Adjuvant Chemotherapy *versus* Radiotherapy in High-risk, Early-stage Endometrioid Endometrial Carcinoma

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[Abstract] Objective: The present study was designed to evaluate the effects of adjuvant chemotherapy (CT) *vs.* radiotherapy (RT, alone or combined with CT) on the prognosis of patients with high-risk, early-stage (stage Ⅰ and stage Ⅱ) endometrioid endometrial carcinoma. **Methods:** This single-center retrospective clinical study was conducted in Union Hospital, Tongji Medical College, Huazhong University of Science and Technology between 2010 and 2019. In the present study, endometrioid endometrial carcinoma patients, who underwent total hysterectomy and bilateral salpingo-oophorectomy followed by postoperative adjuvant CT or RT (alone or combined with CT), and were diagnosed with stage IA grade 2/3 with lymph-vascular space invasion (LVSI), and stage IB with two or more uterine risks, including old age, histological grade 2 or 3, LVSI and stage II, were included. According to the postoperative adjuvant therapy, all eligible patients were divided into two groups: CT group and RT (RT±CT) group. The primary objective was to investigate overall survival (OS) and disease-free survival (DFS) between the CT and RT groups. Grade 3 or worse adverse events were also presented in the present study. **Results:** A total of 145 eligible patients were included. Among these patients, 97 patients underwent adjuvant CT and 48 patients underwent adjuvant RT (RT±CT). The median follow-up was 47.2 months, and the five-year OS rate was 92.7% in the CT group and 88.6 % in the RT group [hazard ratio (HR): 0.81, 95% confidence interval (CI): 0.22–2.99). The 5-year DFS rate for the two groups was 85.7% and 80.2%, respectively (HR: 0.82, 95% CI: 0.33–2.05). The cumulative incidence of local-regional disease recurrence at 60 months of follow-up was 6.2% in the CT group and 6.3% in the RT group (HR=1.11; 95%CI: 0.28–4.35). The cumulative incidence of distant recurrence at 60 months of follow-up was 5.2% in the CT group and 10.4% in the RT group (HR=0.65; 95%CI: 0.19–2.24). Both groups of patients were well-tolerant, and the only grade 3 or worse adverse events were neutropenia and thrombocytopenia. **Conclusion:** There was no difference in efficacy for adjuvant CT or adjuvant RT (RT±CT) in high-risk, early-stage endometrioid endometrial carcinoma. CT exhibited a trend of reducing the distant relapse, although there was no significant difference, when compared with adjuvant RT (RT±CT).

Key words: endometrioid endometrial carcinoma; chemotherapy; radiotherapy

Endometrial carcinoma is one of the most common gynecologic malignancies, and its incidence has continuously increased worldwide over recent years[1–3]. The majority of these patients are diagnosed with early-stage, favorable histology tumors, and have a 5-year survival rate of approximately 90%[4]. The main treatment is hysterectomy with or without pelvic lymph node and para aortic lymph node dissection. However, patients with high risk factors of recurrence and death, such as older age, higher grade, deep myometrial invasion, lymph-vascular space invasion (LVSI), and the involvement of the cervical stroma, require postoperative adjuvant treatment to reduce its recurrence and death[5–7]. Radiotherapy (RT) has traditionally followed surgical resection as the postoperative adjuvant treatment in decades. However, randomized clinical trials had demonstrated that adjuvant RT would definitely reduce the risk of its local recurrence, rather than the distant disease[8, 9], and that this has no benefit in overall survival (OS)[8–14]. In contrast, CT was supposed to be superior in reducing systematic recurrence in advanced endometrial cancer[15, 16]. However, adjuvant chemotherapy (CT) for early-stage endometrial cancer remains controversial[17]. Merely few studies have discussed the effect of postoperative CT in high-risk, early-stage endometrial carcinoma. Kodama *et al* and Aoki *et al* reported that patients who received adjuvant CT had improved

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disease-free survival (DFS) and OS rates, when compared to patients who did not undergo CT, for early-stage endometrial carcinoma[18, 19]. However, can CT be used as an alternative adjuvant therapy to RT in high-risk, early-stage endometrial carcinoma? The present clinical evidence remains insufficient. The present study aims to determine whether adjuvant CT would be advantageous over adjuvant RT (alone or combined with CT), in terms of 5-year DFS and 5-year OS, in patients with high-risk, early-stage endometrioid endometrial carcinoma.

1 MATERIALS AND METHODS

1.1 Patients

Patients who were admitted to Wuhan Union Hospital of Tongji Medical College of Huazhong University of Science from 2010 to 2019 were enrolled for the present study. The inclusion criteria were as follows: (1) patients diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IA grade 2/3 with LVSI, and FIGO stage IB with two or more uterine risks, including old age, histological grade 2 or 3, LVSI[20], and stage Ⅱ endometrial endometrioid carcinoma; (2) patients who underwent surgery and postoperative adjuvant CT or RT; (3) patients who were followed up for more than three months after treatment. Patients without risk factors, patients with advanced stage Ⅲ–Ⅳ, clear cell carcinoma, serous carcinoma and other pathological types of endometrial carcinoma, and patients with other malignancies or serious medical diseases were excluded. Patients who were followed up for less than three months, or patients who did not undergo surgery were also excluded. According to the postoperative adjuvant therapy, all eligible patients were divided into two groups: CT group and RT (RT±CT) group. The clinical data (age, surgical procedure, tumor pathology, postoperative treatment, and grade 3 or worse toxicity events) were extracted by reviewing the electronic patient record and pathology reports. The toxicity was graded using the Common Terminology Criteria for Adverse Events version 5.0[21].

1.2 Surgery and Adjuvant Therapy

RT or CT was not performed before the operation. The primary operation was abdominal or laparoscopic hysterectomy, and bilateral salpingo-oophorectomy, with or without pelvic lymph node and para aortic lymph node resection or sampling. During the operation, ascites cytology examination and comprehensive abdominal cavity examination were performed, and the omentum, intestinal and peritoneal surfaces were carefully cheked.

The CT was initiated within 30 days after surgery, which included 2–6 cycles of carboplatinum (AUC 4–6) and paclitaxel (135–175 mg/m^2) CT, with an interval of three weeks.

The RT was initiated within 30 days after surgery, and the methods of RT included vaginal brachytherapy (VB) and external pelvic radiation (EPR). Furthermore, some patients received adjuvant CT before or after (or before and after) adjuvant RT, which included 2–6 cycles of carboplatin and paclitaxel, with an interval of three weeks. The VB dose was equivalent to 25–30 Gy, with 5 Gy fractions per week, and this was specified at 5 mm from the vaginal vault surface. The EPR therapy was adopted for a total of 45–50 Gy, with 1.8–2.0 Gy fractions, for five days a week. The upper limit of the pelvic field was at L5, the lower limit was at the ischial tuberosity, and the lateral limits fell behind the border of the lateral and common iliac lymph nodes.

1.3 Follow-up

After treatment, the patients were assessed at 3-month intervals within the first two years, 6-monthly intervals within the subsequent three years, and yearly after five years. These patients received regular pelvic and abdominal physical examinations, pelvic ultrasound examinations, blood examinations, pelvic and abdominal image examinations and biopsies, when necessary. The disease relapse was classified as local-regional relapse (vaginal and pelvic) and distant relapse (para-aortic nodes, liver, lungs, etc.). The DFS was calculated as the time interval from surgery to the first clinical or radiologic evidence of recurrence, or death, whichever occurred first. Patients who did not have recurrence during the last follow-up were censored. The OS was calculated as the time interval from surgery to the date of death from any cause or last known follow-up.

1.4 Statistical Methods

In order to analyze the characteristics between the two treatment groups, chi-square test was performed for categorical variables. The Kaplan-Meier method was used to estimate the DFS and OS, and the log-rank test was used to calculate the survival outcomes between different variables for risk factors. HR with 95% CI was used to calculate the relative risks for DFS and OS. $P<0.05$ was considered statistically significant.

2 RESULTS

2.1 Patient Characteristics

A total of 171 patients met the inclusion criteria. During the follow-up period, 26 patients were lost to follow-up, while 145 patients were available for the present study. Among these 145 patients, 97 patients received adjuvant CT and 48 patients received adjuvant RT. The patient characteristics, and surgical and pathological characteristics of patients in the two groups were all well-balanced (table 1).

All patients underwent surgery and postoperative treatment. The ratio of patients who underwent surgery

Table 1 Clinical and pathologic characteristics in high-risk, early-stage endometrial endometrioid carcinoma (*n*=145)

Characteristics	CT (*n*=97)	RT±CT (*n*=48)	*P*
Age (years)			0.022
<60	71 (73.2%)	26 (54.2%)	
≥60	26 (26.8%)	22 (45.8%)	
FIGO 2009 stage			0.076
Stage Ⅰ	76 (79.4%)	31 (64.6%)	
Stage Ⅱ	21 (20.6%)	17 (35.4%)	
Histological grade			0.054
Grade 1	20 (20.6%)	17 (35.4%)	
Grade 2–3	77 (79.4%)	31 (64.6%)	
Myometrial invasion			0.145
<50%	36 (37.1%)	12 (25%)	
≥50%	61 (62.9%)	36 (75%)	
LVSI			0.286
Yes	26 (26.8%)	9 (18.8%)	
No	71 (73.2%)	39 (81.2%)	
Surgical approach			0.631
Laparotomy	6 (6.2%)	4 (8.3%)	
MIS	91 (93.8%)	44 (91.7%)	
Lymphadenectomy			0.736
Pelvic lymphadenectomy	36 (37.1%)	21 (43.7%)	
Pelvic+para-aortic lymphadenectomy	57 (58.8%)	25 (52.1%)	
No lymphadenectomy	4 (4.1%)	2 (4.2%)	
Chemotherapy completed			
≤ 4 cycles	76 (78.4%)		
> 4 cycles	21 (21.6%)		
Radiotherapy completed			
VB±CT		4 (8.4%)	
EPR only		22 (45.8%)	
EPR+CT		22 (45.8%)	

LVSI: lymph-vascular space invasion; MIS: minimally invasive surgery; VB: vaginal brachytherapy; EPR: external pelvic radiation; CT: chemotherapy; RT: radiotherapy

was 93.8% in the CT group and 91.7% in the RT group. Approximately 96% of patients underwent pelvic lymph node resection in both groups. The para-aortic lymph node resection rate for the CT group and RT group was 58.8% and 52.1%, respectively. Among all these patients, merely six patients did not undergo lymphadenectomy (four patients in the CT group and two patients in the RT group, table 1).

Among the 145 eligible patients, 97 patients received adjuvant CT only after surgery, and 48 patients received adjuvant RT (RT±CT). In the adjuvant CT group, 76 patients (78.4%) received ≤4 cycles of carboplatinum and paclitaxel agents, while 21 patients received 5–6 cycles of carboplatinum and paclitaxel agents. In the adjuvant RT group, four (8.4%) patients received VB, 22 (45.8%) patients received EPR, and 22 (45.8%) patients received EPR combined with CT. Among the 22 patients who received EPR combined with CT, eight patients received CT followed by EPR, six patients received EPR followed by CT, and eight patients were treated with CT, followed by interval EPR and further CT (the "sandwich" regimen).

2.2 Recurrence and Overall Survival

The median follow-up was 46.2 months (range: 8–119 months) in the CT group and 50.2 months (range: 8–86 months) in the RT group. In the CT group, there were six (6.2%) deaths, in which five (5.2%) deaths were due to disease progression and one death was due to diabetes. Furthermore, 12 (12.4%) patients developed a recurrent disease, six (6.2%) patients had distant recurrence (three recurrences in the lungs, two recurrences in the bone, and one recurrence in the liver and bone), and six (6.2%) patients had local-regional recurrence. In the RT group, there were four (8.3%) deaths, in which three (6.3%) deaths were due to disease progression and one death was due to cerebral infarction. Furthermore, eight (16.7%) patients developed recurrent disease, five (10.4%) patients had distant recurrence (two recurrences in the lungs, two recurrences in the bone, and one recurrence in the intestines), and three (6.3%) patients had local-regional recurrence (table 2).

The estimated 5-year OS was 92.7% (95% CI: 86.8–98.8) for patients in the CT group *vs.* 88.6% (95% CI: 77.2-99.9) for patients in the RT group (HR: 0.81, 95% CI: 0.22–2.99, *P*=0.75; table 3, fig. 1A). Furthermore, the 5-year DFS was 85.7% (95% CI: 77.3–94.1) in the CT group *vs.* 80.2% (95% CI: 67.7–92.7) in the RT group (HR: 0.82, 95% CI: 0.33–2.05, *P*=0.67; table 3, fig. 1B).

Table 2 Survival and recurrence outcomes for different treatment arm in high-risk, early-stage stage endometrial endometrioid carcinoma (*n*=145)

Characteristics	All (*n*=145)	Chemotherapy (*n*=97)	Radiotherapy±Chemotherapy (*n*=48)	*P*
Death				
All	10 (6.9%)	6 (6.2%)	4 (8.3%)	0.75
Disease-specific	8 (5.5%)	5 (5.2%)	3 (6.3%)	0.92
Recurrence	20 (13.8%)	12 (12.4%)	8 (16.7%)	0.67
Distant	11 (7.6%)	6 (6.2%)	5 (10.4%)	0.47
Local-regional	9 (6.2%)	6 (6.2%)	3 (6.3%)	0.89

Table 3 Univariate analysis for disease-free survival and overall survival in high-risk, early-stage stage endometrial endometrioid carcinoma (*n*=145)

	n	Disease free survival		Overall survival	
		HR (95%CI)	*P*	HR (95%CI)	*P*
Treatment arm					
Radiotherepy±chemotherapy	48	1	0.67	1	0.75
Chemotherapy	97	0.82 (0.33–2.05)		0.81 (0.22–2.99)	
Age					
<60 years	48	1	0.86	1	0.66
≥60 years	97	0.86 (0.34–2.21)		0.75 (0.20–2.80)	
LVSI					
Positive	35	1	0.43	1	0.85
Negative	110	0.69 (0.24–1.95)		1.16 (0.26–5.12)	
Grade					
2–3	108	1	0.04*	1	0.77
1	37	0.166 (0.06–0.46)		0.79 (0.19–3.38)	
FIGO 2009 Stage					
Ⅱ	38	1	0.24	1	0.25
Ⅰ	107	0.58 (0.21–1.63)		0.48 (0.11–2.05)	
Myometrial invasion					
≥50%	97	1	0.52	1	0.39
<50%	48	0.72 (0.28–1.84)		0.52 (0.14–1.94)	
Chemotherapy completed					
>4 cycles	76	1	0.76	1	0.19
≤4 cycles	21	0.82 (0.22–3.02)		3.69 (0.52–24.92)	
Lymphadenectomy					
Pelvic+para-aortic lymphadenectomy	82	1	0.24	1	0.38
Pelvic lymphadenectomy	57	1.73 (0.64–4.66)		1.78 (0.43–7.29)	

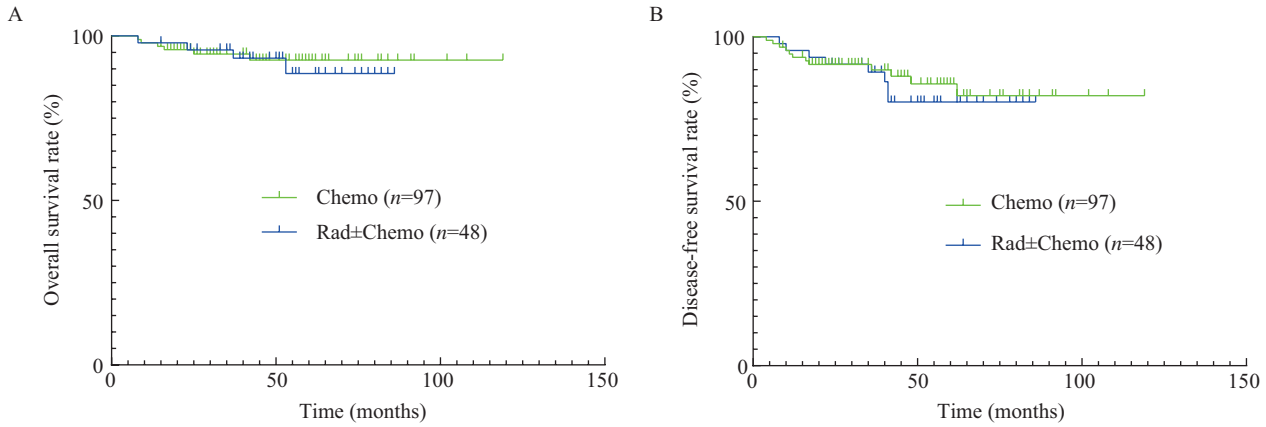

Fig. 1 The Kaplan-Meier curve for comparing overall survival and disease-free survival in high-risk, early stage endometrial endometrioid carcinoma patients receiving chemotherapy (Chemo) or radiotherapy±chemotherapy (Rad±Chemo)
A: overall survival; B: disease-free survival

In the univariate analysis for DFS, the following covariates were included with the treatment: age, surgical stage, histologic grade, myometrial invasion and LVSI. In addition, the CT cycles and lymph node resection approach were also discussed. As shown in table 3, the only significant factor associated with DFS was the histological grade. Patients with a low grade histological grade (G1) had a greater DFS, when

compared to patients with a high histological grade (G2–3) (HR: 0.166, 95% CI: 0.06–0.46, *P*=0.046). However, low grade was not a protective factor for OS, when compared to high grade (HR: 0.79, 95% CI: 0.19–3.38, *P*=0.77; table 3). Patients who underwent para-aortic lymph node resection did not have any benefits, in terms of DFS or OS, when compared to patients who underwent pelvic lymph node resection. In the CT group, patients did not benefit from receiving more CT cycles (table 3).

The cumulative incidence of local-regional disease recurrence at 60th month of follow-up was 6.2% in the CT group and 6.25% in the RT group (HR: 1.11, 95% CI: 0.28–4.35, *P*=0.88; fig. 2A). The cumulative incidence of distant recurrence at 60th month was 5.2% in the CT group and 10.4% in the RT group (HR: 0.65, 95% CI: 0.19–2.24, *P*=0.47; fig. 2B).

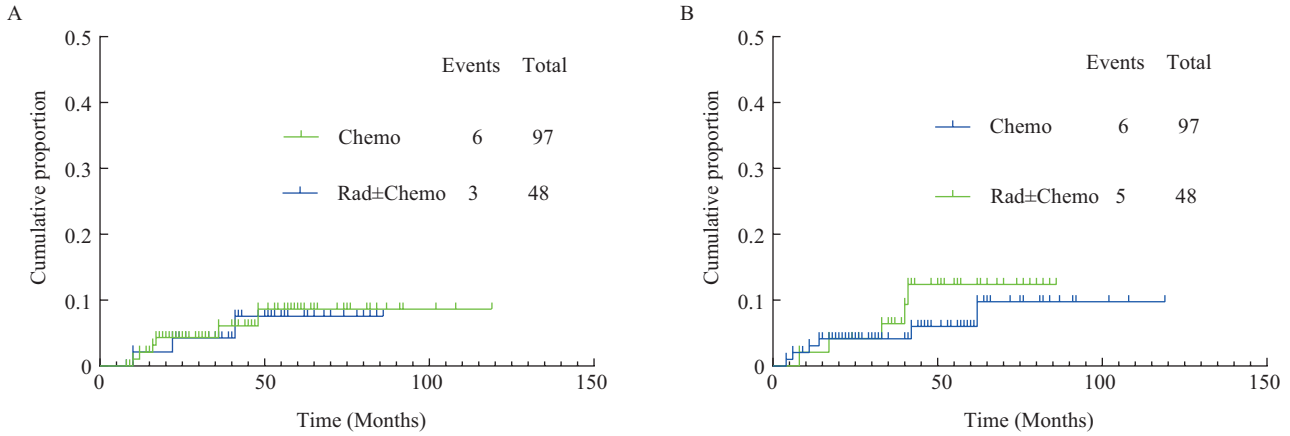

Fig. 2 Cumulative incidence of distal and local-regional relapse in high-risk, early stage endometrial endometrioid carcinoma patients receiving chemotherapy (Chemo) or radiotherapy±chemotherapy (Rad±Chemo).
A: local-regional relapse; B: distant relapse

2.3 Toxicity

The grade 3 or worse adverse events were collected for the two groups of patients. Grade 3 and 4 neutropenia occurred in 15 patients (15.5%) in the CT group and six patients (12.5%) in the RT group, while grade 3 and 4 thrombocytopenia was reported in three patients (3.1%) in the CT group and one patient (2.1%) in the RT group. The myelosuppression was cured within three months after completion of treatment for both groups. Furthermore, no serious toxicities were reported, such as radiation proctitis or cystitis. Moreover, no treatment-related death was reported. The difference in grade 3 or worse adverse events between the two groups was not significant.

3 DISCUSSION

The final results of the present study revealed that the efficacy of adjuvant CT was equal to that of adjuvant RT (RT±CT) for patients with high-risk, early-stage endometrioid endometrial carcinoma. However, adjuvant CT exhibited a trend of preventing distant relapse, although there was no significant difference in the incidence of relapse between the two groups. Both treatment arms were associated with acceptable toxicities.

In the present study, the estimated 5-year DFS rate was 85.7% and 80.2%, respectively, and the estimated 5-year OS rate was 92.7% and 88.6%, respectively, for the adjuvant CT group and adjuvant RT group. However, there was no significant difference between the two groups, and several randomized trials have confirmed these results. An Italian randomized clinical trial that involved 345 patients with high-risk endometrial carcinoma revealed that there was no improvement in the survival of patients treated with CT or standard adjuvant RT. However, it was demonstrated that CT appeared to be more able to prevent or delay distance relapses, when compared to RT[22]. In addition, the GOG-122 trial revealed that CT decreased the rate of initial distant extra-abdominal relapse associated with RT from 19% to 10% in advanced patients[23].

The cumulative incidence of distant recurrence within 60 months in the RT group was twice that in the CT group (10.4% *vs.* 5.2%). In contrast to local disease relapses, distant disease relapse poses more management challenges, and a number of patients have been left with only limited treatment options, thereby leading to high disease-related death rates. PORTEC-1[8] revealed that local-regional recurrence was not reflected in the OS, because most local-regional relapses can reach complete remission through external and intracavitary RT, surgery, or both. After vaginal recurrence, the 3-year survival rate was 69%, in contrast to the 3-year survival rate of 13% after pelvic or distant relapse, and the difference was statistically significant (*P*<0.001). A randomized trial conducted by the Japanese Gynecologic Oncology

Group further supported the efficacy of CT, and revealed that adjuvant CT has a significantly higher PFS rate (83.8% *vs.* 66.2%) and OS rate (89.7% *vs.* 73.6%), when compared to RT in high-to-intermediate risk endometrial cancer patients[24].

In the present study, it was found that the pathological risk factors for endometrial cancers, such as the involvement of the cervical stroma, LVSI positive and deep myometrial invasion, were not associated with the prognosis of early-stage endometrioid endometrial cancer. Since the publication of the Cancer Genome Atlas (TCGA) research in 2013, the molecular classification has gradually become the focus of endometrial cancer research. The TCGA research identified four categories of endometrial carcinomas with distinct clinical, pathologic and molecular features: POLE (ultra-mutated), microsatellite instability (MSI)/hypermutated, copy number low/microsatellite stable, and serous-like/copy number high[25]. In order to better evaluate prognosis of patients with endometrial cancer and drive the selection of personalized therapy, combining molecular classification with clinicopathology may be a potential method in the future.

In the present study, patients exhibited good tolerance in both CT and RT alone or combined with CT. All patients in the adjuvant CT group received carboplatin plus paclitaxel agents 2–6 times every three weeks. In the past decade, carboplatin plus paclitaxel has demonstrated superior survival outcomes and less toxicity in the adjuvant treatment of advanced endometrial carcinoma[26–28]. At present, carboplatin plus paclitaxel is the first line CT agent for endometrial cancer. Due to its toxicity and potential effect on the quality of life of stage Ⅰ and stage Ⅱ patients, PORTEC-3 suggested that further studies are required, and advised against the routine use of adjuvant CT for stage Ⅰ and stage Ⅱ patients[29]. However, no significant difference in grade 3 adverse events was found between the two groups, regardless of whether CT was administered[30]. In addition, other studies have reported good tolerance with little toxicity in the addition of CT[26–28, 31].

Most of the trials mentioned above included advanced diseases. Furthermore, few studies have focused on comparing the effects on survival between patients treated with adjuvant CT alone and patients treated with RT in high-risk early-stage endometrial carcinoma. However, the important strength of this trial was the homogeneity of the patient population. Furthermore, the inclusion criteria were narrow, and endometrioid endometrial cancer had a better prognosis when compared to other histological types, such as serous and clear cell cancers[32, 33]. The present study focused on women with early-stage endometrioid endometrial carcinoma, and patients with serous or clear cell features, or patients in the advanced stage were not included. Furthermore, there was minimal treatment variability in the operation approach and CT regimen. Moreover, more than 95% of the patients experienced pelvic±para aortic lymphadenectomy. Hence, patients with positive lymph node involvement, which had worse survival, were excluded. The present study has limitations. The present retrospective study introduced a potential selection bias, and the study cannot be applied for patients with other histological types or advanced stages.

In conclusion, there was no difference in the efficacy of adjuvant CT or adjuvant RT (RT or combined with CT) in high-risk, early-stage endometrioid endometrial carcinoma, and CT exhibited a trend of reducing the distant relapse. However, in the absence of level I evidence from randomized controlled trials, future prospective studies are needed to provide stronger evidence.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

Author Ze-hua WANG is a member of the Editorial Board for Current Medical Science. The paper was handled by the other editor and has undergone rigorous peer review process. Author Ze-hua WANG was not involved in the journal's review of, or decision related to, this manuscript.

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(Received Jul. 12, 2021; accepted Aug. 4, 2021)