, 5.68	0.046	2.15	0.64, 7.13	0.213
Tumor size (cm) (≤ 2 vs > 2 cm)	1.01	0.14,7.56	0.990	0.41	0.05,3.17	0.392
Myometrial invasion (< 50 % vs ≥ 50 %)	0.92	0.31, 2.74	0.888	2.09	0.27, 16.20	0.480
LVSI (no vs yes)	1.34	0.31, 5.72	0.694	0.00	0.00, ∞	1.000
Isthmic involvement (no vs yes)	2.36	1.03, 5.41	0.042	2.03	0.61, 6.75	0.246
Cervical involvement (no vs yes)	1.72	0.78, 3.79	0.182	1.90	0.61, 5.89	0.267
Uterine serosal involvement (no vs yes)	0.92	0.27, 3.12	0.897	1.87	0.51, 6.90	0.349
Adnexal involvement (no vs yes)	0.53	0.22, 1.28	0.159	0.49	0.13, 1.81	0.286
Pelvic LN metastasis (no vs yes)	1.47	0.61, 3.53	0.385	1.14	0.34, 3.79	0.828
Paraaortic LN metastasis (no vs yes)	1.14	0.50, 2.61	0.758	2.70	0.87, 8.37	0.086

Group A: 1-2 cycles of CT followed by RT and additional 4-5 cycles of CT

Group B: 3 cycles of CT followed by RT and additional 3 cycles of CT

Group C: 4-5 cycles of CT followed by RT and additional 1-2 cycles of CT

OS: overall survival, PFS: progression free survival, HR: Hazard Ratio, CI: Confidence Intervals, BMI: body mass index, LVSI: lymphovascular space invasion, LN: lymph node

Discussion

Advanced stage EC is related to the unfavorable prognosis due to the tendency of disease progression. The rationale of multimodal treatment using CT and RT is to control local and distal relapse. Most publications demonstrated promising survival outcomes and toxicity safety of multimodal therapy. The fundamental concern about the combination of RT and CT is the optimal timing of RT and CT. Patients receiving RT before CT may develop tumor progression

outside the radiation field. Moreover, when CT is initially given, the patient may experience CT toxic effects, and the ability to complete RT may be limited. To balance the benefits of each treatment modality while limiting therapy toxicities, sandwich therapy has been investigated. In the sandwich method, several prospective and retrospective studies revealed the superior PFS (53-80%) and OS (52-91%) compared to those receiving RT followed by CT or CT followed by RT in the setting of advanced staged EC with acceptable toxicity profile[7-9, 13-19]. To date, there is uncertainty regarding the optimal number of CT cycles to administer before and after RT. Treatment in the sandwich method facilitates administration of both planned modalities, with the ability to provide at least some systemic therapy before initiating RT. Generally, three cycles of CT, followed by RT, and then three cycles of CT are frequently used.

In this study, all patients achieved complete surgery, CT, and RT without treatment-related mortality. The three years OS and PFS in all patients were 90.0% and 93.5%, respectively, and we found no statistical significance in the three years OS and PFS when compared among the three groups. Different CT and RT sequences in the sandwich treatment were feasible and accomplished the excellent three years OS and PFS rate in stage III EC patients. However, the three years OS and PFS in group A tended to be better than the other group. It is probably caused by the high percentage of an optimal cytoreductive status (100%) and histology of endometrioid adenocarcinoma (93.3%). As well as there was a lower rate of pelvic (53.5%) and paraaortic (16.7%) LN metastasis.

Differ from the other studies, there were very high OS and PFS rates in all patients. Furthermore, the three years OS was 100%, 86.8%, and 94.7% in groups A, B, and C, respectively. In addition, the 3-year PFS was 100%, 91.88%, and 94.7% in groups A, B, and C, respectively. We demonstrated an outstanding OS and PFS because of complete treatment, including surgery, CT, and RT in all patients with a significant number of optimal cytoreductive surgery[11, 14-19]. Moreover, we limited our selection of patients to only those with stage III disease, and the most common histologic subtype was endometrioid adenocarcinoma (80.9%). No negative prognostic factor was identified in the multivariate analysis for both OS and PFS.

The strengths of this study included only surgically complete staged patients and were well balanced in terms of clinic-pathological distribution and cytoreduction status. The present study had several limitations. First, it was retrospective in nature. Second, we collected only information about treatment-related death. Data of overall treatment-related toxicities, both short and long-term, were omitted. Third, the number of patients in group A and C was relatively small. It may need to be careful when the results are interpreted. Lastly, although most patients had endometrioid histology, patients with non-endometrioid histology were also included in the analyses. Further prospective randomized trials conducted on larger scales with well-defined patient populations and molecular classification analysis are needed to clarify the impact of various sequencing schedules on clinical outcomes.

Conclusion

In conclusion, the sandwich method offered excellent clinical efficacy and no treatment-related mortality in stage III EC. Different sequences of CT and RT in the sandwich method did not impact the three years OS and PFS in stage III EC. The trend of giving 1-2 cycles of CT, followed by RT, and additional 4-5 cycles of CT (group A) seemed to have the highest OS and PFS. However, the number of patients in group A and C was relatively small. It may need to be careful when the results are interpreted.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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