

High-risk endometrial cancer may benefit from adjuvant radiotherapy plus chemotherapy

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Objective: To present patterns of practice and outcomes in the adjuvant treatment of intermediate- and high-risk endometrial cancer.

Methods: Retrospective data on 224 women with intermediate-risk and high-risk endometrial cancer from 1999 to 2006 were reviewed. All patients underwent surgical staging. Patterns of adjuvant treatment, consisting of pelvic radiotherapy, chemotherapy, and radiotherapy plus chemotherapy, were assessed. The 3- and 5-year disease-specific survival (DSS) rates were calculated using the Kaplan-Meier method.

Results: The difference in 5-year DSS rate was statistically significant between adjuvant group and non-adjuvant group (80.65% vs. 63.80%, $P=0.040$). In 110 high-risk patients who underwent adjuvant treatment, both 5-year DSS rate and recurrent rate were significantly different in combined radiotherapy and chemotherapy group compared with radiotherapy alone and chemotherapy alone groups (DSS rate, $P=0.049$; recurrent rate, $P=0.047$). In 83 intermediate-risk women who underwent adjuvant treatment, there was no significant difference in 5-year DSS rate and recurrence rate among the combined radiotherapy and chemotherapy, radiotherapy alone and chemotherapy alone groups (DSS rate, $P=0.776$; recurrent rate, $P=0.937$).

Conclusions: Adjuvant radiotherapy plus chemotherapy is associated with a higher 5-year DSS rate and lower recurrence rate compared with radiotherapy alone and chemotherapy alone in high-risk endometrial cancer patients. Patients with intermediate-risk endometrial cancer may be not likely to benefit from adjuvant combined radiotherapy and chemotherapy.

Key Words: Adjuvant treatment; chemotherapy; endometrial cancer; radiotherapy; recurrence



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Introduction

Endometrial cancer is one of the most common gynecologic malignancies, with an ever-increasing incidence (1). Although consensus on surgical staging has been reached, postoperative adjuvant treatment remains controversial. Major prognostic factors are stage, histological type, grade, depth of myometrial invasion, and lymph-vascular space invasion (LVSI). Adjuvant treatment has been tailored to these risk factors.

Radiation therapy (RT) is the conventional postoperative adjuvant treatment for patients with intermediate- and

high-risk endometrial cancer. However, a number of studies have indicated that postoperative adjuvant pelvic external beam radiotherapy (EBRT) or vaginal brachytherapy (VBT) reduced the local recurrence rate without increasing the overall survival (OS) rate (2,3). In the past 20 years, much attention has been paid to postoperative chemotherapy (CHEMO), concurrent RT and CHEMO, as well as combined RT and CHEMO (RT&CHEMO). However, relatively little is known regarding regimen selection and efficacy of chemotherapy-containing adjuvant treatments.

The aim of this study was to explore the feasibility,

effectivity and toxicity of adjuvant treatment for intermediate- and high-risk endometrial cancer.

Materials and methods

General information

This study included 224 patients with intermediate-risk and high-risk factors treated from January 1999 to December 2006 in Beijing Obstetrics and Gynecology Hospital, of which, 193 cases received postsurgical treatment (adjuvant treatment group) and 31 patients did not undergo any adjuvant treatment (non-adjuvant treatment group). Surgical staging [International Federation of Gynaecology and Obstetrics (FIGO) 2009], including extrafascial total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy (PLN)/para-aortic lymph node dissection, was administered in all patients. The intermediate-risk group (105 cases) included patients with stage IA G3 or other non-endometrial adenocarcinoma pathological type; stage IB, G1 and G2, with endometrioid type histology (4). The high-risk group (119 cases) are stage IB of grade 3 or of non-endometrioid histology; or stage II or III (4).

Adjuvant treatment: postoperative pelvic EBRT with or without VBT (RT group)

A total of 162 patients (including 109 RT alone and 53 RT+CHEMO cases) were treated with EBRT, of which 148 (91.36%) had pelvic standard rectangular field RT and 14 (8.64%) received BOX field RT, with a dose range of 40-45 Gy. Four Patients (2.47%) with positive common iliac lymph nodes or para-aortic lymph nodes were assigned to concurrent pelvic irradiation and para-abdominal aortic extended field irradiation with a dose range of 40-45 Gy, and 7 patients (4.32%) with parametrial metastasis or local pelvic lymph node metastasis were given the above pelvic EBRT and subsequent reduced field irradiation covering the parametrial region or lymph node metastatic region with the dose range of 5-10 Gy. Ten patients (6.17%) including 6 intermediate-risk patients and 4 high-risk patients consented to receive EBRT followed by immediate VBT with a dose range of 10-20 Gy. None of the patients in this study underwent postoperative VBT alone.

Postoperative CHEMO

Among 84 patients (45.52%, including 31 CHEMO

alone and 53 RT+CHEMO cases) who were assigned to postoperative systemic CHEMO, 31 (36.90%) adopted 4-6 cycles of CHEMO, 32 (38.10%) underwent 2-3 cycles of CHEMO followed by RT (CHEMO-RT); 3 (3.57%) received RT followed by 2-3 cycles of CHEMO (RT-CHEMO); 9 (10.71%) had 2-3 cycles of CHEMO first and then RT followed by same regimen CHEMO for 2-3 cycles (CHEMO-RT-CHEMO); 3 (3.57%) received RT plus 2-3 cycles of CHEMO at the same time (RT+CHEMO); and 6 (7.14%) underwent 2-3 cycles of CHEMO first followed by RT plus the same CHEMO regimen at the same time for 2-3 cycles (CHEMO-CHEMO+RT). CHEMO was delivered at 21-d intervals. The regimens were: cisplatin, doxorubicin plus cyclophosphamide (PAC) for 36 patients (42.86%); cisplatin plus paclitaxel (PT) for 33 patients (39.29%); cisplatin plus doxorubicin (PA) for 10 patients (11.90%); cisplatin, vincristine plus doxorubicin (PVA) for 1 patient (1.19%); cisplatin, ifosfamide plus doxorubicin (PIA) for 1 patient (1.19%); cisplatin, etoposide plus cyclophosphamide (PEC) for 1 patient (1.19%); cisplatin plus cyclophosphamide (PC) for 1 patient (1.19%); and cyclophosphamide, doxorubicin plus 5-fluorouracil (CAF) for 1 patient (1.19%).

Follow up

The median follow-up time was 49 months (range, 3-130 months). Fifty-nine (26.34%) of the 224 patients were lost during the follow-up period. Survival time was calculated as the time from diagnosis to death or the last follow up. Disease-specific survival (DSS) time was calculated under the following situations: patients were died of diseases, or patients' death was caused by treatment-induced complications directly or indirectly.

Statistical analysis

SPSS 17.0 statistical software package (SPSS Inc., Chicago, IL, USA) was adopted for the statistical analysis. The Kaplan-Meier method was used to estimate the survival rates and log-rank test was used to analyze the significance. Comparison of rates including recurrence rates and toxicity rates was performed by Pearson Chi-square and continuity correction test.

Results

General characteristics

The study included 224 patients with a median age of 57 years

Table 1 General characteristics of 224 cases with high- and intermediate-risk endometrial cancer

Characteristics	No adjuvant therapy (N=31) n (%)	RT (N=109) n (%)	CHEMO (N=31) n (%)	RT+CHEMO (N=53) n (%)
Age (year)				
>60	23 (74.19)	27 (24.77)	18 (58.06)	9 (16.98)
≤60	8 (25.80)	82 (75.23)	13 (41.94)	44 (83.02)
FIGO (2009 staging)				
Stage I				
Ia	17 (54.84)	38 (34.86)	4 (12.90)	9 (16.98)
Ib	13 (41.94)	41 (37.61)	18 (58.06)	17 (32.08)
Stage II		4 (3.67)	0	2 (3.77)
Stage III				
IIIa	1 (3.23)	13 (11.93)	2 (6.45)	1 (1.89)
IIIb		5 (4.59)	7 (22.58)	1 (1.89)
IIIc1		8 (7.34)		19 (35.85)
IIIc2				4 (7.55)
Pathological classification				
Endometrial adenocarcinoma	29 (93.55)	67 (61.47)	25 (80.65)	18 (33.96)
Non-endometrioid carcinoma	2 (6.45)	42 (38.53)	6 (19.35)	35 (66.04)
Histological grade				
1		7 (6.42)	7 (22.58)	1 (1.87)
2	11 (35.48)	74 (67.89)	10 (32.26)	19 (35.85)
3	20 (64.52)	28 (25.69)	14 (45.16)	33 (62.26)
Intermediate risk	22/105	58/105	10/105	15/105
High risk	9/119	51/119	21/119	38/119

Table 2 Sequencing of postoperative RT and CHEMO and toxicity in intermediate- and high-risk endometrial cancer patients

Manner	RT	CHEMO	RT+CHEMO				
			CHEMO-RT	RT-CHEMO	CHEMO-RT- CHEMO	CHEMO+RT	CHEMO- RT+CHEMO
N	109	31	32	3	9	3	6
% [†]	56.48	16.06	19.75	1.85	5.56	1.85	3.70
High risk	51	21	18	2	8	2	6
Intermediate risk	58	10	14	1	1	1	0
≥G3	14	4	10	2	4	3	5
% [#]	12.84	12.90	31.25	66.67	44.44	100	83.33

[†]Percentage based on a total of 193 patients; [#]Percentage based on the treatment

(range, 23-75 years). Of the 224 patients, 109 (48.66%) received RT alone postoperatively, 31 (13.84%) received postoperative CHEMO alone, and 53 (23.66%) received postoperative RT plus CHEMO. Stage and CHEMO-RT sequences are shown in *Tables 1,2*.

DSS and recurrence rates

The 3- and 5-year DSS rates were 90.09% and 80.65%, respectively, in adjuvant treatment group, and 80.2% and 63.80%, respectively, in non-adjuvant treatment group. The difference in 5-year DSS was statistically significant

Table 3 Effect of postoperative adjuvant treatment on DSS and recurrence rates

	<i>n</i>	5-y DSS rate (%)	3-y DSS rate (%)	5-y recurrence rate (%)
High risk	110	79.9	91.2	22 (20.00)
RT	51	59.2	83.7	14 (27.45)
RT&CHEMO	38	85.4	92.5	3 (7.89)
CHEMO	21	76.7	86.3	5 (23.81)
P [*]		0.049 [#]		0.047
Intermediate risk	83	89.10	90.99	6 (7.23)
RT	58	87.09	89.18	4 (6.90)
RT&CHEMO	15	92.04	92.31	1 (6.67)
CHEMO	10	90.89	91.66	1 (10)
P		0.776 [#]		0.937

^{*}Comparison among the three groups (Pearson Chi-square test). [#]Comparison of DSS (Kaplan-Meier log-rank)

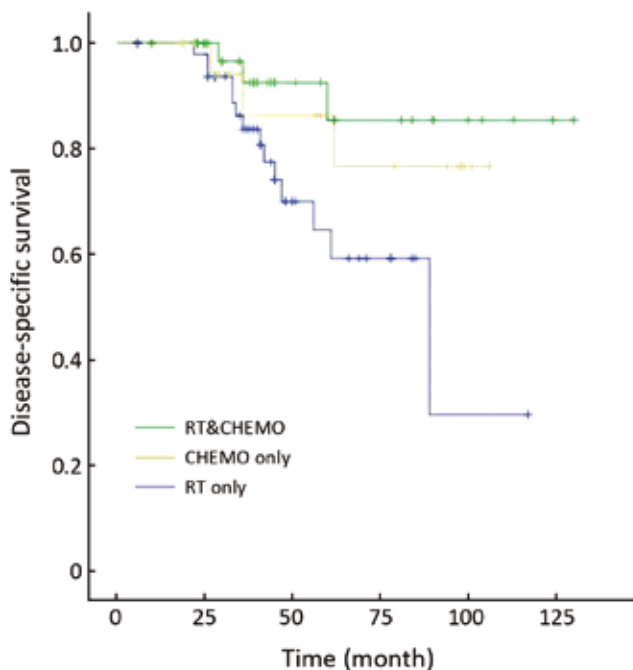


Figure 1 Kaplan-Meier DSS in high-risk patients who received simple postoperative RT, CHEMO vs. combined RT and CHEMO

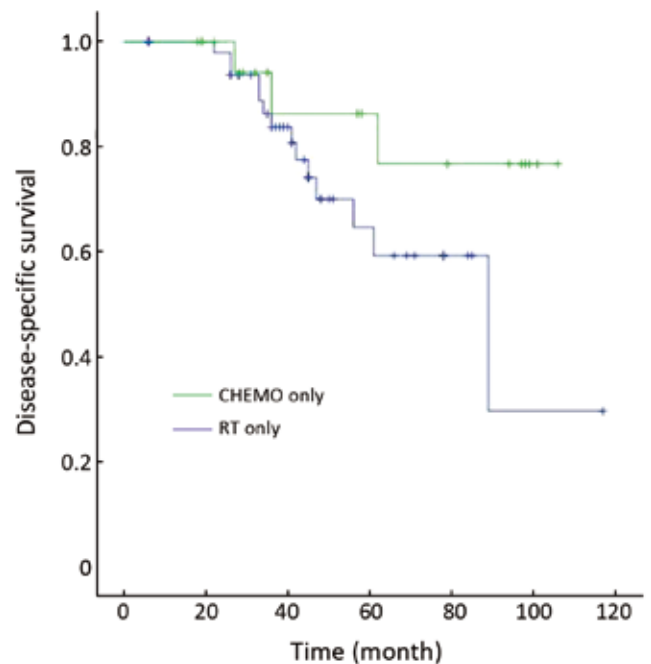


Figure 2 Kaplan-Meier DSS in high-risk patients who received simple postoperative RT vs. CHEMO

between the two groups (Kaplan-Meier log-rank, $P=0.040$).

Table 3 showed that the DSS rate was significantly different among the three different adjuvant treatment groups (Kaplan-Meier log-rank, $P=0.049$) in high-risk patients, in which the difference between RT&CHEMO and RT alone groups was statistically significant (Kaplan-Meier log-rank, $P=0.017$), whereas, the other two

comparisons were not significant (RT&CHEMO vs. CHEMO: Kaplan-Meier log-rank, $P=0.503$; RT vs. CHEMO alone: Kaplan-Meier log-rank, $P=0.135$). The survival curves are shown in Figures 1-4. The 5-year DSS rates were not significantly different among patients who received different sequences of RT plus CHEMO (Kaplan-Meier log-rank, $P=0.455$).

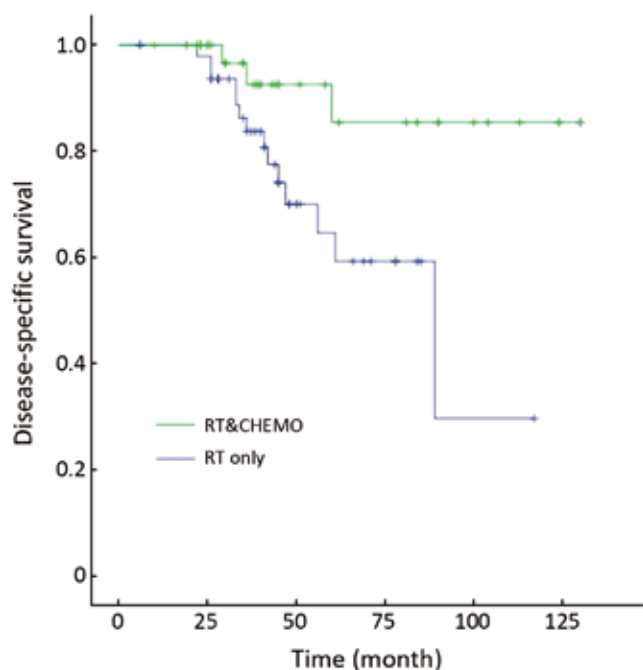


Figure 3 Kaplan-Meier DSS in high-risk patients who received simple postoperative RT *vs.* combined RT and CHEMO

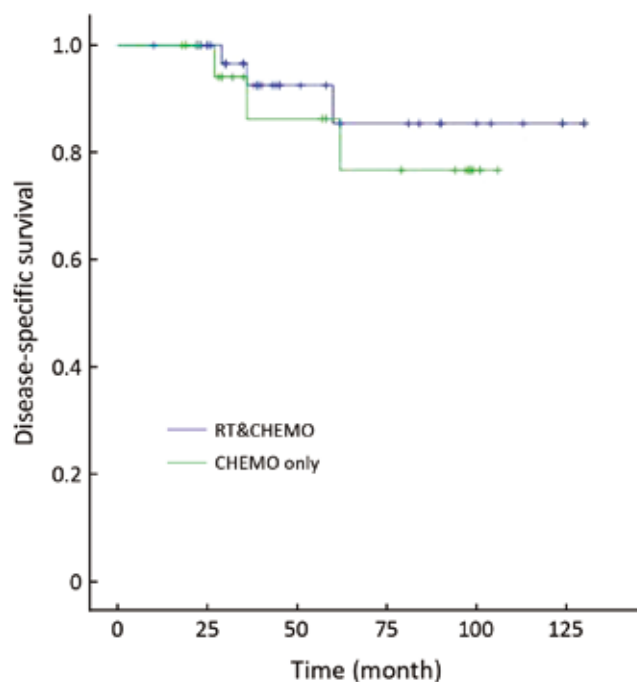


Figure 4 Kaplan-Meier DSS in high-risk patients who received simple postoperative CHEMO *vs.* combined RT and CHEMO

In intermediate-risk group, the DSS rate was not significantly different among RT alone, CHEMO alone and RT&CHEMO groups (Kaplan-Meier log-rank, $P=0.776$). The 5-year recurrence rate was not significantly different among these three treatment groups (Pearson Chi-square test, $P=0.937$).

During treatment, 5 (2.59%) of 193 patients had progressive disease, in which 3 underwent simple RT, 1 received CHEMO alone and the remaining 1 patient received combined RT and CHEMO (CHEMO-RT).

Toxicity of adjuvant treatment

Forty-two patients (21.76%) experienced \geq grade 3 ($G3^+$) toxicity (Table 2). $G3^+$ toxicity of RT+CHEMO/CHEMO-RT+CHEMO and sequential CHEMO-RT-CHEMO patients was significantly higher than that in CHEMO-RT/RT-CHEMO and RT alone patients (66.67% *vs.* 18.06%, continuity correction test, $P=0.001$). $G3^+$ toxicity of CHEMO-RT/RT-CHEMO was significantly higher than that of RT alone (34.28% *vs.* 12.84%, Continuity Correction test, $P=0.004$).

Twenty-four patients stopped treatment in the middle

of RT due to $G3^+$ toxicity. Such experience happened in 8 patients (7.34%) undergoing RT alone, 4 patients (12.50%) undergoing CHEMO-RT, 2 patients (66.67%) undergoing RT-CHEMO, 2 patients (22.22%) undergoing CHEMO-RT-CHEMO, 3 patients (100%) undergoing RT+CHEMO, and 5 patients (83.33%) undergoing CHEMO-RT+CHEMO. The percentage of patients who stopped RT halfway was significantly higher in groups of combined RT and CHEMO than RT alone (30.19% *vs.* 7.34%, continuity correction test, $P=0.001$), whereas there was no significant difference between CHEMO-RT group and simple RT group. (7.34% *vs.* 12.50%, continuity correction, $P=0.576$).

Discussion

Despite many years of exploration into the postoperative treatment for intermediate- and high-risk endometrial cancer, more work is needed.

Guidelines from the *National Comprehensive Cancer Network* (NCCN) and other studies have suggested that postoperative pelvic EBRT or VBT is helpful in reducing local recurrence (pelvic and vaginal cuff) in most patients

with intermediate- and high-risk endometrial cancer (5-10). The GOG-99 trial has shown that adjuvant pelvic RT can reduce the relapse rate in intermediate-risk patients, but that the OS time was not extended (11). Other studies have reported 5-year survival rates in the range of 84-89% in patients with intermediate-risk endometrial cancer who received postoperative RT (4,8,12-14). In our study, in intermediate-risk patients who received RT alone, the 3- and 5-year DSS rates were 90.99% and 89.10%, respectively, similar to the results of the above mentioned studies.

Side effects of postoperative pelvic EBRT are marked, particularly in the small intestine (4,7,15). In our study, the G3+ side effect rate in patients receiving RT alone was 12.84%; in fact, 7.34% of the patients had to stop RT halfway.

GOG-122 and other studies suggested that high-risk patients would benefit more from postoperative CHEMO than from pelvic RT (16-22). However, researchers suggested that neither progression-free survival nor OS was significantly different in patients with high-risk endometrial cancer treated with postoperative adjuvant CHEMO compared with RT (23). In our study, 3- and 5-year DSS rates went up to 86.3% and 76.7% in patients assigned to postsurgical CHEMO alone, compared with 83.7% and 59.2%, respectively, in patients treated with postoperative RT alone, even these differences were not statistically significant. The recurrence rate in CHEMO group was not significantly lower compared with RT alone.

Postoperative RT does not improve OS and postoperative CHEMO alone has higher local recurrence rate in patients with high-risk endometrial cancer. Therefore, much attention has been paid to combined postoperative RT and CHEMO (18,24-32). The most recent research showed that the addition of CHEMO to RT improved the rate of clinical benefit from 55% to 77% (20). However, no large multicenter study has reported on the efficacy of combined RT and CHEMO, selection of the most appropriate CHEMO regimen, and most appropriate sequence combination for RT and CHEMO (CHEMO-RT, RT-CHEMO, RT+CHEMO, or the "sandwich" program of CHEMO-RT-CHEMO). Our retrospective analysis indicated that patients with high-risk cancer treated with combined RT and CHEMO had better DSS rates and lower recurrence rate. In this combined RT and CHEMO group, the sequence of CHEMO-RT has fewer side effects than other combining sequence, whereas, the benefit was not presented in intermediate-risk patients.

We propose that the treatment for high-risk endometrial cancer patients with combined adjuvant RT and CHEMO can lead to a reduction in recurrence rate as well as improvements in the DSS rate, compared with postoperative RT alone and CHEMO alone. The beneficial trend for postoperative RT combined with CHEMO found in this non-randomized study should be further examined in a large randomized study.

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