

Postoperative Adjuvant Chemoradiotherapy Versus Chemotherapy Alone for Stage III Endometrial Cancer: A Multicenter Retrospective Study

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Ji Geun Yoo, MD¹ , Jin Hwi Kim, MD, PhD², Chan Joo Kim, MD, PhD², Hae Nam Lee, MD, PhD³, Min Jong Song, MD, PhD⁴, Dong Choon Park, MD, PhD⁵ , Joo Hee Yoon, MD, PhD⁵, Sang Il Kim, MD, PhD⁵, Soo Young Hur, MD, PhD⁶, and Sung Jong Lee, MD, PhD⁶

Abstract

Introduction: We aimed to evaluate the efficacy and toxicity of the combination of 6 cycles of chemotherapy and radiation therapy compared with chemotherapy alone as postoperative adjuvant therapy for patients with stage III endometrial cancer.

Methods: This retrospective cohort study included patients with stage III endometrial cancer who received postoperative chemoradiotherapy or chemotherapy alone at 6 hospitals between January 2009 and December 2019. The progression-free survival (PFS) and overall survival (OS) for each treatment group were analyzed using the Kaplan–Meier method. We also assessed differences in toxicity profiles between the treatment groups.

Results: A total of 133 patients met the inclusion criteria. Of these, 80 patients (60.2%) received adjuvant chemoradiotherapy and 53 (39.8%) received chemotherapy alone. The PFS and OS did not differ significantly between the groups. For patients with stage IIIC endometrioid subtype, the chemoradiotherapy group had significantly longer PFS rate than did the chemotherapy alone group (log-rank test, $P = .019$), although there was no significant difference in the OS (log-rank test, $P = .100$). CRT was identified as a favorable prognostic factor for PFS in multivariate analysis (adjusted HR, .37; 95% CI, .16–.87; $P = .022$). Patients treated with chemoradiotherapy more frequently suffered from grade 4 neutropenia (73.8% vs 52.8%; $P = .018$) and grade 3 or worse thrombocytopenia (36.3% vs 9.4%; $P = .001$) compared with the chemotherapy alone group. There were no differences between the 2 treatment groups in the frequency of toxicity-related treatment discontinuation or dose reduction.

Conclusion: We confirmed that chemoradiotherapy yields longer progression-free survival than does chemotherapy alone for patients with stage IIIC endometrioid endometrial cancer, with an acceptable toxicity profile.

¹Department of Obstetrics and Gynecology, Daejeon St Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, South Korea

²Department of Obstetrics and Gynecology, Uijeongbu St Mary's Hospital, College of Medicine, The Catholic University of Korea, Uijeongbu, South Korea

³Department of Obstetrics and Gynecology, Bucheon St Mary's Hospital, College of Medicine, The Catholic University of Korea, Bucheon, South Korea

⁴Department of Obstetrics and Gynecology, Yeouido St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

⁵Department of Obstetrics and Gynecology, St Vincent's Hospital, College of Medicine, The Catholic University of Korea, Suwon, South Korea

⁶Department of Obstetrics and Gynecology, Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea

Corresponding Author:

Sung Jong Lee, Department of Obstetrics and Gynecology, Seoul St Mary's Hospital, (06591) 222 Banpo-Daero, Seocho-gu, Seoul 06591, South Korea.
Email: orlando@catholic.ac.kr



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Keywords

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Introduction

Endometrial cancer is the second most common gynecologic malignancy worldwide.¹ It has favorable prognosis because it is usually diagnosed at an early stage. However, locally advanced endometrial carcinoma, which accounts for over 20% of cases, has a high risk of both local and systemic recurrence.^{2,3} Stage III endometrial cancer constitutes a very heterogeneous group of patients, with tumor metastasis to the vagina, uterine serosa, adnexa, or lymph nodes.⁴ Therefore, multimodal therapeutic approaches such as radiation, chemotherapy, and combination chemoradiotherapy (CRT) have been used for this disease subtype.⁵⁻⁸

Recently, the Gynecologic Oncology Group (GOG) 258 trial, a large-scale, phase 3, randomized controlled trial comparing the efficacy and toxicity of CRT and chemotherapy, reported that CRT does not confer a survival benefit over chemotherapy alone.² Patients who were randomized to the CRT group received cisplatin on days 1 and 29 together with external beam radiation therapy (EBRT), followed by 4 cycles of carboplatin plus paclitaxel.² However, in real-world clinical practice, most clinicians have been using 6 cycles of chemotherapy for CRT. A reduced number of chemotherapy cycles in the CRT group of the GOG 258 has been proposed as 1 of the reasons why that group did not achieve survival benefits over the group with chemotherapy alone, showing a higher than anticipated frequency of distant recurrence.⁹⁻¹¹

Against this background, we aimed to evaluate the efficacy and toxicity of the combination of 6 cycles of chemotherapy and radiation therapy compared with chemotherapy alone as postoperative adjuvant therapy for patients with stage III endometrial cancer.

Materials and Methods

This retrospective cohort study was approved by the Institutional Review Board of the Catholic University of Korea Catholic Medical Center (Seoul, Korea) on 3 August 2020 (Approval number: XC20RADI0092). Due to the retrospective nature of the study, the requirement for informed consent in this study was waived. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.¹²

Study Population

We identified patients who had been diagnosed with endometrial cancer and received primary surgical treatment at

6 South Korean university hospitals between January 2009 and December 2019. Surgery included total hysterectomy and bilateral salpingo-oophorectomy, with retroperitoneal lymph node dissection or sampling. Patients who had a postoperative diagnosis of stage III endometrial cancer using the criteria of the International Federation of Gynecology and Obstetrics (FIGO) and received postoperative adjuvant CRT or chemotherapy were included. Postoperative adjuvant treatment was planned individually for each patient; the therapy was determined either by their clinician or based on the decision reached at a multidisciplinary tumor board conference. Most patients received carboplatin (area under the concentration-time curve, 5) plus paclitaxel (175 mg/m²) or doxorubicin (60 mg/m²) plus cisplatin (50 mg/m²). Both regimens were administered every 21 days until progression or toxicity-related treatment discontinuation, for up to 6 cycles. Adjuvant EBRT consisted of whole-pelvic radiotherapy, with or without para-aortic fields, with a total dose of 45 - 50 Gy over 25 - 28 fractions, at 180 cGy per fraction. We included patients with endometrioid, serous, and clear cell histologic types. The exclusion criteria were as follows: other histologic types such as mucinous, neuroendocrine, and carcinosarcoma; coexistent advanced ovarian cancer; adjuvant radiation therapy only; and unevaluable follow-up data.

Data Collection

Clinical data were collected by reviewing each patient's electronic medical records. All patient data were anonymized and de-identified. Pathology reports for the primary surgical treatment were reviewed for FIGO stage, histologic types and grades, tumor size, lymphovascular space invasion, and lymph node metastasis. Clinical information such as the date of primary surgery; type of adjuvant therapy; disease recurrence or progression; date and site of recurrence; adverse events during adjuvant treatment; chemotherapy dose modifications or early discontinuation; timing, dose, and location of radiation therapy; and date of last follow-up or death was taken from the hospital records.

Cancer recurrence was determined based on the Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1).¹³ During the follow-up period, the clinical findings and the cancer antigen (CA)-125 level were evaluated every 3 months for the first 2 years, every 6 months for the following 3 years, and then annually. Abdominopelvic computed tomography was performed when clinical evidence of recurrence or elevation of the CA-125 level was observed;

otherwise, computed tomography was performed every 6 months for the first 5 years. Progression-free survival (PFS) was defined as the period from the start of treatment to the date of cancer recurrence, and overall survival (OS) was defined as the period from the start of treatment to the time of death from any cause.

Statistical Analysis

We assessed differences in clinicopathologic characteristics between patients who received adjuvant CRT and those who received chemotherapy alone. We conducted Fisher's exact test and chi-squared test to compare categorical variables, and we used Student's t-test and Mann-Whitney test to compare continuous variables. The PFS and OS were analyzed using the Kaplan–Meier method, and significance was confirmed using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards regression method, and the hazard ratio (HR) and 95% confidence interval (CI) to identify independent predictors of survival. We performed the statistical analyses using R, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 133 patients met the inclusion criteria. Of these, 80 patients (60.2%) received CRT and 53 (39.8%) received adjuvant chemotherapy alone after primary surgical treatment. A flow diagram of the study population is provided in [Supplementary Figure 1](#).

Adjuvant Treatment

In the CRT group, 55 patients (68.8%) were treated with doxorubicin plus cisplatin and 22 (27.5%) with carboplatin plus paclitaxel. Twenty patients received radiotherapy before chemotherapy, 25 received radiotherapy after chemotherapy, and 35 were treated with a “sandwich” method (3 cycles of chemotherapy followed by radiotherapy, then an additional 3 cycles of chemotherapy). In the chemotherapy alone group, 19 (35.8%) and 33 (62.3%) patients received doxorubicin plus cisplatin and carboplatin plus paclitaxel, respectively. The adjuvant treatments included in this study are summarized in [Supplementary Table 1](#).

The clinicopathologic characteristics of each group are presented in [Table 1](#). There was a significantly higher proportion of patients with stage IIIC disease in the CRT group than in the chemotherapy alone group (83.8% vs 58.5%; $P = .001$). In addition, the CRT group also had a higher frequency of lymphovascular space involvement (80.0% vs 56.6%; $P = .004$).

Treatment Outcomes in the Cohort With FIGO Stage III Endometrial Cancer

The median follow-up period was 42.5 months in the CRT group and 36.0 months in the chemotherapy alone group. In the CRT group, 20 patients (25.0%) had recurrence during or after adjuvant treatment and 10 patients (12.5%) died. In the chemotherapy alone group, 16 patients (27.1%) had recurrence and 8 patients (15.0%) died. The PFS did not differ significantly between the groups (log-rank test, $P = .410$), nor did the OS rate (log-rank test, $P = .200$) ([Figure 1](#)). All recurrences occurred within 3 years from the start of treatment, except for a single patient (2.8%) in whom recurrence was noted at 44 months.

Subgroup Analysis

The Kaplan–Meier survival analyses for subgroups are presented in [Figure 2](#). The PFS and OS for patients with FIGO stages IIIA–B and IIIC were similar between the treatment groups. In a subset of patients with stage IIIC endometrioid histology, the CRT group had significantly longer PFS than did the chemotherapy alone group (log-rank test, $P = .019$), while there was no significant difference in the OS (log-rank test, $P = .100$). CRT was identified as a favorable prognostic factor for PFS in multivariate analysis adjusted for age; medical comorbidities; performance status; tumor size, stage, and grade; invasion depth; and treatment discontinuation or dose reduction (adjusted HR, .37; 95% CI, .16–.87; $P = .022$) ([Table 2](#)). The CRT group showed reduced vaginal (1.8% vs 13.0%, $P = .017$) and pelvic or para-aortic lymph node recurrence (7.1% vs 21.7%, $P = .036$) compared with the chemotherapy alone group, but did not show a significant difference in the rate of distant recurrence (19.6% vs 26.1%, $P = .267$) ([Table 3](#)). Survival analysis for patients with stage IIIC non-endometrioid histology did not show a significant difference in PFS (log-rank test, $P = .500$) or OS (log-rank test, $P = .780$) between the treatment groups ([Supplementary Figure 2](#)).

Treatment-Related Toxicity

The adverse events related to adjuvant treatment are summarized in [Table 4](#). The CRT group more frequently suffered grade 4 neutropenia (73.8% vs 52.8%; $P = .018$) and grade 3 or worse thrombocytopenia (36.3% vs 9.4%; $P = .001$) than the chemotherapy alone group. The CRT group had a tendency to have higher rates of gastrointestinal toxicity, genitourinary toxicity, and infection than the chemotherapy alone group, although these did not reach statistical significance. In addition, the rates of toxicity-related treatment discontinuation and dose reduction did not differ significantly between the groups. Overall, 27 patients (20.3%) required dose reduction and 16 (12.0%) eventually discontinued treatment earlier than planned due to toxicity.

Table I. Baseline Characteristics of the Patients in the two Treatment Groups.

Characteristics	CRT (n = 80)	Chemotherapy (n = 53)	P
Age, years	57.0 (39–76)	59.0 (26–83)	.299
BMI, kg/m ²	24.1 (17.8–33.0)	25.2 (12.7–36.0)	.167
WHO performance status score			
0–2	76 (95.0)	47 (88.7)	.196
3–4	4 (5.0)	6 (11.3)	
Medical comorbidities			
Hypertension	29 (36.3)	20 (37.7)	.862
Diabetes	11 (13.8)	8 (15.1)	.828
FIGO stage			
IIIA	11 (13.8)	16 (30.2)	.010
IIIB	2 (2.5)	6 (11.3)	
IIIC1	31 (38.8)	13 (24.5)	
IIIC2	36 (45.0)	18 (34.0)	
Histology and grade			
Endometrioid, grade 1	13 (16.3)	8 (15.1)	.716
Endometrioid, grade 2	37 (46.3)	26 (49.1)	
Endometrioid, grade 3	17 (21.3)	10 (18.9)	
Serous	8 (10.0)	8 (15.1)	
Clear cell	3 (3.8)	0	
Mixed	2 (2.5)	1 (1.9)	
Tumor size, cm (range)	4.3 (.8–11.5)	5.5 (.4–14.0)	.077
Lymphovascular space invasion	64 (80.0)	30 (56.6)	.004
Pelvic lymph node dissection	76 (95.0)	49 (92.5)	.545
Para-aortic lymph node dissection	55 (68.8)	38 (71.7)	.717
Duration of primary treatment, days (range) ^a	195.0 (32–288)	135.0 (42–211)	<.001

All values are expressed as the median (range) or number (%)

Abbreviation: CRT, chemoradiotherapy; BMI, body mass index; WHO, World Health Organization; FIGO, International Federation of Gynecology and Obstetrics.

^aThe time period from the date of surgery to the date of last adjudant.

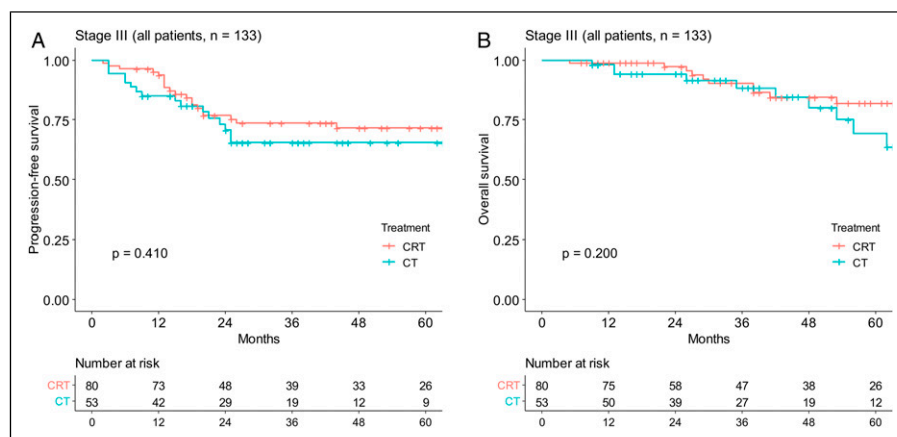


Figure 1. Kaplan-Meier curves illustrating the progression-free survival (A) and overall survival (B) in all patients. CRT, chemoradiotherapy; CT, chemotherapy alone.

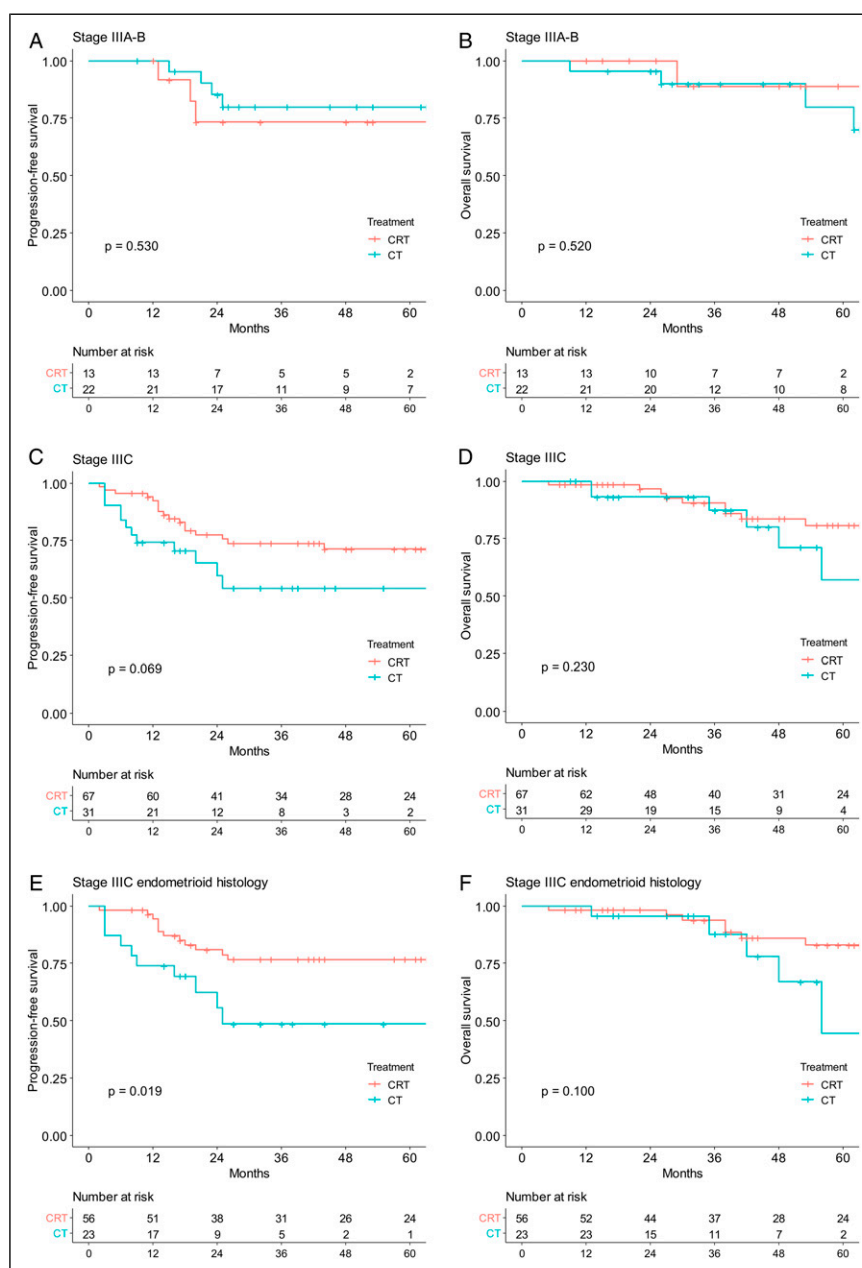


Figure 2. Kaplan-Meier survival curves for progression-free survival (A) and overall survival (B) for patients with stage IIIA and stage IIIB endometrial cancer, progression-free survival (C) and overall survival (D) for patients with stage IIIC endometrial cancer, and progression-free survival (E) and overall survival (F) for patients with stage IIIC endometrioid endometrial cancer. CRT, chemoradiotherapy; CT, chemotherapy alone.

Discussion

This multicenter retrospective study confirmed that CRT was associated with longer PFS than chemotherapy alone for stage IIIC endometrioid endometrial cancer. For patients with locally advanced endometrial cancer, CRT has been proposed for the purpose of preventing both local and distant recurrence.⁵⁻⁸ Various types of CRT regimens have been studied, but no optimal standard regimen has yet been

established.^{14,15} The CRT regimen of GOG 258 was based on the Radiation Therapy Oncology Group (RTOG) protocol 9708 phase 2 study, which demonstrated outstanding locoregional control of disease with 4-year overall and relapse-free survival rates of 77% and 72%, respectively.¹⁶

However, CRT did not improve survival compared with chemotherapy alone in the GOG 258, showing a higher-than-anticipated frequency of distant recurrence for CRT (27% vs 21%; HR, 1.36; 95% CI 1.00-1.86).² This may have been due to

Table 2. Factors Associated With Disease-Free Survival in FIGO Stage IIIC Endometrioid Endometrial.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (≥ 60 vs < 60)	3.04	(.92–10.04)	.067	1.40	(.50–3.92)	.522
Medical comorbidities						
Hypertension (yes vs no)	.84	(.33–2.14)	.711			
Diabetes (yes vs no)	1.07	(.25–4.58)	.927			
WHO Performance status score (3–4 vs 1–2)	4.06	(1.16–14.14)	.028	2.30	(.61–8.62)	.217
Tumor size (≥ 4 cm vs < 4 cm)	2.13	(.83–5.44)	.114			
Invasion depth ($\geq 50\%$ vs $< 50\%$)	2.54	(.75–8.57)	.134			
Stage (IIIC2 vs IIIC1)	1.10	(.48–2.54)	.822			
Grade						
2–3 vs 1	1.15	(.39–3.41)	.797			
3 vs 1–2	.93	(.36–2.38)	.880			
Open surgery vs MIS	2.07	(.87–4.94)	.102			
CRT vs chemotherapy alone	.38	(.16–.88)	.025	.37	(.16–.87)	.022
Dose reduction or discontinuation (yes vs no)	2.19	(.93–5.14)	.072	2.25	(.96–5.31)	.063

Covariates with $P < .1$ on univariate analysis were included in multivariate model.

Abbreviation: FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; MIS, minimally invasive surgery; CRT, chemoradiotherapy.

Table 3. Sites of Initial Recurrence.

Site of recurrence	All patients			Stage IIIC endometrioid histology		
	CRT (n = 80)	CT (n = 53)	P	CRT (n = 56)	CT (n = 23)	P
No recurrence	60 (75.0%)	37 (69.8%)	.408	44 (78.6%)	13 (56.5%)	.019
Local	3 (3.8%)	5 (9.4%)	.155	1 (1.8%)	3 (13.0%)	.017
Vagina	2 (2.5%)	4 (7.5%)	.144	1 (1.8%)	3 (13.0%)	.017
Pelvic soft tissue	1 (1.3%)	1 (1.9%)	.756	0		
Regional lymph nodes	9 (11.3%)	8 (15.1%)	.471	4 (7.1%)	5 (21.7%)	.036
Pelvic	5 (6.3%)	6 (11.3%)	.286	2 (3.6%)	4 (17.4%)	.023
Para-aortic	7 (8.8%)	5 (9.4%)	.822	3 (5.4%)	3 (13.0%)	.156
Distant	18 (22.5%)	11 (20.8%)	.973	11 (19.6%)	6 (26.1%)	.267
Lymph nodes	6 (7.5%)	4 (7.5%)	.856	3 (5.4%)	3 (13.0%)	.106
Abdominal cavity	11 (13.8%)	7 (13.2%)	.942	7 (12.5%)	3 (13.0%)	.687
Hematogenous	8 (10.0%)	3 (5.7%)	.470	4 (7.1%)	1 (4.3%)	.863
Incisional site	2 (2.5%)	0	.272	1 (1.8%)	0	.548

a reduced number of chemotherapy cycles, diminished rate of completion of the intended 4 courses of chemotherapy due to the preceding radiation therapy, or a delay in chemotherapy because of preceding radiation therapy.^{2,9–11} On the other hand, the completion of 6 cycles of chemotherapy was observed more frequently in the CRT regimen with chemotherapy followed by radiation,^{17,18} or the sandwich method in which radiotherapy is provided between 2 short courses of chemotherapy.^{19–22}

In our study, CRT showed longer PFS than chemotherapy alone in patients with stage IIIC endometrioid endometrial cancer. Although the mechanism behind this is not yet fully understood, endometrioid adenocarcinoma is radiosensitive due to its specific molecular characteristics. First, phosphatase

and tensin homolog (PTEN), a tumor suppressor gene that plays a vital role in the repair of DNA damage, including double-strand breaks and nucleotide excision.²³ Loss of PTEN is frequently observed in endometrioid adenocarcinoma,²⁴ and is associated with a failure to establish an effective response to DNA damage induced by radiation therapy.^{23,25} Second, DNA mismatch repair (MMR) is system responsible for repairing base mismatches. Aberrations of MMR are detected in 20%–40% of endometrioid endometrial carcinomas.²⁶ In 1 study, radiation therapy improved disease-specific survival in patients with MMR-deficient endometrial cancer, indicating that MMR status can be considered a predictive biomarker of sensitivity to radiation therapy.²⁷

Table 4. Adverse Events of Each Treatment Groups.

Adverse events	CRT (n = 80)	Chemotherapy (n = 53)	P
Anemia ($\geq$ grade 3)	17 (21.3)	8 (15.1)	.401
Neutropenia			
$\geq$ grade 3	71 (88.8)	41 (77.4)	.121
$\geq$ grade 4	59 (73.8)	28 (52.8)	.018
Thrombocytopenia			
$\geq$ grade 3	39 (48.8)	14 (26.4)	.012
$\geq$ grade 4	29 (36.3)	5 (9.4)	.001
Gastrointestinal ($\geq$ grade 3)	8 (10.0)	4 (7.5)	.762
Genitourinary (any grade)	12 (15.0)	4 (7.5)	.209
Infection ($\geq$ grade 3)	18 (22.5)	9 (17.0)	.470
Dose reduction/discontinuation	21 (26.3)	17 (32.1)	.467
Treatment discontinuation	11 (13.8)	5 (9.4)	.454
Dose reduction	13 (16.3)	14 (26.4)	.154

All values are expressed as number (%). CRT, chemoradiotherapy. Numbers marked in bold indicate *P* values less than .05, which is considered statistically significant.

For patients with node-positive stage IIIC endometrial cancer, adding EBRT to chemotherapy is thought to have more benefit for controlling microscopic residual disease in the lymphatic channels than chemotherapy alone.^{9,28} In contrast, CRT did not show survival benefit in stage IIIA where the disease extends to the peritoneal cavity, compared to chemotherapy alone.⁹

In the analysis of patients with non-endometrioid adenocarcinoma, CRT did not show survival benefit over chemotherapy alone. Uterine papillary serous carcinoma (UPSC), which accounted for 78.9% of cases in the non-endometrioid adenocarcinoma group in our study, is known to be less radiosensitive than non-UPSC tumors.^{29,30} Genetic changes frequently seen in UPSC, such as p53, p27, Cyclin D1, and Her-2 overexpression, are associated with evasion of radiation-induced apoptosis and/or alterations in cell cycle checkpoint control.²⁹

In the analysis of the toxicity results, CRT showed acceptable dose reduction or treatment discontinuation rates compared with the chemotherapy alone group. Grade 4 neutropenia and grade 3-4 thrombocytopenia were more common in the CRT group, but they were reversible and manageable with conservative treatment such as granulocyte colony-stimulating factor support and platelet transfusion.

Our study had strengths in terms of its multicenter design, and included various sequences of radiation and chemotherapy used in real-world clinical settings. However, our study has several limitations. First, due to the retrospective study design, selection bias may have been introduced. Second, the short follow-up period in our study is insufficient to analyze long-term survival data: further study is needed with long-term follow-up. Third, power calculation for estimation of the required sample size was not conducted.

Conclusions

We confirmed that CRT yields longer PFS than does chemotherapy alone for patients with stage IIIC endometrioid adenocarcinoma, with an acceptable toxicity profile. Future work should focus on identifying the most effective and safe CRT regimen, and validating it in a randomized controlled trial.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

The study was conducted in accordance with Declaration of Helsinki, and the protocol was approved by the Institutional Review Board of the Catholic University of Korea Catholic Medical Center (XC20RADI0092).

Consent to Participate

Due to the retrospective nature of the study, the requirement for informed consent in this study was waived.

ORCID iDs

Ji Geun Yoo  <https://orcid.org/0000-0001-5359-8729>

Dong Choon Park  <https://orcid.org/0000-0001-9485-4987>

Supplemental Material

Supplementary material for this article is available on the online.

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