

Original Article

Meta-analysis of cisplatin-based chemotherapy combination with radiotherapy versus radiotherapy alone in the treatment of locally advanced cervical carcinoma

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Abstract: Objective: To systematically assess the efficacy of chemotherapy based on cisplatin combination with radiotherapy versus radiotherapy alone in the treatment of locally advanced cervical carcinoma. Methods: We comprehensively searched EMBase, PubMed, the Cochrane Library, VIP, CNKI, Chinese biomedicine literature database for randomized controlled trials comparing chemotherapy combination with radiotherapy versus radiotherapy alone in the treatment of locally advanced cervical carcinoma. Two reviewers independently assessed the quality of included studies and extracted data. We analyzed the data using Review Manager (version 5.2). Results: Nine randomized controlled trials were included totally. Meta-analysis showed that there were statistical difference between the radiotherapy alone group and chemotherapy combination with radiotherapy group in overall survival rate (RR = 1.62, 95% CI: 1.34-1.95) and overall response rate (RR = 2.09, 95% CI: 1.642-2.65). Conclusion: Current evidence indicated that compared with radiotherapy alone, chemotherapy combination with radiotherapy could improve overall survival rate and overall response rate for patient with locally advanced cervical carcinoma.

Keywords: Uterine cervical neoplasms, radiotherapy, drug therapy, meta-analysis

Introduction

Cervical cancer is the most common female malignancy with the morbidity and mortality second only to breast cancer [1]. The main treatment methods for cervical cancer are surgery (at early stage) and radiotherapy (advanced stages). The current international trends in the treatment emphasize comprehensive treatment. In the 1990s, the US National Cancer Institute used cisplatin-based concurrent chemoradiotherapy as standard therapy in the treatment of advanced cervical cancer model [2]. Radiotherapy alone has a higher cure rate for smaller tumors, while for larger tumors, it is difficult to achieve a cure by radiotherapy [3]. Chemotherapy can eliminate subclinical lesions; a large number of clinical studies have shown that application of radiation sensitizer, particularly low-dose chemotherapy drugs, can increase radiotherapy sensitivity, reduce the radiation dose and long-term complications of radiotherapy, and improve the quality of life of

patients [4]. Currently, concurrent chemoradiotherapy is one of the most promising research directions in comprehensive treatments. In recent years, although there are some reports on the efficacy of concurrent chemoradiotherapy for cervical cancer and the comparison with radiotherapy alone [5, 6], recent literatures are not included. In order to objectively evaluate the safety and efficacy of concurrent chemoradiotherapy in the treatment of advanced cervical cancer, this study systematically evaluated the results of randomized controlled trials on concurrent chemoradiotherapy and radiotherapy alone in cervical cancer and compared the effectiveness and improvement of patient survival to provide a basis for clinical decision.

Material and methods

Inclusion and exclusion criteria

We included the studies designed as Randomized controlled trials (RCT). And the subjects

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met to the following criteria: 1) Cervical cancer patients confirmed by cytology or pathology examination; 2) The test group received concurrent chemoradiotherapy and the control group received radiotherapy; 3) The initial treated patients had not accepted prior radiotherapy, chemotherapy and biological therapy; 4) Cancer without distant metastasis; 5) Functions of vital organs were normal.

The intervention methods are 1) the test group received chemoradiotherapy and 2) the control group received radiotherapy.

We excluded the studies if 1) the patients who had allergy history of chemotherapy drugs and the allergies, and 2) who are pregnant and lactating women.

Document retrieval

We searched EmMBase, PubMed, the Cochrane Library, VIP, CNKI, Chinese biomedicine literature database using the following search terms: "radio chemotherapy", "radiation", "radiotherapy", "cervical cancer", "cervical carcinoma", "randomized controlled trial", and "cisplatin". The language of literature was not restricted.

Literature screening and data extraction

Two researchers firstly independently screened the literatures. If there are difficult to determine whether to include, they were addressed by the group discussion. Two researchers independently extracted the data, filled form using the extracted information and cross-checked the extracted information. For the literatures which lack of information, we tried to contact the authors to make up.

Quality assessment

The methodological quality assessment was performed on included literatures. Cochrane handbook systematic evaluation method was used. Quality assessment included the following four areas: 1) whether the random method was correct; 2) whether using allocation concealment (concealment of allocation); 3) whether using blinded method; 4) whether described the occurrence of lost and withdraw. If the patients have quitted or lost, whether or not the intention to treat analysis was performed. Two reviewers independently evaluated the quality of literature, through discussion or contact the

original author to determine if there was controversy.

Statistical analysis

Cochrane collaboration's RevMan 5.2 statistical software was used for statistical analysis. Count data were expressed with risk ratio (risk ratio, RR) or odds ratio (odds ratio, OR). Measurement data were expressed with the weighted mean difference (weighted mean, difference, MD) or standard mean difference (standard, mean, difference, SMD) and the 95% confidence interval (confidence interval, CI) said. If there was no statistical heterogeneity ($I^2 < 50\%$, $P < 0.1$) in the included studies, the fixed effect model was used in the Meta analysis; conversely, if there was statistical heterogeneity between the studies ($I^2 < 50\%$, $P < 0.1$) and without significant clinical heterogeneity, the random effects model was used for analysis and carefully interpreting the results. If there is significant clinical heterogeneity, descriptive analysis was used. If there were enough incorporated researches, then the funnel plot analysis was observed to determine whether the presence of publication bias was exist.

Results

Literature search results and the Characteristics of included studies

512 documents were obtained after initial selection. Two reviewers excluded 401 documents obviously inconsistent with the inclusion criteria by reading the title and abstract. Remaining documents were further evaluated by pre-reading full text; after initial and rescreening, ultimately 9 randomized controlled trials were included [7-15], including 6 English documents and 3 Chinese documents. All included studies were comparable at baseline. The basic characteristics of the included studies were shown in **Table 1**.

Quality assessment of included studies

The majority of included documents had high quality. Most literature reported the generation of random sequences in detail. Center randomization and allocation concealment were used in most studies. The blinding cannot be implemented in this study, so none of included studies used blinding method. The majority of rese-

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Table 1. The characteristics of included studies

Studies	Publication Year	Country	Sample size	TNM	Chemotherapy	Randomization	Allocation concealment	Blind method	Intentional analysis	Jadad score
Morris et al.	1999	USA	195/193	Ib-Iva	Cisplatin + Fluorouracil	Yes	Yes	No	Yes	5
Keys et al.	1999	USA	183/186	Ib	Cisplatin	Yes	Yes	No	Yes	5
Peters et al.	2000	USA	127/116	Ia-IIb	Cisplatin + Fluorouracil	Yes	Yes	No	Yes	5
Herod et al.	2000	UK	86/86	Ib-Iva	Cisplatin + Bleomycin + Ifosfamide	Yes	Yes	No	Yes	5
Pearcey et al.	2002	Canada	127/126	Ib-Iva	Cisplatin	Yes	Yes	No	Yes	5
Cheng et al.	2007	China	32/30	IIb-IIIb	Cisplatin + Gemcitabine	Yes	No	No	No	5
Liu et al.	2007	China	29/29	IIb-IIIb	Cisplatin + Fluorouracil	No	No	No	No	4
Nagy et al.	2009	Romania	282/284	IIb-IIIb	Cisplatin	Yes	Yes	No	Yes	5
Zhu et al.	2010	China	60/60	IIb-Iva	Cisplatin	No	No	No	No	4

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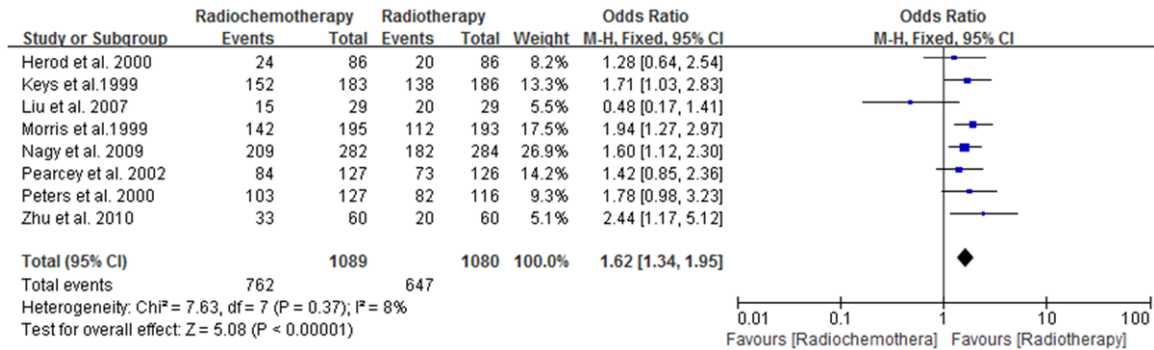


Figure 1. Forest plot of cisplatin-based chemotherapy combination with radiotherapy versus radiotherapy alone in the treatment of locally advanced cervical carcinoma (Overall survival).

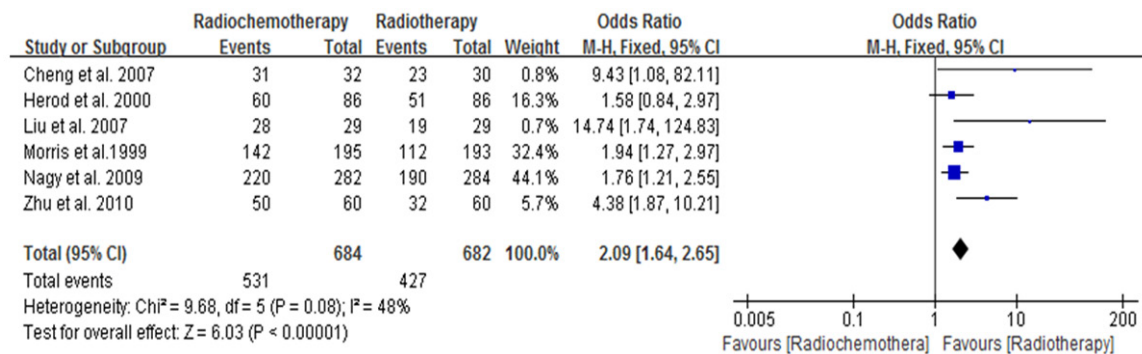


Figure 2. Forest plot of cisplatin-based chemotherapy combination with radiotherapy versus radiotherapy alone in the treatment of locally advanced cervical carcinoma (Effect rate).

arch had reported the number of lost and used intention analysis approach. Quality assessment was shown in **Table 1**.

Meta-analysis results

Overall survival: Eight studies reported overall survival. 2169 patients with locally advanced cervical cancer were included, including 1089 patients in chemoradiotherapy group and 1080 patients in radiotherapy alone group. Meta-analysis showed that: There was statistical homogeneity among the included studies ($I^2 = 8\%$, $P = 0.37$), therefore, the fixed effects model was used. There were statistically significant differences in overall survival between the two groups (OR: 1.62, 95% CI: 1.34-1.95, $P < 0.0001$, **Figure 1**).

Effective rate: Six studies had reported the effective rate. Totally 1366 patients with locally advanced cervical cancer were included, including 684 patients in chemoradiotherapy group and 682 patients in radiotherapy alone

group. There were statistically significant differences in overall effective rate between two groups (OR: 2.09, 95% CI: 1.64-2.65, $P < 0.0001$), shown in **Figure 2**.

Funnel plot: Funnel plot showed that the included literature were basically at the bottom of the funnel and basically symmetrical, suggesting low possibility of published bias in the included studies, shown in **Figure 3**.

Discussion

The prognosis of patients with locally advanced cervical cancer is often poor, so how to improve its therapeutic effect has become the focus of scholars. To this end, since the 1980s concurrent chemoradiotherapy began to be used in the treatment of cervical cancer. However, some scholars believe that toxicity of concurrent chemoradiotherapy is greater. Therefore, this study compared the effectiveness of concurrent chemoradiotherapy and radiotherapy alone in treating locally advanced cervical can-

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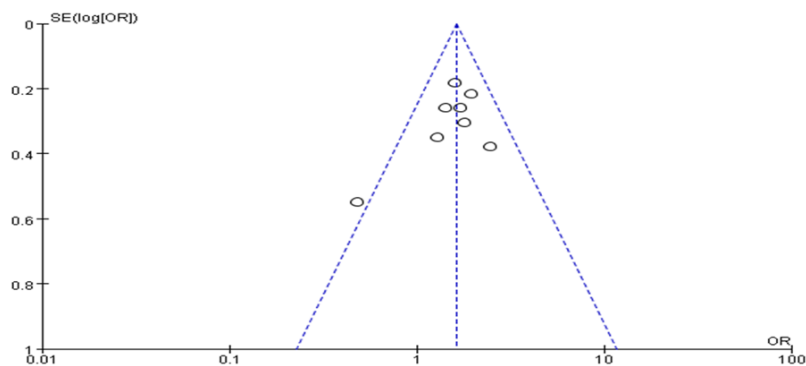


Figure 3. Funnel plot for publication bias tests.

cer by Meta-analysis. The results showed that there was statistically significant difference in overall survival and overall efficiency between concurrent chemoradiotherapy group and radiotherapy group, suggesting that the efficacy of concurrent chemoradiotherapy was superior to radiotherapy alone and it can improve overall survival in patients with locally advanced cervical cancer.

Studies have shown that concurrent radiotherapy and chemotherapy may improve the therapeutic effect through the following mechanisms: (1) inhibiting the repair of radiation damage to reduce the further proliferation of tumor cells; (2) reducing the tumor size to prompt further oxygenation of hypoxic cells, thus increasing cell radiotherapy sensitivity; (3) promoting more cells in G0 phase enter into the cell cycle and synchronize the tumor cells to increase radiation dose-response curve gradients and induce tumor cell death [4]. However, current studies mostly focus on the preoperative and postoperative concurrent chemoradiotherapy or concurrent chemoradiotherapy alone. Although the present findings suggest that concurrent chemotherapy can improve the survival of patients, this research is still unable to determine the best treatment option and dose. At present, domestic and foreign scholars recommend cisplatin-based chemotherapy, mainly because that cisplatin can intensify the free tumor genes and inhibit the repair itself of tumor cells to radiation damage.

Morris et al [7] and Nagy et al [14] found that fluorouracil could affect the cells in S phase, delay cells in the G1/S boundary, and inhibit DNA repair of radiation damage; while radiore-sistant peaks often appear in S and G1 phase.

For locally advanced cervical cancer, cisplatin + fluorouracil chemotherapy synchronously combined with radiotherapy is better than radiotherapy alone, which can significantly reduce local and distant recurrence and improve overall survival. Compared with radiotherapy alone, concurrent chemoradiotherapy may benefit the survival of all cervical cancer patients.

Keys et al [8] and Peters et al [9] randomly divided patients with risk factors [node-positive and (or) positive margin and (or) microscopic parametrial invasion] into concurrent chemoradiotherapy group and postoperative radiotherapy alone group after radical cervical cancer surgery, and pointed out that postoperative adjuvant concurrent chemoradiotherapy of early cervical cancer with risk factors can improve survival and reduce the recurrence rate, which can be used as the new guideline for cervical cancer treatment. Peters et al [9] also believed that in patients with poor prognosis, such as gland adenocarcinoma and squamous cell carcinoma patients, the application of postoperative concurrent chemoradiotherapy can improve progression-free survival. Herod et al [10] reported that cisplatin-based concurrent chemoradiotherapy can significantly reduce the rate of invasion and metastasis and improve disease-free survival. Cheng et al [12] considered that the three-dimensional conformal radiotherapy combined with concurrent chemotherapy in the treatment of advanced cervical cancer can improve the short-time efficiency. Liu et al [13] believed that cisplatin + fluorouracil chemotherapy concurrently in combination with radiotherapy in the treatment of advanced cervical cancer could improve the local control rate of patients, reduce pelvic recurrence and distant metastasis rate, and improve the efficacy and survival. Zhu et al [15] considered that cisplatin chemotherapy combined with concurrent radiotherapy was the ideal option in treating advanced cervical cancer. Concurrent chemoradiotherapy improved local tumor control rate, eliminated small metastases, reduced the rate of recurrence and metastasis, increased radiosensitivity of the tumor, thereby increasing the 5-year survival and disease-free

survival. On the selection of concurrent chemoradiotherapy programs, domestic and foreign researchers recognize cisplatin-based chemotherapy, but there is a big difference in the specific drug choices, which to some extent will affect the internal validity of this study.

Most studies did not report the chemotherapy-related toxicity, so this study did not quantitatively evaluate the safety indicators; and all the included studies showed that the majority of patients were able to tolerate concurrent chemoradiotherapy.

In conclusion, the concurrent chemoradiotherapy, compared with radiotherapy alone, can improve the efficiency and survival in patients with locally advanced cervical cancer. However, the toxicity of chemotherapy drugs may increase the patient's response to treatment, resulting in decreased treatment compliance. There were differences in pathological stage, radiation dose and chemotherapy regimens of patients among included studies, and there were some differences in treatment regimens among various countries, which affected the internal validity of this study to some extent, so how to choose the best drug, program, course, medication way and chemotherapy treatment matching with radiotherapy requires further exploration.

Disclosure of conflict of interest

None.

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