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Review Article

Adjuvant chemoradiotherapy versus radiotherapy alone in high-risk endometrial cancer: A systematic review and meta-analysis

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HIGHLIGHTS

- Systematic review and meta-analysis of high-risk endometrial cancer (FIGO stages I–III).
- Includes 6 randomized trials comparing chemoradiotherapy vs. radiotherapy alone.
- Chemoradiotherapy significantly improves progression-free survival and cancer-specific survival.
- Chemoradiotherapy provides no statistically significant improvement in overall survival and recurrence rates.
- Chemoradiotherapy significantly increases the incidence of acute toxicities.

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ABSTRACT

Background. The benefits of adjuvant chemoradiotherapy (CRT) for high-risk endometrial cancer (HREC) in International Federation of Gynecology and Obstetrics (FIGO) stages I-III remain controversial. A systematic review and meta-analysis was conducted to evaluate the clinical effectiveness and safety of postoperative CRT over radiotherapy (RT) alone, exclusively for patients with HREC for the following key endpoints: overall survival (OS), progression-free survival (PFS), the local recurrence rate, the distant metastasis rate, cancer-specific survival (CSS), grade III/IV acute and late toxicities, and the small bowel obstruction rate.

Methods. Five databases, namely, PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov, were systematically explored and supplemented by manual searching to identify relevant studies published before Dec 9, 2017. Only prospective randomized controlled trials (RCTs) conducted for HREC comparing CRT and RT alone after surgery were included. All statistical analyses were performed using RevMan Version 5.3 software.

Results. Six eligible trials involving 2105 patients were identified for the final meta-analysis (CRT: $n = 1064$; RT: $n = 1041$). No statistically significant differences were evident between the CRT and RT groups regarding OS ($n = 2105$, RR = 1.02, 95% CI 0.98–1.06, $P = 0.40$). Additionally, no differences were apparent in terms of the local recurrence rate ($n = 690$, RR = 0.48, 95% CI 0.19–1.18, $P = 0.11$) or distant metastasis rate ($n = 1445$, RR = 0.94, 95% CI 0.72–1.23, $P = 0.67$). However, CRT significantly prolonged overall five-year PFS (80.2% vs. 74.5%, +5.7%; RR = 1.08, $P = 0.005$) and five-year CSS (86.1% vs. 79.0%, +7.1%; RR = 1.09, $P = 0.03$). A higher incidence of grade III/IV toxicities ($P < 0.00001$) was evident with CRT, while grade III/IV late toxicities and the small bowel obstruction rate were not significantly different between the two groups.

Conclusions. For patients with endometrial cancers with stage I-III risk factors, adjuvant CRT can significantly improve PFS and CSS compared with RT. With the exception of increased acute toxicities, CRT is well accepted and tolerated in HREC patients.

Contents

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1. Introduction

With an estimated 310,000 new cases globally each year, endometrial cancer is a common gynecological malignancy that seriously threatens the health of women [1,2]. Approximately 70%–80% of patients present in the early stages, and consequently, most patients have favorable prognoses with surgical treatment alone [3,4]. However, patients in International Federation of Gynecology and Obstetrics (FIGO) stages I-III with specific factors, namely, a high histologic grade, myometrial invasion, lymphovascular space involvement (LVSI), lymph node involvement, and a specific pathological type of uterine papillary serous carcinoma (UPSC) or clear cell carcinoma (CCC), have shown an increased risk of both local recurrence and distant metastasis [5–9]. The Gynecologic Oncology Group (GOG) published a prospective study to analyze the risk of extrauterine recurrence in patients with early endometrial cancer. This study showed that patients with deep myometrial invasion and poorly differentiated histology had 34% and 23% chances of abdominal and para-aortic nodal involvement, respectively [7]. Recently, the Postoperative Radiation Therapy for Endometrial Carcinoma (PORTEC)-1 trial according to 15-year follow-up data revealed that high-risk endometrial cancer (HREC) patients with adjuvant radiotherapy (RT) alone had a distant metastasis rate of 9.3%, while the GOG 99 trial reported a similar 10% risk of distant recurrence [8,9]. Often, adjuvant chemotherapy or radiation therapy is applied to reduce the rate of recurrence. At present, the optimal postoperative adjuvant treatment for endometrial carcinoma is controversial [10].

Postoperative RT is an important adjuvant treatment for HREC patients. Previous studies have shown that adjuvant RT can reduce the local recurrence rate in HREC patients [11–13]. Studies have reported that external beam RT (EBRT) can control isolated local recurrence effectively, but there is no evidence that EBRT reduces the distant recurrence rate or improves overall survival (OS) [8,14]. Approximately 10%–15% of HRECs recur [15], and most of the patients eventually die from distant organ metastasis. Therefore, some scholars have noted that systemic chemotherapy is expected to eliminate small metastatic foci to reduce the recurrence rate [16,17]. The GOG 122 study was the first to confirm the status of adjuvant chemotherapy in the treatment of endometrial carcinoma. The results suggested that systemic chemotherapy could improve the OS and progression-free survival (PFS) times of the patients compared with whole abdominal irradiation (WAR), but a higher local recurrence rate was observed in the chemotherapy alone arm than in the WAR arm (18% vs. 13%) [18].

Due to differences in the effectiveness of survival, several different randomized controlled trials (RCTs) have compared the efficacy of chemoradiotherapy (CRT) to RT alone in the treatment of HREC after surgery. Nevertheless, the conclusions indicating that the addition of adjuvant chemotherapy to radiation can provide a variable therapeutic benefit, with either an improvement in PFS alone or no benefit at all, have led to controversy over the utility of the regimen; the combination therapy has increased acute toxicities, however, in most cases it did not lead to long-term or permanent effects, and the regimen is well tolerated [19–25]. A meta-analysis including three RCTs and three observational studies suggested that no significant difference in survival was evident with CRT for HREC in FIGO stages I-III; however, a significant difference in survival was evident with CRT for advanced-stage endometrial cancer [26]. This meta-analysis included patients with all FIGO stages and a small number of RCT samples. In addition, the inclusion of retrospective studies may have led to high potential bias risks and the low credibility of the results. Currently, there is insufficient evidence to suggest that patients with lesions limited to the uterus should routinely receive adjuvant therapy. Whether postoperative CRT rather than RT alone can improve OS, PFS, or other survival outcomes in endometrial cancer patients remains unclear. Furthermore, the characteristics of the patients who actually benefit from postoperative adjuvant CRT are not clearly defined. Therefore, a study that includes only HREC in FIGO stages I-III patients who receive either CRT or RT alone as adjuvant therapy is necessary to truly evaluate whether CRT provides any benefit over RT alone.

This systematic review and meta-analysis was conducted to determine the impacts of these treatment strategies on efficacy and safety for patients with HREC receiving either CRT or RT alone. Efficacy was evaluated with key therapeutic endpoints, and grade III/IV acute and late toxicities were examined.

2. Materials and methods

2.1. Search strategy

This systematic review was performed based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table S1) [27]. The RCTs of patients with endometrial cancer randomly subjected to CRT or RT alone were searched in five databases: PubMed, EMBASE, Cochrane library, Web of Science, and ClinicalTrials.gov. The last search was performed on Dec 9, 2017. The Medical Subject Headings (MeSH) terms used were “Endometrial Neoplasms,” “Radiotherapy,” and “Drug therapy.” The search was limited to RCTs and had no date or language restrictions. Furthermore, additional relevant studies were retrieved manually. The detailed search strategy for each database is described in the supplemental materials (Supplementary Table S2).

2.2. Selection criteria

The inclusion criteria in this meta-analysis were as follows: (a) histologically verified endometrial cancer; (b) International FIGO stage I to stage III disease with one or more of seven high-risk features after surgery, namely, grade III histology (G3), deep invasion of the myometrium, lymphovascular space involvement (LVSI), pelvic or para-aortic nodal metastasis, cervical involvement,

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