

ORIGINAL RESEARCH

Comparing survivals according to different adjuvant treatments in high-risk endometrial carcinoma: an international and propensity score matching study

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Abstract

Background: This study aimed to compare the effectiveness of different adjuvant therapies on oncological outcomes in high-risk endometrial cancer. **Methods:** A retrospective cohort study analysed data from two tertiary medical centres in Korea and Taiwan (01 January 2000 to 31 December 2020). Patients with high-risk endometrial cancer who underwent debulking surgery were eligible for inclusion. Cohort 1 included patients with early stage-to-stage IIIC1 disease who achieved complete surgical resection, while Cohort 2 comprised those with residual disease post-surgery or stage IIIC2/IV disease. Propensity score matching was performed. **Results:** Following propensity score matching, 110 and 70 patients were analysed in Cohorts 1 and 2, respectively. In cohort 1, progression-free survival (PFS) and overall survival (OS) did not differ significantly between patients treated with adjuvant radiotherapy alone and those receiving combined chemotherapy and radiotherapy (PFS hazard ratio (HR) 0.691, 95% confidence interval (CI) 0.360–1.324, $p = 0.265$; OS HR 0.953, 95% CI 0.375–2.423, $p = 0.920$). Subgroup analysis suggested a potential improvement in PFS with combination therapy among stage III patients (HR 0.362, 95% CI 0.129–1.015, $p = 0.0534$), although no OS differences were observed (HR 0.305, 95% CI 0.063–1.471, $p = 0.139$). In cohort 2, no significant differences were observed in PFS or OS between treatment groups (PFS adjusted HR (aHR) 1.435, 95% CI 0.725–2.841, $p = 0.3$; OS aHR 1.194, 95% CI 0.505–2.824, $p = 0.687$). **Conclusions:** Combined chemotherapy and radiotherapy may improve progression-free outcomes in patients with stage III high-risk endometrial cancer without residual disease post-surgery, compared to radiotherapy alone.

Keywords

High-risk endometrial cancer; Adjuvant treatment; Propensity score matching

1. Introduction

The incidence of endometrial cancer is rising, making it the most common gynaecological malignancy [1, 2]. Unlike many cancers, both its incidence and mortality continue to increase [3–5]. According to the American Cancer Society, endometrial cancer-related mortality has risen annually since the mid-2000s [6], primarily owing to high-risk cases with a greater likelihood of recurrence [7]. While definitions of high-risk endometrial cancer vary slightly among researchers and academic societies, they generally include advanced stages of disease (International Federation of Gynecology and Obstetrics (FIGO) stage III or IV) with any histologic subtypes or aggressive histology (endometrioid grade 3 or non-endometrioid histology) at any stages [8]. Given the poor prognosis associated with these cases, effective treatment strategies are urgently needed, prompting extensive clinical trials.

Clinical trials for high-risk endometrial cancer have been

designed based on curability. In high-risk endometrial cancer, patients with a relatively high possibility of cure, classified as 2009 FIGO stage IIIC1 or lower, who have undergone complete surgical resection, have been the focus of research investigating the addition of chemotherapy to standard adjuvant radiation in a combined therapy approach, with Project for the Treatment of Endometrial Cancer (PORTEC) 3 as an example [9]. In contrast, for patients with FIGO stage IIIC2 or higher disease, or those with residual disease following suboptimal surgery, research has evaluated the addition of radiotherapy to standard chemotherapy, as exemplified by the Gynecologic Oncology Group (GOG) 258 trial [10]. While these trials inform clinical practice, further research is needed to assess whether real-world outcomes align with clinical trial results [11]. Additionally, evaluating the efficacy of regimens not included in clinical trials, such as the sandwich regimen, remains essential [12, 13].

This international multi-institutional study stratifies high-

risk endometrial cancer patients into curable and incurable cohorts. Using propensity score matching, it aims to compare various adjuvant regimens and assess real-world differences in survival outcomes.

2. Materials and methods

This retrospective cohort study utilized data collected between 01 January 2000 and 31 December 2020 from two tertiary academic centres in Korea and Taiwan. Patients with high-risk endometrial cancer who underwent complete staging or debulking surgery were included. Surgical procedures comprised total hysterectomy with bilateral salpingo-oophorectomy, pelvic lymph node dissection, and/or para-aortic lymph node dissection, according to the extent of the disease. Suspicious lesions were biopsied, and omentectomy was performed in cases with aggressive histology. This study adhered to ethical principles and was approved by the Institutional Review Boards (IRB) of Samsung Medical Center (approval number SMC2021-06-070) and National Taiwan University Hospital (approval number 202108087RINC). Informed consent was not required because the study utilized pre-existing data that had been collected for clinical purposes. The data were anonymized to protect participants' confidentiality.

Patients were divided into two cohorts based on surgical stage and residual disease status (no gross residual disease *vs.* any residual disease). The level of residual disease was determined based on surgical records and/or postoperative imaging (*e.g.*, abdominopelvic Computed Tomography (CT) and pelvic Magnetic Resonance Imaging (MRI)). Cohort 1 comprised patients with high-risk endometrial cancer who have undergone complete resection, covering early stages up to stage IIIC1, where it is deemed amenable to cure. Patients who had residual disease after surgery or stage IIIC2 or IV disease were categorized into cohort 2, where curative treatment was not possible. This cohort included patients with stage IIIC2 endometrial cancer and those who underwent suboptimal tumour resection during surgery at stages IIIA, IIIB or IIIC1. Patients with gross residual disease detected on postoperative imaging were assigned to Cohort 2.

Progression-free survival (PFS) and overall survival (OS) were compared across different adjuvant treatments within each cohort. In Cohort 1, analyses were conducted to determine whether the addition of chemotherapy to adjuvant radiotherapy affected survival rates compared with adjuvant radiotherapy alone. Radiotherapy involves pelvic external-beam radiotherapy (EBRT), vaginal brachytherapy, or a combination of both. EBRT is typically delivered to the whole pelvis at a dose of 45–50.4 Gy in 25–28 fractions, while vaginal brachytherapy is administered as high-dose-rate intracavitary radiation (HDR ICR) at 30 Gy in six fractions or 21 Gy in three fractions. Combinations of chemotherapy and radiotherapy comprise various types: concomitant chemoradiotherapy, including the PORTEC 3 regimen; sequential therapy (radiotherapy followed by chemotherapy); and a sandwich regimen (1–3 cycles of chemotherapy prior to radiotherapy followed by chemotherapy). Patients who received chemotherapy alone as adjuvant therapy or received no adjuvant treatment were excluded. Several chemotherapy regimens are used,

with the most frequently used regimens being paclitaxel (175 mg/m²) with carboplatin (AUC5) every 3 weeks, paclitaxel (175 mg/m²) with cisplatin (75 mg/m²) every 3 weeks, doxorubicin (60 mg/m²) with cisplatin (50 mg/m²) every 4 weeks, and etoposide (100 mg/m²) with cisplatin (20 mg/m²) every 3 weeks. Dose reduction was implemented for patients who experience grade 3 or 4 adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE). The dose was reduced by 25% for the subsequent cycle if severe toxicities, including neutropenia or thrombocytopenia, were observed.

In cohort 2, comparisons were made between patients who received combined chemotherapy and radiotherapy and those who received chemotherapy alone. Patients who underwent radiotherapy alone or did not receive adjuvant treatment were excluded.

For continuous variables, means and standard deviations are presented if the variables satisfied the normality assumption, and an independent two-sample *t*-test was used to compare the means of each treatment modality. If the variables did not satisfy the normality assumption, medians and interquartile ranges (Q1 and Q3) were calculated, and the Wilcoxon rank-sum test was used for comparison. Categorical variables are presented as numbers and frequencies, and chi-square tests or Fisher's exact tests were used for baseline characteristic comparisons.

The propensity score was calculated by fitting a logistic regression model, including age, postoperative pathological stage, grade, lymphovascular space invasion (LVSI), and treatment start date. Propensity score matching was performed using nearest-neighbour greedy matching with a calliper width of 0.25.

Kaplan-Meier curves were used to graphically represent OS and PFS, and the log-rank test was used to determine differences in survival curves between the groups. A Cox proportional hazards model was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the risk of survival according to treatment modality. Adjusted HRs (aHRs) were used in cohort 2 after adjusting for American Society of Anesthesiologist (ASA) classification and surgical approach. Subgroup analysis divided the subgroups by postoperative stage using log-rank tests and Cox regression to check for differences in survival curves and HRs between the groups.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and Kaplan-Meier plots were visualised using R (version 3.6.4; The R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a *p*-value < 0.05.

3. Results

Of the 626 patients initially identified in this study, 501 belonged to cohort 1, and 485 showed no residual disease following surgery. The exclusion criteria included 118 patients who received chemotherapy only, 96 who declined adjuvant treatment, and 4 with incomplete treatment data, leaving 267 eligible patients. Of these patients, 170 received radiotherapy and 97 underwent both chemotherapy and radiotherapy (Fig. 1).

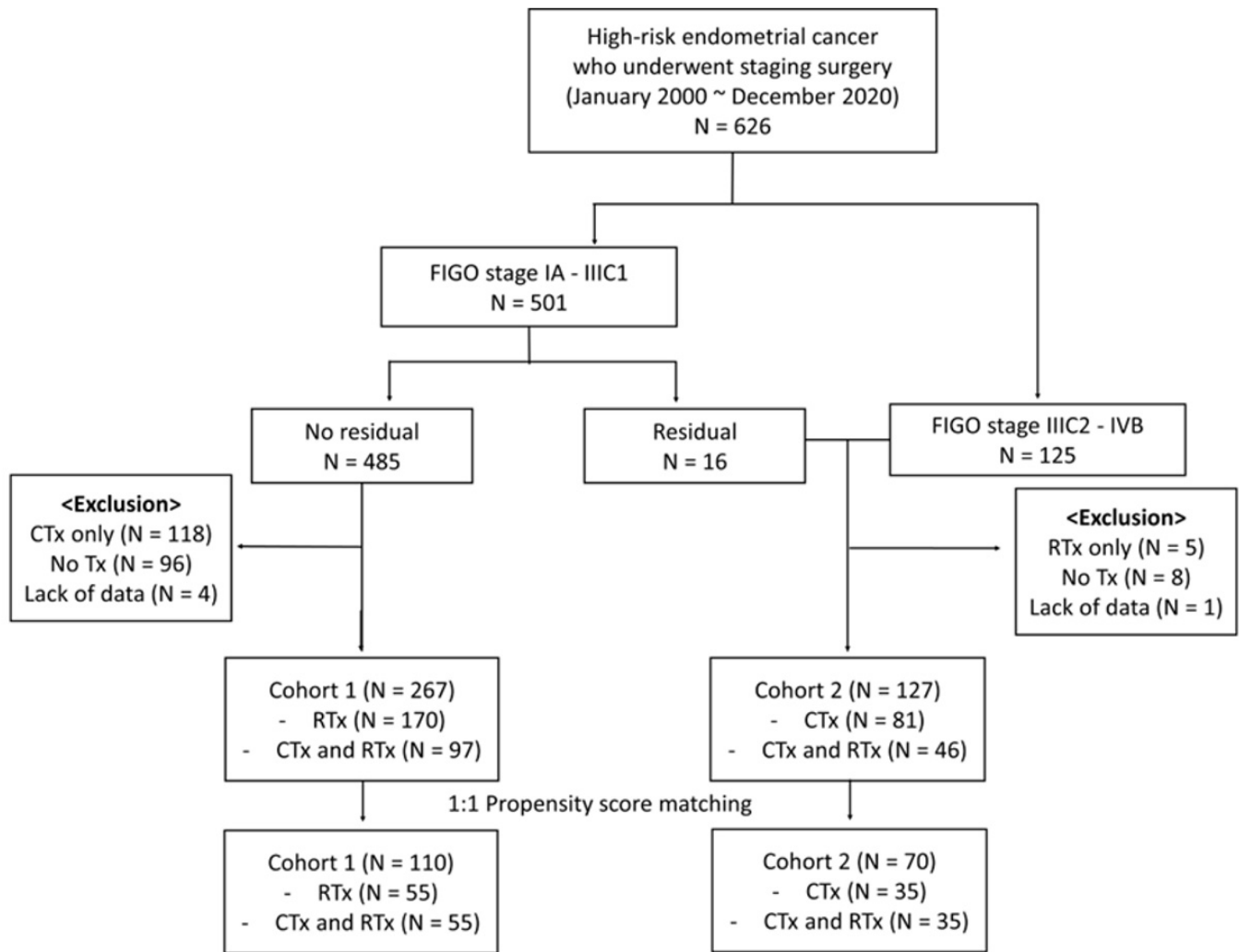


FIGURE 1. Study population. FIGO: International Federation of Gynecology and Obstetrics staging; CTx: Chemotherapy; RTx: Radiotherapy; Tx: Treatment.

Propensity matching was conducted based on age, pathological staging, grade, treatment start date and LVSI, resulting in 110 patients who were finally included in Cohort 1. There were no significant differences in baseline characteristics between the groups after matching (Table 1). The median treatment duration was 50 days (8, 72) in the radiotherapy group and 90 days (35, 197) in the radiotherapy and chemotherapy groups. Median follow-up time was 3.96 years (1.95, 6.17) and 2.34 years (1.54, 4.78) in each group.

Cohort 2 included 141 patients classified as stage IIIC2, IVA and IVB and classified as stage IIIA, IIIB and IIIC1 with residual disease post-surgery. After excluding 5 patients who received radiotherapy alone, 8 who declined adjuvant therapy, and 1 with incomplete data, 127 patients were analysed. Among them, 81 received chemotherapy as adjuvant therapy and 46 received both chemotherapy and radiotherapy (Fig. 1).

Propensity matching based on age, postoperative stage, grade, LVSI and treatment start date resulted in 70 patients being finally analysed in Cohort 2; however, differences in ASA and surgical approach persisted after matching (Table 2). The median treatment duration was 115 days (28, 280) in the combination radiotherapy and chemotherapy group and 112

days (63, 172) in the chemotherapy group. Median follow-up time was 2.56 years (1.74, 4.87) and 2.12 years (1.21, 5.30) in each group.

In cohort 1, Kaplan-Meier analysis showed no significant differences in PFS between the radiotherapy and combined chemotherapy-radiotherapy groups (HR 0.691, 95% CI 0.360–1.324, $p = 0.265$). Similarly, no differences were observed in OS (HR 0.953, 95% CI 0.375–2.423, $p = 0.920$) (Fig. 2).

Subgroup analysis of patients with stage III endometrial cancer in cohort 1 suggested improved PFS with combined therapy (HR 0.362, 95% CI 0.129–1.015, $p = 0.0534$), although the difference was not statistically significant. OS showed no improvement (HR 0.305, 95% CI 0.063–1.471, $p = 0.139$) (Fig. 3). In patients with stage I and II endometrial cancer, there were no significant differences in PFS (HR 1.246, 95% CI 0.518–2.997, $p = 0.624$) or OS (HR 2.604, 95% CI 0.647–10.484, $p = 0.178$) (Fig. 4). Further subgroup analyses according to age, ASA classification, surgical approach, grade and LVSI revealed no significant differences in survival (Fig. 5).

TABLE 1. Baseline characteristics of cohort 1 before and after propensity score matching.

	Before matching (N = 267)				After matching (N = 110)			
	RTx (N = 170)	RTx + CTx (N = 97)	p-value	SD**	RTx (N = 55)	RTx + CTx (N = 55)	p-value	SD**
Age (yr)								
<65	125 (73.53)	79 (81.44)	0.143	-0.190	41 (74.55)	45 (81.82)	0.356	-0.177
≥65	45 (26.47)	18 (18.56)		0.190	14 (25.45)	10 (18.18)		0.177
Age	59.32 ± 9.91	56.43 ± 8.42	0.017	0.314	58.51 ± 11.06	56.78 ± 7.55	0.341	0.182
BMI	24.13 ± 3.50	24.28 ± 3.95	0.751	-0.040	23.88 ± 3.71	24.78 ± 3.99	0.226	-0.232
Pre-op Tumour size	3.50 (2.30, 4.80)	4.65 (2.60, 6.45)	0.001	-0.477	3.90 (2.60, 5.50)	4.00 (2.40, 6.25)	0.764	-0.113
Pre-op CA-125	10.60 (7.10, 18.70)	18.40 (10.10, 50.00)	<0.001	-0.371	11.60 (8.10, 21.60)	15.20 (8.60, 36.50)	0.204	-0.186
ASA								
1	45 (26.47)	32 (32.99)	0.374	-0.143	17 (30.91)	15 (27.27)	0.906	0.080
2	116 (68.24)	58 (59.79)		0.177	35 (63.64)	36 (65.45)		-0.038
3	9 (5.29)	7 (7.22)		-0.079	3 (5.45)	4 (7.27)		-0.075
Surgical approach								
MIS	75 (44.12)	38 (39.18)	0.432	0.100	20 (36.36)	28 (50.91)	0.124	-0.297
Open	95 (55.88)	59 (60.82)		-0.100	35 (63.64)	27 (49.09)		0.297
Pathologic stage								
Stage I, II	144 (84.71)	29 (29.90)	<0.001	1.330	29 (52.73)	29 (52.73)	>0.999	0.000
Stage III	26 (15.29)	68 (70.10)		-1.330	26 (47.27)	26 (47.27)		0.000
Grade								
Low	9 (5.29)	17 (17.53)	0.001	-0.392	9 (16.36)	12 (21.82)	0.467	-0.139
High	161 (94.71)	80 (82.47)		0.392	46 (83.64)	43 (78.18)		0.139
LVSI								
No	97 (57.06)	37 (38.14)	0.003	0.386	22 (40.00)	23 (41.82)	0.846	-0.037
Yes	73 (42.94)	60 (61.86)		-0.386				0.037
Follow-up time (recur)	2.99 (1.59, 4.86)	2.68 (1.17, 4.94)	0.354		2.47 (1.06, 4.74)	2.09 (1.02, 4.72)	0.700	
Follow-up time (death)	3.93 (1.99, 5.84)	2.94 (1.85, 5.25)	0.090		3.96 (1.95, 6.17)	2.34 (1.54, 4.78)	0.101	

RTx: radiotherapy; CTx: chemotherapy; BMI: body mass index; ASA: American Society of Anesthesiologists classification; MIS: minimally invasive surgery; LVSI: lymphovascular space invasion; CA-125: Cancer Antigen-125; SD: Standard Deviation.

Data are median (IQR) or n (%).

**Standardized Difference.

TABLE 2. Baseline characteristics of cohort 2 before and after propensity score matching.

	Before matching (N = 127)				After matching (N = 70)			
	CTx (N = 81)	RTx + CTx (N = 46)	p-value	SD**	CTx (N = 35)	RTx + CTx (N = 35)	p-value	SD**
Age (yr)								
<65	62 (76.54)	38 (82.61)	0.422	−0.151	28 (80.00)	28 (80.00)	>0.999	0.000
≥65	19 (23.46)	8 (17.39)		0.151	7 (20.00)	7 (20.00)		0.000
Age	57.80 ± 9.32	56.28 ± 9.80	0.387	0.159	55.57 ± 8.78	57.11 ± 10.26	0.501	−0.162
BMI	23.74 ± 4.07	24.94 ± 4.29	0.119	−0.288	23.92 ± 4.68	25.04 ± 4.27	0.297	−0.251
Pre-op Tumour size	5.20 (4.00, 8.10)	5.20 (3.00, 7.50)	0.627	0.006	5.35 (3.90, 7.20)	5.30 (3.00, 8.20)	0.810	−0.055
Pre-op CA-125	46.20 (13.80, 140.70)	38.10 (11.10, 114.00)	0.286	0.265	50.90 (19.20, 103.50)	42.60 (10.30, 136.20)	0.697	0.201
ASA								
1	11 (13.58)	13 (28.26)	0.050	−0.367	4 (11.43)	11 (31.43)	0.023	−0.503
2	62 (76.54)	32 (69.57)		0.158	24 (68.57)	23 (65.71)		0.061
3	8 (9.88)	1 (2.17)		0.328	7 (20.00)	1 (2.86)		0.560
Surgical approach								
MIS	7 (8.64)	16 (34.78)	<0.001	−0.669	2 (5.71)	11 (31.43)	0.006	−0.701
Open	74 (91.36)	30 (65.22)		0.669	33 (94.29)	24 (68.57)		0.701
Pathologic stage								
Stage I, II	0 (0.00)	0 (0.00)	>0.999	0.000	0 (0.00)	0 (0.00)	>0.999	0.000
Stage III, IV	81 (100.00)	46 (100.00)		0.000	35 (100.00)	35 (100.00)		0.000
Grade								
Low	6 (7.41)	15 (32.61)	<0.001	−0.664	5 (14.29)	5 (14.29)	1.000	0.000
High	75 (92.59)	31 (67.39)		0.664	30 (85.71)	30 (85.71)		0.000
LVSI								
No	10 (12.35)	11 (23.91)	0.092	−0.304	8 (22.86)	8 (22.86)	1.000	0.000
Yes	71 (87.65)	35 (76.09)		0.304	27 (77.14)	27 (77.14)		0.000
Follow-up time (recur)	1.30 (0.42, 3.07)	1.92 (0.87, 3.89)	0.120		1.73 (0.71, 4.66)	1.47 (0.47, 2.82)	0.716	
Follow-up time (death)	2.18 (0.98, 4.70)	2.40 (1.60, 5.08)	0.371		2.56 (1.74, 4.87)	2.12 (1.21, 5.30)	0.503	

RTx: radiotherapy; CTx: chemotherapy; BMI: body mass index; ASA: American Society of Anesthesiologists classification; MIS: minimally invasive surgery; LVSI: lymphovascular space invasion; CA-125: Cancer Antigen-125; SD: Standard Deviation.

Data are median (IQR) or n (%).

**Standardized Difference.

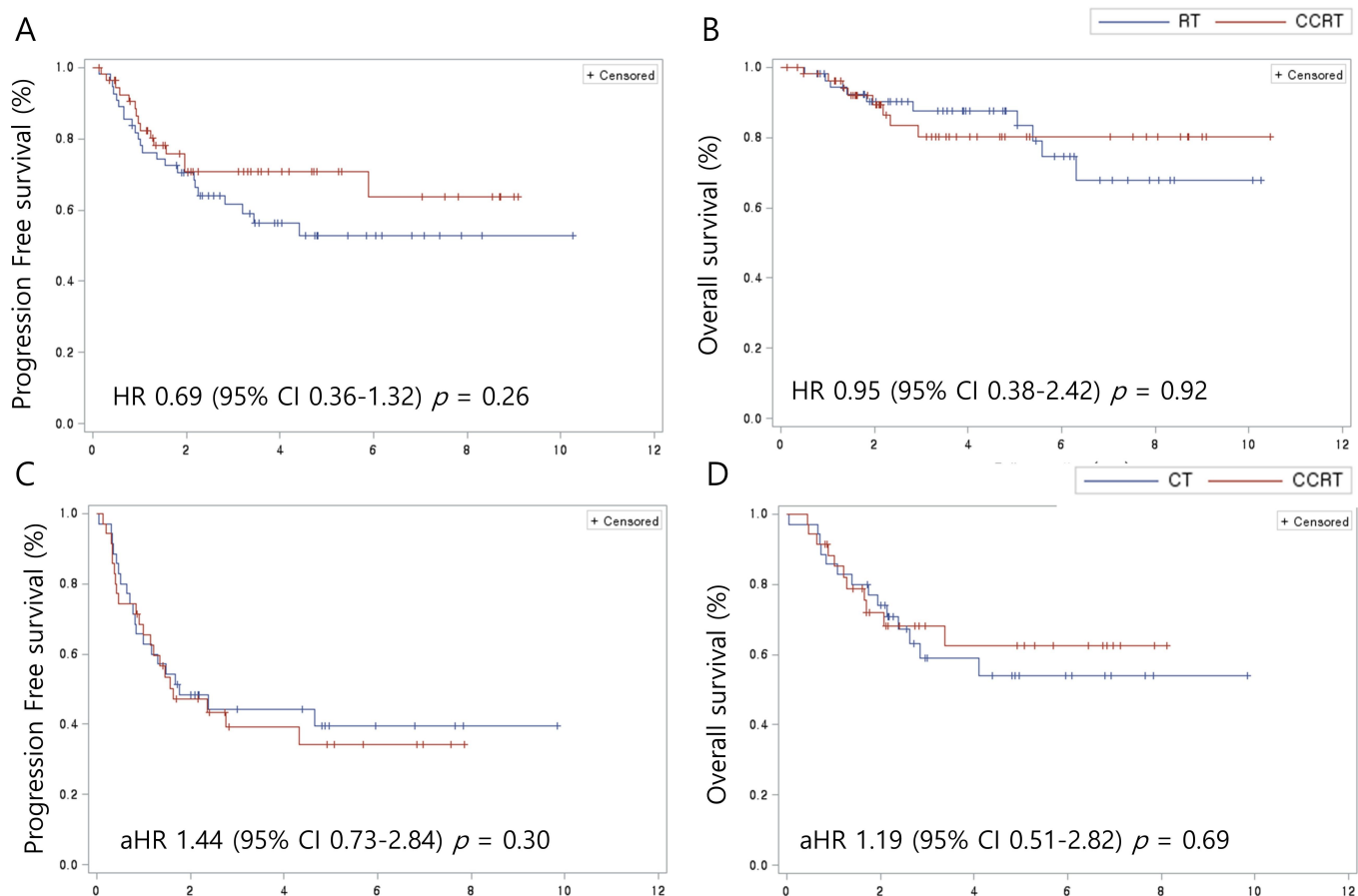


FIGURE 2. Kaplan-Meier survival curves for progression-free survival (PFS) (A) and overall survival (OS) (B) in cohort 1, progression-free survival (C) and overall survival (D) in cohort 2. HR: hazard ratio; CI: confidence interval; aHR: adjusted HR; RT: Radiotherapy; CCRT: Combined Chemotherapy-Radiotherapy; CT: Chemotherapy.

In cohort 1, analysis of treatment regimens revealed that concomitant chemoradiotherapy provided better PFS (HR 0.297, 95% CI 0.105–0.840, $p = 0.0221$) than sequential therapy, although no OS differences were identified (HR 0.501, 95% CI 0.125–2.012, $p = 0.330$) (Fig. 6). Subgroup analysis of stage III patients showed no PFS or OS differences between the treatment regimens (PFS HR 0.884, 95% CI 0.099–7.924, $p = 0.913$; OS HR 1.022, 95% CI 0.027–39.09, $p = 0.991$) (Fig. 7).

In Cohort 2, multivariate analysis revealed no differences in PFS and OS based on each adjuvant treatment (PFS aHR 1.435, 95% CI 0.725–2.841, $p = 0.3$; OS aHR 1.194, 95% CI 0.505–2.824, $p = 0.687$) (Fig. 2).

4. Discussion

This international multi-institutional study compared the survival outcomes among high-risk patients with endometrial cancer treated with different adjuvant therapies using propensity score matching. No statistically significant differences in PFS or OS were observed between the treatment modalities in cohorts 1 and 2. However, the subgroup of patients (FIGO stage III) in Cohort 1 showed a trend towards better survival with the combination of chemotherapy and radiation therapy than with radiation therapy alone. These findings are consistent with those of previous studies [9, 10].

The PORTEC 3 trial examined the efficacy of chemoradiotherapy versus radiotherapy alone in high-risk endometrial cancer. The patients included were FIGO stage I with grade 3 endometrioid histology and deep myometrial invasion or lymphovascular space invasion, stage II or III endometrioid histology, and stages I to III with serous or clear cell histology. While no significant difference in the 5-year OS was reported, chemoradiotherapy improved the 5-year failure-free survival compared to radiotherapy alone. Subgroup analysis demonstrated significantly better outcomes in patients with stage III disease who received chemoradiotherapy [9]. Updated results with a median follow-up of 72.6 months revealed improved OS and failure-free survival in the chemoradiotherapy group compared to the radiotherapy alone group [14]. Similarly, our study observed a trend toward better PFS in patients with stage III disease treated with combination therapy, reflecting comparable patterns.

In the GOG 258 trial, chemotherapy alone was compared with concurrent chemoradiotherapy in patients with surgical stage III or IVA endometrial cancer, or stage I and II clear cell or serous carcinoma. This study found no significant differences in OS or relapse-free survival between the two treatment groups [10]. Consistent with these findings, our analysis did not show significant differences in OS or PFS between combination therapy and chemotherapy alone in cohort 2, suggesting that combined treatment may not provide

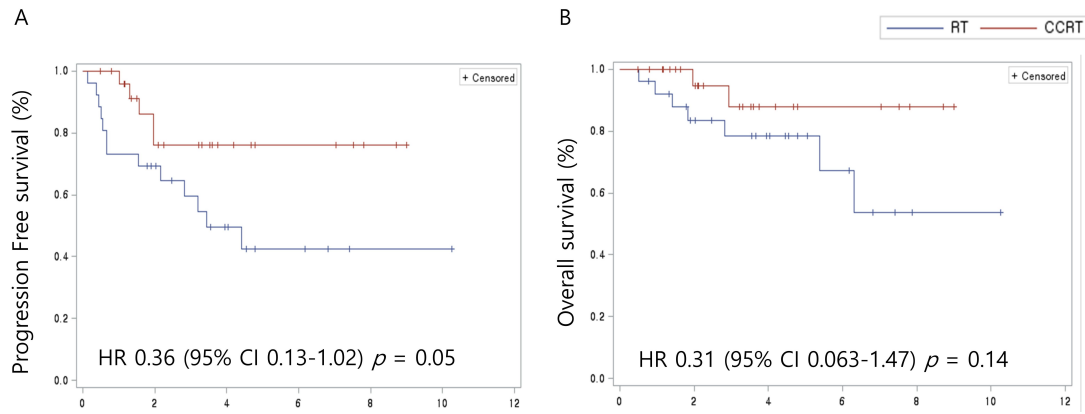


FIGURE 3. Kaplan-Meier survival curves for PFS (A) and OS (B) of FIGO stage III endometrial cancer patients in cohort 1. HR: hazard ratio; CI: confidence interval; RT: Radiotherapy; CCRT: Combined Chemotherapy-Radiotherapy.

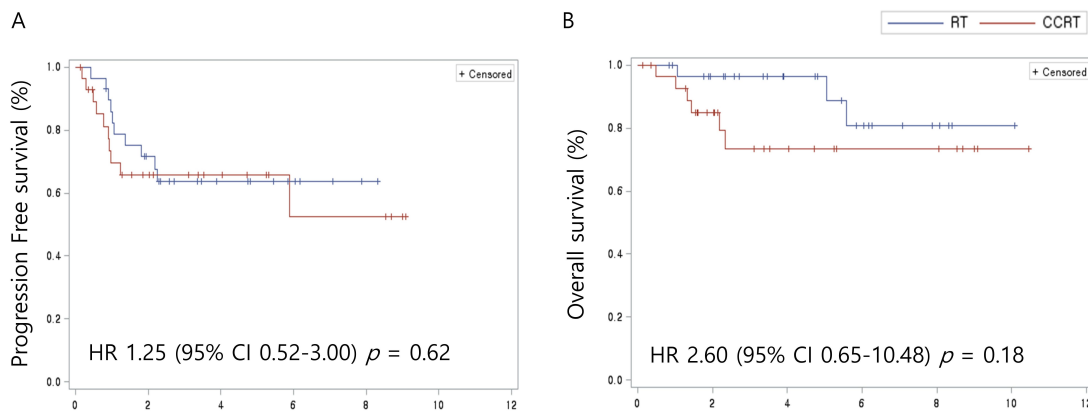


FIGURE 4. Kaplan-Meier survival curves for PFS (A) and OS (B) of FIGO stage I, II endometrial cancer patients in cohort 1. HR: hazard ratio; CI: confidence interval; RT: Radiotherapy; CCRT: Combined Chemotherapy-Radiotherapy.

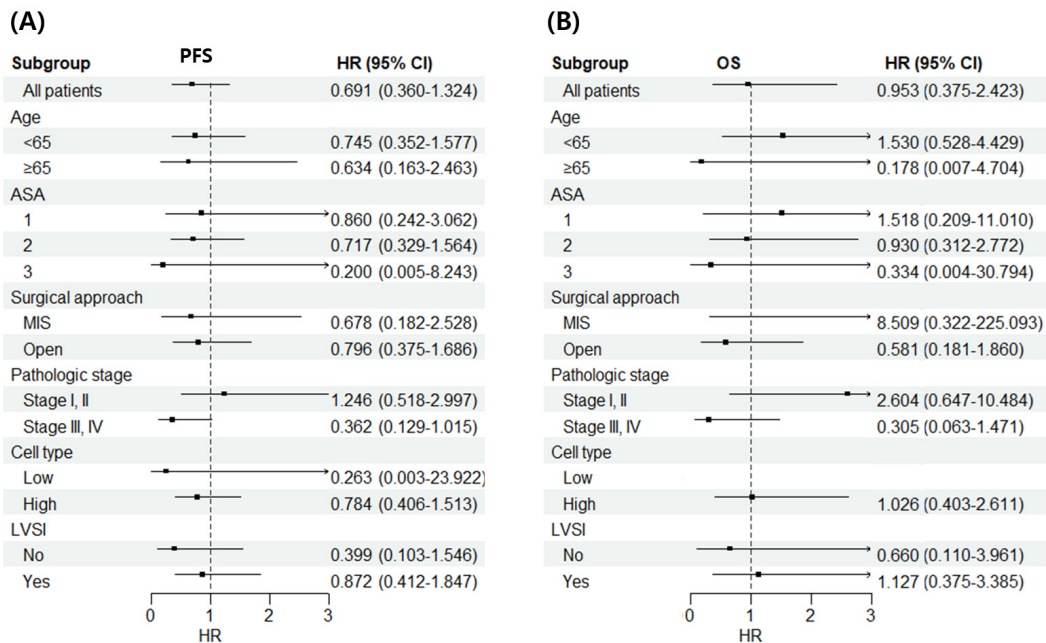


FIGURE 5. Forest plot of hazard ratio (HR) for (A) progression and (B) death in subgroup analysis of cohort 1. ASA: American Society of Anesthesiologists classification; MIS: minimally invasive surgery; LVSI: lymphovascular space invasion; CI: confidence interval; PFS: progression-free survival; OS: overall survival.

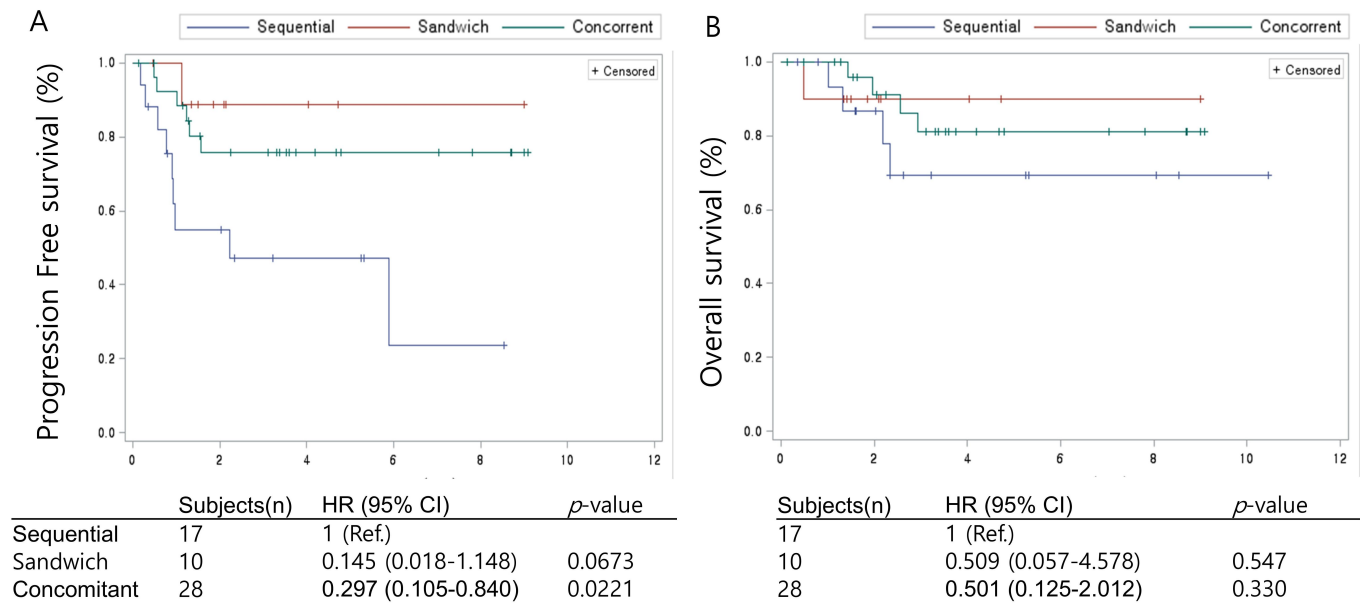


FIGURE 6. Kaplan-Meier survival curves for PFS (A) and OS (B) in each type of adjuvant chemotherapy and radiotherapy in cohort 1. HR: hazard ratio; CI: confidence interval; Ref.: Reference.

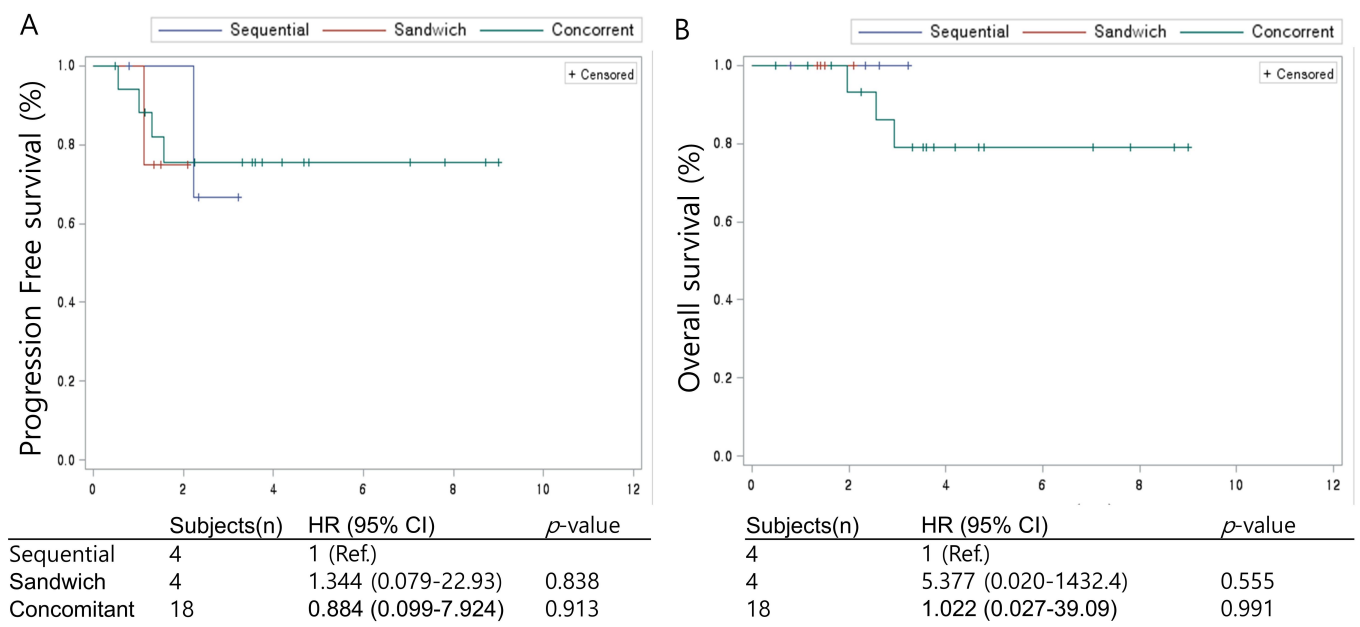


FIGURE 7. Kaplan-Meier survival curves for PFS (A) and OS (B) in each type of adjuvant chemotherapy and radiotherapy in stage III endometrial cancer patients. HR: hazard ratio; CI: confidence interval; Ref.: Reference.

additional benefits in advanced-stage cases.

The “Lunchbox” trial, a randomised phase III study, evaluated cisplatin and irradiation followed by carboplatin and paclitaxel against a sandwich regimen (chemotherapy, radiotherapy, followed by chemotherapy) for advanced endometrial cancer. Despite its limitations, small sample size, and low accrual, no significant differences were found in recurrence-free survival, OS or adverse events between the two approaches [15]. Our findings align with these results, as no differences in OS were observed between the concomitant and sequential treatment regimens in Cohort 1. However, PFS improved with concomitant chemoradiotherapy compared to sequential therapy.

Several studies have explored the use of adjuvant treatments for endometrial cancer. One phase III study compared vaginal cuff brachytherapy with chemotherapy and pelvic radiation therapy in high-intermediate and high-risk early stage patients but found no superiority of vaginal brachytherapy with chemotherapy over pelvic radiotherapy [16]. A systematic review by Galaal *et al.* [17] included trials such as GOG 122, Maggi 2006, and Susumu 2008, demonstrating that adjuvant chemotherapy increased survival by approximately 25% compared to radiotherapy in stage III and IV patients [18, 19]. Mauro *et al.* [20] further showed that sequential chemoradiotherapy improved survival rates compared with single-modality treatments, particularly in stage III patients.

Several studies have evaluated adjuvant treatments in real-world settings. Kang *et al.* [21] conducted a phase II trial to evaluate the efficacy of docetaxel/cisplatin chemotherapy followed by pelvic radiation therapy. The study concluded that adjuvant chemotherapy followed by radiation could benefit patients with high-risk endometrial cancer. Similarly, Ferrero *et al.* [22] suggested that a sandwich schedule for chemotherapy and radiotherapy combination is an effective adjuvant treatment with low toxicity in patients with intermediate- and high-risk endometrial cancer. Sahin *et al.* [23] evaluated the effects of different treatment modalities in patients with high-risk endometrioid endometrial cancer. This study suggests that adding chemotherapy to radiotherapy could improve outcomes in high-risk stage III endometrioid endometrial cancer.

This retrospective cohort study, which utilized data from two tertiary centres across different countries, had certain limitations. The small sample size may have led to underpowered statistical results, potentially explaining the lack of statistical significance in the observed trend toward improved PFS in the chemotherapy plus radiotherapy group among patients with stage III endometrial cancer. In addition, because the collected data were relatively old, this could be a potential limitation of this study. Another limitation is the lack of information regarding the molecular classification of the study population, which can limit the assessment of outcomes based on molecular classification. The study also had limited data on preoperative imaging (*e.g.*, MRI or abdominal CT) and radiomics, which can provide information before treatment [24]. The absence of such information may have acted as an unknown confounding factor. Additionally, limited data on the toxicity and side effects of each treatment have hindered investigations into patients' quality of life and treatment risks. Finally, the relatively long recruitment period and institutional diversity resulted in some variability in chemotherapy regimens and combined chemotherapy and radiotherapy treatment methods, leading to high heterogeneity in adjuvant treatment within the study population. To adjust for high heterogeneity, propensity score matching was performed based on the treatment start date.

Despite these limitations, this study has clinical implications as it compares the outcomes of adjuvant therapies in patients with high-risk endometrial cancer in real-world settings in alignment with various clinical trials. Categorising patients with high-risk endometrial cancer based on the presence or absence of residual disease after surgery enabled the comparison of treatment outcomes according to disease status within patient groups. Finally, confounding factors were minimised by controlling for baseline characteristics between the groups using propensity score matching.

5. Conclusions

This study suggests that the combination of radiotherapy and chemotherapy as an adjuvant treatment in patients with stage III high-risk endometrial cancer with no residual disease after surgery may lead to better outcomes than adjuvant radiotherapy alone.

ABBREVIATIONS

HR, hazard ratio; aHR, adjusted hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival; IRB, Institutional Review Boards; EBRT, external-beam radiotherapy; HDR ICR, high-dose-rate intracavitary radiation; CTCAE, Common Terminology Criteria for Adverse Events; LVSI, lymphovascular space invasion; ASA, American Society of Anesthesiologist; FIGO, International Federation of Gynecology and Obstetrics; PORTEC, Post Operative Radiation Therapy in Endometrial Carcinoma; GOG, Gynecologic Oncology Group; CT, Computed Tomography; MRI, Magnetic Resonance Imaging.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

AUTHOR CONTRIBUTIONS

YLC and YYL—conceptualised the study and designed the methodology. YLL—performed the primary data analysis. JYH—conducted the literature review, assisted with data interpretation, and drafted the manuscript. JC and TSY—provided critical revisions, contributed to the Discussion section, and ensured the accuracy of the final version. Each author made a significant contribution to the research and the preparation of the manuscript. All authors have reviewed and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study adhered to ethical principles and was approved by the Institutional Review Boards (IRB) of Samsung Medical Center (approval number SMC2021-06-070) and National Taiwan University Hospital (approval number 202108087RINC). Because the study utilized pre-existing data that had been collected for clinical purposes, the Ethics Committee waived informed consent for this study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1] eBioMedicine. Endometrial cancer: improving management among increasing incidence rates. *EBioMedicine*. 2024; 103: 105159.
- [2] Yun BS, Park EH, Ha J, Lee J, Lee KH, Lee TS, *et al*. Incidence and survival of gynecologic cancer including cervical, uterine, ovarian, vaginal, vulvar cancer and gestational trophoblastic neoplasia in Korea, 1999–2019: Korea Central Cancer Registry. *Obstetrics & Gynecology Science*. 2023; 66: 545–561.
- [3] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA: A Cancer Journal for Clinicians*. 2023; 73: 17–48.
- [4] Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. *The Lancet*. 2022; 399: 1412–1428.
- [5] Rodriguez VE, Tanjasiri SP, Ro A, Hoyt MA, Bristow RE, LeBrón AMW. Trends in endometrial cancer incidence in the United States by race/ethnicity and age of onset from 2000 to 2019. *American Journal of Epidemiology*. 2025; 194: 103–113.
- [6] Saka AH, Giaquinto AN, McCullough LE, Tossas KY, Star J, Jemal A, *et al*. Cancer statistics for African American and Black people, 2025. *CA: A Cancer Journal for Clinicians*. 2025; 75: 111–140.
- [7] Odagiri T, Watari H, Hosaka M, Mitamura T, Konno Y, Kato T, *et al*. Multivariate survival analysis of the patients with recurrent endometrial cancer. *Journal of Gynecologic Oncology*. 2011; 22: 3–8.
- [8] Perera J, Hoskin P. Adjuvant therapy for high-risk endometrial carcinoma. *Clinical Oncology*. 2021; 33: 560–566.
- [9] de Boer SM, Powell ME, Mileshekin L, Katsaros D, Bessette P, Haie-Meder C, *et al*. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. *The Lancet Oncology*. 2018; 19: 295–309.
- [10] Matei D, Filiaci V, Randall ME, Mutch D, Steinhoff MM, DiSilvestro PA, *et al*. Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer. *The New England Journal of Medicine*. 2019; 380: 2317–2326.
- [11] Lee SS, Weil CR, Boyd LR, DeCesaris C, Gaffney D, Suneja G. Trends in use of radiation therapy, chemotherapy, and combination chemoradiotherapy in advanced uterine cancer before, during, and after GOG 258. *International Journal of Gynecological Cancer*. 2023; 33: 1408–1418.
- [12] Albuquerque K, Chino J, Klopp A, Kamrava M, Beriwal S. Defining the place of adjuvant chemotherapy and radiation for high-risk endometrial cancer from recent randomized clinical trials: some answers, more questions. *International Journal of Radiation Oncology, Biology, Physics*. 2018; 102: 473–477.
- [13] Chinnadurai A, Breadner D, Baloush Z, Lohmann AE, Black M, D’Souza D, *et al*. Adjuvant carboplatin and paclitaxel with “sandwich” method radiotherapy for stage III or IV endometrial cancer: long-term follow-up at a single-institution. *Journal of Gynecologic Oncology*. 2024; 35: e16.
- [14] de Boer SM, Powell ME, Mileshekin L, Katsaros D, Bessette P, Haie-Meder C, *et al*. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and *post-hoc* survival analysis of a randomised phase 3 trial. *The Lancet Oncology*. 2019; 20: 1273–1285.
- [15] Barlin JN, Mahar B, Ata A, Cormier B, Michelin D, Salani R, *et al*. Lunchbox trial: a randomized phase III trial of cisplatin and irradiation followed by carboplatin and paclitaxel versus sandwich therapy of carboplatin and paclitaxel followed by irradiation then carboplatin and paclitaxel for advanced endometrial carcinoma. *Gynecologic Oncology*. 2024; 180: 63–69.
- [16] Randall ME, Filiaci V, McMeekin DS, von Gruenigen V, Huang H, Yashar CM, *et al*. Phase III trial: adjuvant pelvic radiation therapy versus vaginal brachytherapy plus paclitaxel/carboplatin in high-intermediate and high-risk early-stage endometrial cancer. *Journal of Clinical Oncology*. 2019; 37: 1810–1818.
- [17] Galaal K, Al Moundhri M, Bryant A, Lopes AD, Lawrie TA. Adjuvant chemotherapy for advanced endometrial cancer. *Cochrane Database of Systematic Reviews*. 2014; 2014: CD010681.
- [18] Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, *et al*. Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *British Journal of Cancer*. 2006; 95: 266–271.
- [19] Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S, *et al*. Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. *Gynecologic Oncology*. 2008; 108: 226–233.
- [20] Signorelli M, Lissoni AA, De Ponti E, Grassi T, Ponti S, Fruscio R. Adjuvant sequential chemo and radiotherapy improves the oncological outcome in high-risk endometrial cancer. *Journal of Gynecologic Oncology*. 2015; 26: 284–292.
- [21] Kang OJ, Cho YJ, Lim MC, Lee YJ, Seo SS, Kang S, *et al*. Docetaxel/cisplatin chemotherapy followed by pelvic radiation therapy in patients with high-risk endometrial cancer after staging surgery: a phase 2 study. *International Journal of Radiation Oncology, Biology, Physics*. 2025; 121:1229–1236.
- [22] Ferrero A, Fuso L, Cipullo I, Danese R, Rossi A, Gribaudo S, *et al*. The “sandwich” schedule: a well-tolerated adjuvant treatment both in intermediate-high- and high-risk endometrial cancer. *Current Oncology*. 2022; 29: 9224–9234.
- [23] Sahin AB, Ocak B, Abakay CD, Cubukcu E, Deligonul A, Caner B, *et al*. Chemotherapy plus radiotherapy vs. radiotherapy alone in high-risk endometrioid endometrial carcinoma. *European Review for Medical and Pharmacological Sciences*. 2022; 26: 8959–8968.
- [24] Guo W, Wang T, Lv B, Jiang J, Liu Y, Zhao P. Advances in radiomics research for endometrial cancer: a comprehensive review. *Journal of Cancer*. 2023; 14: 3523–3531.

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