

Adjuvant chemoradiotherapy vs. radiotherapy alone in early-stage high-risk endometrial cancer: a systematic review and meta-analysis

H. JINGJING¹, J. RUI¹, P. HUI^{2,3}

¹Gynecology Tianjin Gong'an Hospital, Tianjin, China

²Gynecology Tianjin Baodi Hospital, Tianjin, China

³Baodi Clinical College of Tianjin Medical University, Tianjin, China

Abstract. – OBJECTIVE: The benefits of adjuvant chemoradiotherapy (CRT) in patients with International Federation of Gynecology and Obstetrics (FIGO) stages I-II high-risk endometrial cancer remain controversial. We undertook a systematic review and meta-analysis to assess the efficacy of CRT over radiotherapy (RT) in patients with early-stage high-risk endometrial cancer.

PATIENTS AND METHODS: We searched MEDLINE (from 1946 to May 2018), EMBASE (from 1966 to May 2018), and the Cochrane Library database for randomized controlled trials (RCTs) conducted for endometrial cancer comparing CRT to RT alone. The outcomes were overall survival (OS), failure-free survival (FFS), local recurrence rates (LRR) and the distant metastasis rate (DMR).

RESULTS: Three eligible studies with 1120 participants were included in the meta-analysis. All studies were published from 1990 to 2018. The OS rates were 82.5% for the patients in the CRT group and 84.4% for patients in the RT group. The included three RCTs showed no significant difference of OS between the CRT and RT groups (odd ratio 0.98, 95% CI 0.93 to 1.02, $p=0.35$) with no heterogeneity ($I^2=0\%$, $p=0.47$). Two studies reported 382 FFS events in 469 patients with CRT treatment (81.4%) and 376 events of the 470 patients with RT treatment (80.0%). Overall, CRT group didn't provide any benefit over RT alone (1.02, 0.95 to 1.08, $p=0.62$; $I^2=0\%$, $p=0.55$) in FFS. 39 patients in CRT group (10.2%) vs. 16 patients in RT group (4.3%) were diagnosed with local recurrence. LRR was significantly more common in patients receiving adjuvant chemoradiotherapy compared with adjuvant radiotherapy (2.29, 1.31 to 3.98, $p=0.004$; $I^2=0\%$, $p=0.33$). The distant metastasis occurred in 20 patients (5.2%) treated with CRT and 26 patients (7.0%) treated with RT. The effect of reducing DMR was equivocal between the CRT group and the RT group, with an OR of 0.74 (0.43-1.27, $p=0.28$; $I^2=0\%$, $p=0.87$).

CONCLUSIONS: This study demonstrates that adjuvant chemoradiotherapy has no advantage over radiotherapy alone for overall survival and failure-free survival in high-risk patients with FIGO stages I-II endometrial cancer. In addition, CRT is associated with a high risk of local recurrences.

Key Words

Chemoradiotherapy, Radiotherapy, FIGO I-II, Survival, Meta-analysis.

Introduction

Endometrial cancer is the most common gynecologic cancer of the female reproductive tract in women of high-income countries^{1,2}. It is known that most patients in the early stages have a favorable prognosis with surgical treatment. However, about 15% of women with endometrial cancer in International Federation of Gynecology and Obstetrics (FIGO) stages I-II have a high risk of recurrence and distant metastasis^{3,4}. Previous studies^{5,6} have shown that postoperative adjuvant radiotherapy (RT) could reduce the local recurrence rate (LRR) for women with high-risk endometrial cancer, although there is a paucity of evidence to reduce the distant metastasis or survival. Therefore, it seems that chemotherapy should combine with adjuvant RT for patients with risks of distant metastasis.

Recently, the Postoperative Radiation Therapy for Endometrial Carcinoma (PORTEC)-3 trial published in 2018, which provided the overall survival (OS) and failure-free survival (FFS) rates of patients with endometrial cancer in FIGO stages I-II between chemoradiotherapy (CRT) group and RT group, found that CRT has no ad-

vantage over RT alone⁷. Some studies showed the addition of adjuvant chemotherapy to radiation in the early stage of endometrial cancer was associated with improved overall survival⁸.

Therefore, we presented the results of a systematic review summarizing currently available evidence from randomized controlled trials (RCTs) in order to reveal whether adjuvant chemoradiotherapy would be beneficial for the survival of patients with high-risk early stages (FIGO stages I-II) endometrial cancer.

Materials and Methods

Data Sources and Search Strategy

Relevant studies were identified by searching the following data sources: MEDLINE by OVID (from 1950 to May 2018), Embase (from 1970 to May 2018) and the Cochrane Library database (Cochrane Central Register of Active controlled Trials; no date restriction), and abstracts from scientific meetings. Keywords in our search included “endometrial cancer”, “endometrial carcinoma”, “chemotherapy”, “radiotherapy”, “survival” and “randomized controlled trials”. Trials were considered without language restrictions.

Data Extraction and Quality Assessment

Relevant information was extracted into a spreadsheet. The extracted data included study characteristics (study name, country and recruitment period), follow-up time, sample size, chemotherapy regimens, number of chemotherapy cycles, radiotherapy regimens. The endpoints of the assessment were five-year overall survival, failure-free survival, the local recurrence rates and the distant metastasis rate (DMR). Data extraction was undertaken independently by two investigators (HJJ and JR) using a standardized approach. If there were any disagreement between them, a third author (PH) would repeat the procedure until consensus was reached. And the quality assessment of included RCTs was judged according to the Cochrane Collaboration tool for assessing the risk of bias⁹.

Statistical Analysis

We calculated the odds ratio (OR) and 95% confidence interval (CI) for the categorical variable by the random-effects model. Heterogeneity was analyzed using an I^2 statistic on $N-1$ degrees of freedom. An I^2 test less than 50% indicated no significant heterogeneity. Funnel plots, Begg's and Egger's quantitative tests were used to probe for

publication bias. A two-sided p -value < 0.05 was considered statistically significant for all included studies. All statistical analyses were performed using STATA, version 12.0 for the meta-analysis.

Results

Trial Flow and Study Characteristics

Our original search yielded 1548 articles, 1545 citations were excluded based on titles, abstracts or full texts. After a thorough and careful review, 3 trials^{7,10,11} which contained 1120 patients were included in our final analysis. The reasons for exclusion are listed in Figure 1. Among them, two studies included patients in the chemoradiotherapy group received anthracycline-based therapy, and in one study doxorubicin-based chemotherapy was used. In the PORTEC-3 study, chemotherapy was given after radiotherapy⁷. In the GOG-249 trial, cisplatin was synchronized at week 1 and week 4 of radiotherapy, and then it was followed by paclitaxel/carboplatin chemotherapy once every 3 weeks for four cycles¹¹. In another study, sandwich-style therapy was used during the treatment time¹⁰. Radiotherapy in the included studies was mostly based on external beam radiotherapy (EBRT) with or without brachytherapy (BRT). The mean EBRT dose used in these three studies was 45.9 Gy. There was no detailed information on the total dose of BRT delivered in these studies. The follow-up time for patients ranged from 53 to 60.3 months, and the number of patients included in the study ranged from 378 to 660. The characteristics of the included studies are presented in Table I.

Quality of Trials

We evaluated the quality of each study by sequence generation, allocation concealment, performance bias, detection bias, incomplete outcome data, selective reporting, and other possible sources of bias. The summary of the risk of bias is presented in Figure 2.

Effects of Survival

Data regarding the overall survival were available from 3 trials. Of the 561 patients treated with CRT, there were 98 deaths and 87 events occurred in 559 patients treated with RT. The OS rates were 82.5% for the patients in the CRT group and 84.4% for patients in the RT group. The included RCTs showed no significant difference of OS between the CRT and RT groups (OR 0.98, 95% CI 0.93 to 1.02, $p = 0.35$) with no

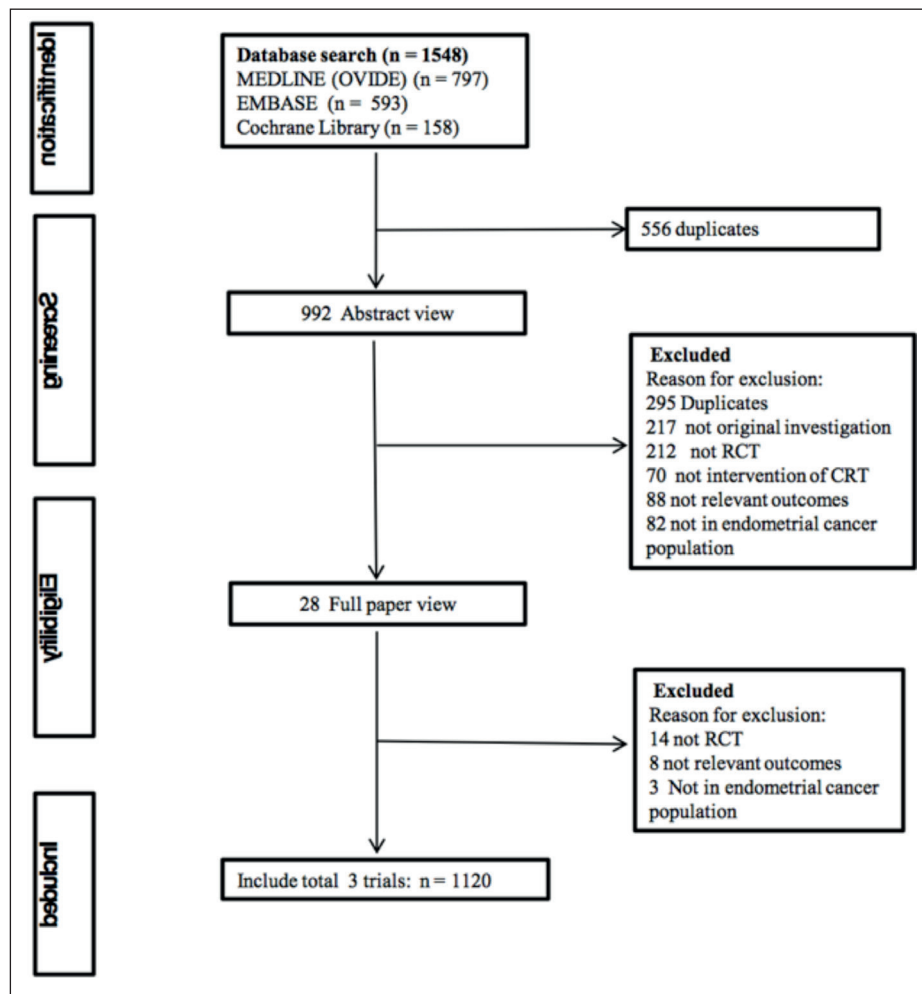


Figure 1. Process for identifying studies eligible for the meta-analysis.

heterogeneity ($I^2 = 0\%$, $p = 0.47$). Two studies reported 382 FFS events in 469 patients with CRT treatment (81.4%) and 376 events of the 470 patients with RT treatment (80.0%). Overall, the CRT group didn't provide any benefit over RT alone (OR 1.02, 95% CI 0.95 to 1.08, $p = 0.62$) in FFS, with no evidence of heterogeneity ($I^2 = 0\%$, $p = 0.55$) (Figure 3).

Effects of Recurrence

Two studies reported the local recurrence rates and distant metastasis rates between the CRT group and RT group. 39 patients in the CRT group (10.2%) vs. 16 patients in the RT group (4.3%) were diagnosed with local recurrence. LRR was significantly more common in patients receiving adjuvant chemoradiotherapy compared

Table I. Characteristics of patients with baseline of included studies.

Study	Country	Recruitment period	Follow-up (months)	Sample size	CT regimens (cycles)
Morrow 1990	United States	1977-1986	60	92/89	Doxorubicin (8)
PORTEC-3 2018	France, Italy, Canada	2006-2013	60.2	178/187	Cisplatin first, followed by Paclitaxel/Carboplatin (4)
GOG-249 2017	United States	2009-2014	53	291/283	Paclitaxel/Carboplatin (3)

Values for number of patients are given in chemoradiotherapy group and radiotherapy group. CT: chemotherapy, EBRT: external beam radiotherapy.

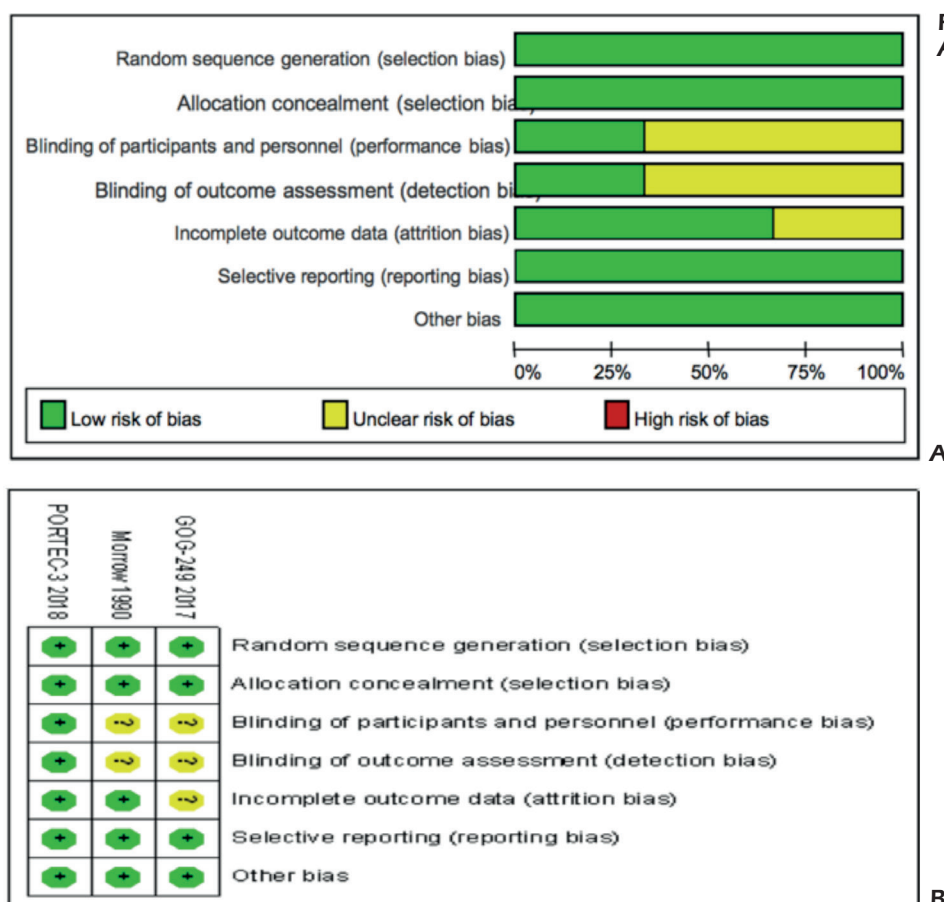


Figure 2. Risk of bias graph **A**, and risk of bias summary, **B**.

with adjuvant radiotherapy (OR 2.29, 95% CI 1.31 to 3.98, $p = 0.004$; $I^2 = 0\%$, $p = 0.33$). The distant metastasis occurred in 20 patients (5.2%) treated with CRT and 26 patients (7.0%) treated with RT. Consequently, the effect of reducing DMR was equivocal between the CRT group and the RT group, with an OR of 0.74 (95% CI 0.43 to 1.27, $p = 0.28$) with no evidence of heterogeneity ($I^2 = 0\%$, $p = 0.87$) (Figure 4).

Publication Bias

Begg's and Egger's quantitative tests showed there was no significant publication bias regarding OS outcomes among studies ($p = 0.60$, Figure 5).

Discussion

To our knowledge, the current study represents the first meta-analysis of RCTs evaluates the effect of adjuvant chemoradiotherapy on survival of patients with early-stage high-risk endometrial cancer. This large quantitative review, including 3 trials, more than 1100 participants,

suggested that adjuvant chemoradiotherapy did not show higher survival advantage than radiotherapy alone for patients with FIGO stage I-II, but had a higher risk of local recurrences.

Whether or not adjuvant chemoradiotherapy gains a survival advantage in early-stage high-risk endometrial cancer remains a matter of debate. Previous data supported the practice of adding CT to RT in early endometrial cancer. The prospective trial of the Nordic Society of Gynecologic Oncology-9501/European Organization for Research and Treatment of Cancer-55991 revealed that the addition of adjuvant CRT was associated with improved 5-year progression-free survival, which included stage II patients¹². A retrospective study from Utah, which included 11746 patients with stage IB and II disease, reported adjuvant CRT was associated with improved OS⁸. Ozgul et al¹³ analyzed data from 5 gynecologic oncology centers in Turkey from 2002 to 2015, in which they found adjuvant external beam radiotherapy plus CT were associated with increased 5-year disease-free survival in patients with stage II endometrial cancer. The

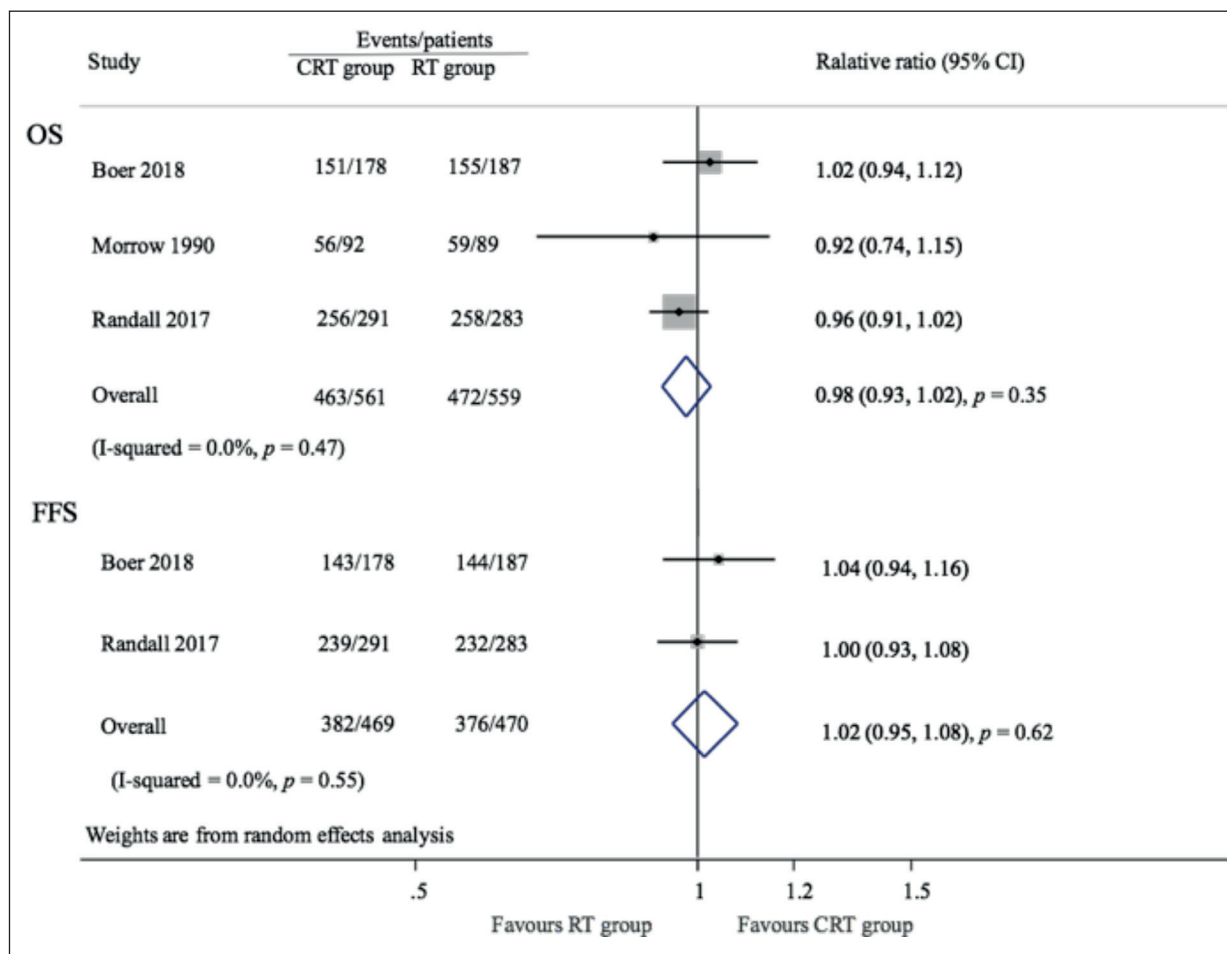


Figure 3. Forest plots for the chemoradiotherapy (CRT) vs. radiotherapy (RT) trials for overall survival (OS), failure-free survival (FFS).

meta-analysis conducted by Yi et al¹⁴ including stage I-III patients showed that adjuvant CRT could significantly improve progression-free survival and cancer-specific survival compared with RT in high-risk patients. Therefore, it has come down to the theory that combining chemotherapy with radiotherapy could control local recurrence and further eliminate the rate of distant metastasis, providing apparently effective effects in such high-risk patients. However, most studies were retrospective or mixing in some patients with stage III.

The results of several randomized controlled trials which have included patients with stage I-II endometrial cancer have been published recently. The PORTEC-3 trial revealed that adjuvant chemotherapy given during and after radiotherapy increased failure-free survival for women with stage III endometrial cancer, but not for patients with stage I-II because pelvic control was high with radiotherapy alone. This work suggested CRT

schedule couldn't be recommended as a standard for early-stage endometrial cancer⁷. The Gynecologic Oncology Group (GOG) 249 trial has not yet been fully published, but has been presented as abstracts at conferences¹¹. This study, which compared pelvic RT with a combination of three cycles of paclitaxel/carboplatin chemotherapy and vaginal brachytherapy in stage I-II patients, showed that the CRT arm was not superior to pelvic RT, and significantly more pelvic recurrences were reported in the CRT group. A subgroup analysis of a prior overview found there was no survival benefit from adjuvant CRT for high-risk stage I endometrial cancer, which also pointed out that the meta-analyses of this subgroup were underpowered due to a small sample size of only one study included¹⁵. Consistent with the results of previously published RCTs and meta-analyses in patients with early-stage high-risk endometrial cancer, our work confirms the main findings that the use of CRT does not improve OS or FFS in stage I-II

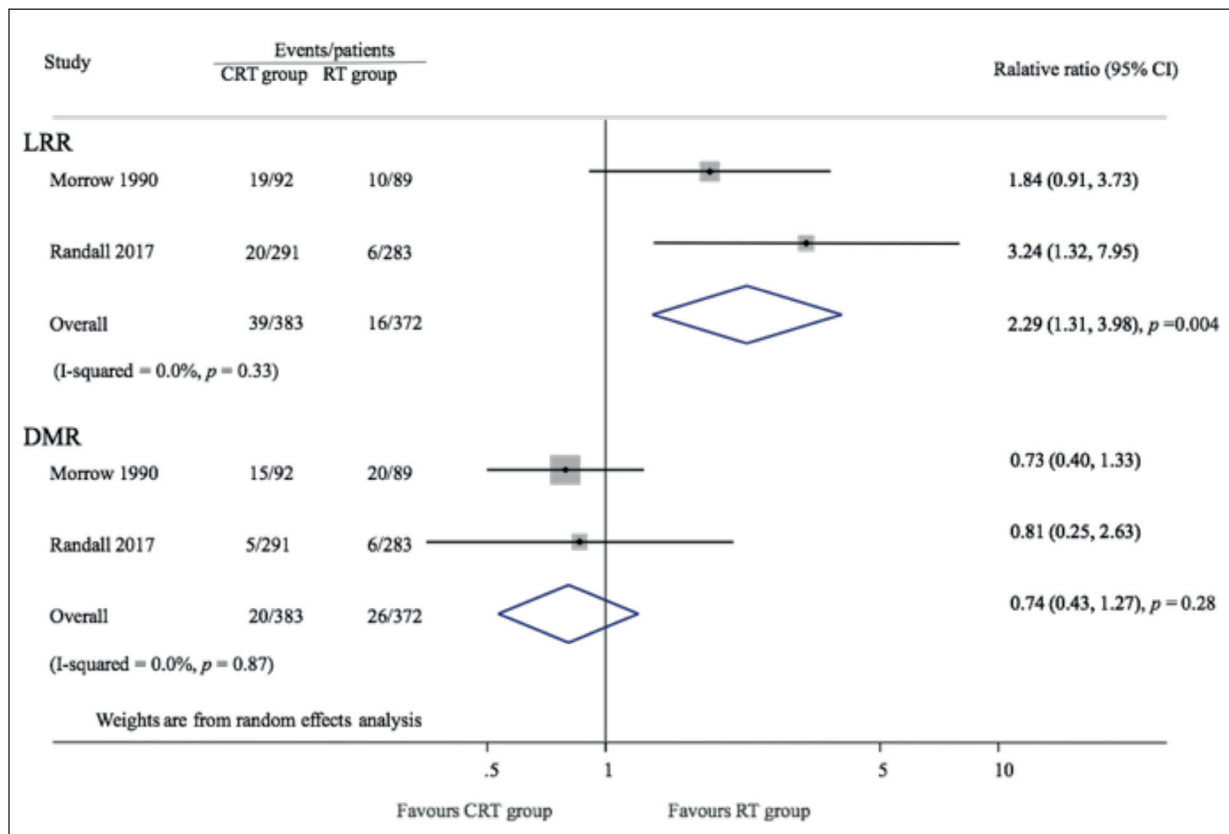


Figure 4. Forest plots for the chemoradiotherapy (CRT) vs. radiotherapy (RT) trials of the local recurrence rate (LRR) and distant metastasis rate (DMR).

endometrial cancer. The possible reason for this result is that patients with early-stage disease have a better prognosis than those with advanced-stage disease. For the early-stage patients, the survival

increases with improved local control with radiotherapy alone. Therefore, multiple appropriate treatment options for women with stage I-II should be individualized.

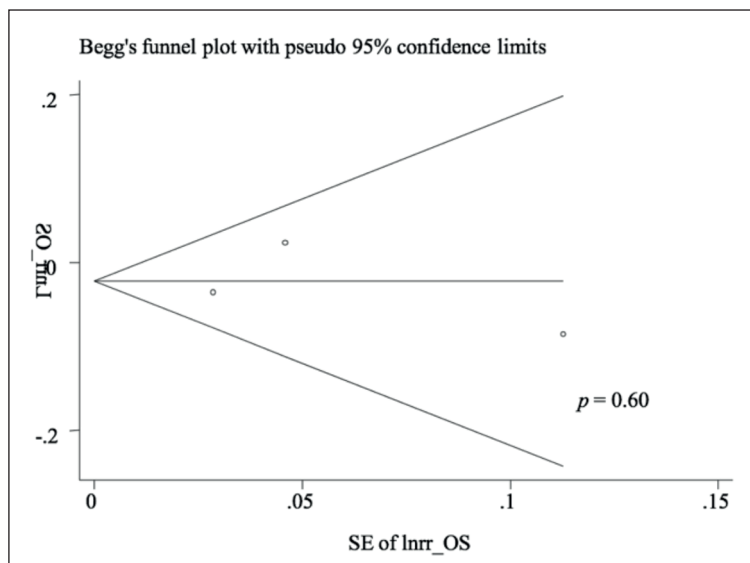


Figure 5. Forest plot for evaluation of publication bias for overall survival (OS).

However, this study has some potential limitations. First, the PORTEC-3 trial was not specifically designed to evaluate OS in patients with FIGO I-II. The relative paucity of high-quality RCTs conducted in early-stage patients limited the conclusions to be drawn about chemoradiotherapy and survival. Second, a different chemotherapy regimen included in each work is not the same. Therefore, the differences in CRT also have impacts on the survival of patients. Third, the number of eligible studies is not large enough, more well-designed large-scale RCTs involving CRT vs. RT alone would be desirable to investigate the therapeutic outcomes for early-stage high-risk endometrial cancer further.

Conclusions

We demonstrated adjuvant chemoradiotherapy has no advantage over radiotherapy alone for overall survival and failure-free survival in high-risk patients with FIGO stages I-II endometrial cancer. In addition, CRT is associated with a high risk of local recurrences. The clinical significance of these results requires confirmation with further studies.

Acknowledgments

We thank all the authors whose publications could be included in our meta-analysis.

Conflict of Interests

The authors declare that they have no conflict of interest.

References

- 1) CANCER GENOME ATLAS RESEARCH NETWORK, KANDOTH C, SCHULTZ N, CHERNIACK AD, AKBANI R, LIU Y, SHEN H, ROBERTSON AG, PASHTAN I, SHEN R, BENZ CC, YAU C, LAIRD PW, DING L, ZHANG W, MILLS GB, KUCHERLAPATI R, MARDIS ER, LEVINE DA. Integrated genomic characterization of endometrial carcinoma. *Nature* 2013; 497: 67-73.
- 2) PARK HJ, NAM EJ, KIM S, KIM YB, KIM YT. The benefit of adjuvant chemotherapy combined with postoperative radiotherapy for endometrial cancer: a meta-analysis. *Eur J Obstet Gynecol Reprod Biol* 2013; 170: 39-44.
- 3) CREUTZBERG CL, VAN PUTTEN WL, WARLAM-RODENHUIS CC, VAN DEN BERGH AC, DE WINTER KA, KOPER PC, LYBEERT ML, SLOT A, LUTGENS LC, STENFERT KROESE MC, BEERMAN H, VAN LENT M. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the postoperative radiation therapy in endometrial carcinoma trial. *J Clin Oncol* 2004; 22: 1234-1241.
- 4) MORROW CP, BUNDY BN, KURMAN RJ, CREASMAN WT, HELLER P, HOMESLEY HD, GRAHAM JE. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group Study. *Gynecol Oncol* 1991; 40: 55-65.
- 5) AALDERS J, ABELER V, KOLSTAD P, ONSRUD M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. *Obstet Gynecol* 1980; 56: 419-427.
- 6) KEYS HM, ROBERTS JA, BRUNETTO VL, ZAINO RJ, SPIRTOS NM, BLOSS JD, PEARLMAN A, MAIMAN MA, BELL JG, GYNECOLOGIC ONCOLOGY G. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group Study. *Gynecol Oncol* 2004; 92: 744-751.
- 7) DE BOER SM, POWELL ME, MILESHKIN L, KATSAROS D, BESSETTE P, HAIE-MEDER C, OTTEVANGER PB, LEDERMANN JA, KHAW P, COLOMBO A, FYLES A, BARON MH, JURGENLIEMK-SCHULZ IM, KITCHENER HC, NIJMAN HW, WILSON G, BROOKS S, CARINELLI S, PROVENCHER D, HANZEN C, LUTGENS LCHW, SMIT VTHBM, SINGH N, DO V, D'AMICO R, NOUT RA, FEENEY A, VERHOEVEN-ADEMA KW, PUTTER H, CREUTZBERG CL. 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. *Lancet Oncol* 2018; 19: 295-309.
- 8) BOOTHE D, WILLIAMS N, ODEI B, POPPE MM, WERNER TL, SUNEJA G, GAFFNEY DK. The addition of adjuvant chemotherapy to radiation in early-stage high-risk endometrial cancer: survival outcomes and patterns of care. *Int J Gynecol Cancer* 2017; 27: 912-922.
- 9) HIGGINS JP, ALTMAN DG, GOTZSCHE PC, JUNI P, MOHER D, OXMAN AD, SAVOVIC J, SCHULZ KF, WEEKS L, STERNE JA. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
- 10) MORROW CP, BUNDY BN, HOMESLEY HD, CREASMAN WT, HORNBACK NB, KURMAN R, THIGPEN JT. Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage I and occult stage II: a Gynecologic Oncology Group Study. *Gynecol Oncol* 1990; 36: 166-171.
- 11) RANDALL M, FILIACI V, McMEekin D, YASHAR CM, MANDEL R, SALANI R, DISILVESTRO P, BURKE J, RUTHERFORD T, SPIRTOS N, CHO J, KIM J, ANDERSON P, BREWSTER W, SMALL W, CARNEY M, AGHAJANIAN C, MILLER DS. Late-breaking abstract 1: a phase 3 trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high-risk, early-stage endometrial cancer: a gynecology oncology group study. *Int J Radiat Oncol Biol Phys* 2017; 99: 1313.

- 12) HOGBERG T, SIGNORELLI M, DE OLIVEIRA CF, FOSSATI R, LISSONI AA, SORBE B, ANDERSSON H, GRENMAN S, LUNDGREN C, ROSENBERG P, BOMAN K, THOLANDER B, SCAMBIA G, REED N, CORMIO G, TOGNON G, CLARKE J, SAWICKI T, ZOLA P, KRISTENSEN G. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. *Eur J Cancer* 2010; 46: 2422-2431.
- 13) OZGUL N, BOYRAZ G, SALMAN MC, GULTEKIN M, YUCE K, IBRAHIMOV A, ERTURK A, GUNGORDUK K, GULSEREN V, SANCİ M, TURKMEN O, KARALOK A, KIMYON G, TURAN T, OZKAN NT, MEYDANLI MM, GUNGOR T, AYIK H, SIMSEK T. Oncological outcomes of stage II endometrial cancer: a retrospective analysis of 250 cases. *Int J Gynecol Cancer* 2018; 28: 161-167.
- 14) Yİ L, ZHANG H, ZOU J, LUO P, ZHANG J. Adjuvant chemo-radiotherapy versus radiotherapy alone in high-risk endometrial cancer: a systematic review and meta-analysis. *Gynecol Oncol* 2018; 149: 612-619.
- 15) KONG A, SIMERA I, COLLINGWOOD M, WILLIAMS C, KITCHENER H. Adjuvant radiotherapy for stage I endometrial cancer: systematic review and meta-analysis. *Ann Oncol* 2007; 18: 1595-1604.