Systematic review/Meta-analysis

Efficacy and safety of radio-chemotherapy combined with thermotherapy for advanced cervical cancer in Chinese women: a meta-analysis

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Abstract

Introduction: Pelvic deep hyperthermia is an important treatment method for cervical cancer, and it has been widely used in Chinese clinics. However, this approach has not been widely adopted all over the world because of its uncertain efficacy and safety. This meta-analysis aims to review the efficacy and safety of radio-chemotherapy combined with local hyperthermia (HT) in the treatment of cervical cancer.

Material and methods: We searched foreign and domestic databases, and also searched the related references for additional information. Data extraction and quality assessment were conducted by two reviewers independently. Rev Man 5.3 software was used to perform the meta-analysis.

Results: The thermotherapy group had a significantly higher 1-year tumor-free survival rate (OR = 2.84, 95% CI (1.14–7.09), $p = 0.03$), complete remission rate (OR = 2.41, 95% CI (1.94–3.01), $p < 0.00001$) and overall effective rate (OR = 4.11, 95% CI (3.11–5.44), $p < 0.00001$) than the sole radio-chemotherapy group. The thermotherapy group had a significantly lower disease stability rate (OR = 0.44, 95% CI (0.32–0.62), $p < 0.00001$) and disease progression rate (OR = 0.15, 95% CI (0.08–0.28), $p < 0.00001$) when compared with the sole radio-chemotherapy group. Both groups were statistically similar with respect to adverse reactions.

Conclusions: Radio-chemotherapy combined with thermotherapy could significantly improve short-term curative effects for patients with cervical cancer. However, due to the limited quantity and quality of the included studies, more high-quality studies with a large sample size and long-term follow-up are still needed to verify the above conclusion and explore its long-term efficacy.

Key words: cervical cancer, thermotherapy, radio-chemotherapy, efficacy, meta-analysis.

Introduction

Cervical cancer is one of the most common gynecological malignancies, and also a serious threat to female physical and mental health. There are about 528,000 new cases of cervical cancer every year in the world, of which about 27,000 die of this disease [1]. Currently, combination of radiotherapy with chemotherapy is widely used and also acts as a standard treatment with excellent local control and low toxicity [2, 3]. However, its long-term survival rate has still not reached the intend-

ed effect. Studies in the early 1990s had already explored the effectiveness of hyperthermia as an adjuvant therapy for radiotherapy or chemotherapy in treating advanced cervical cancer [4]. Recently, locally pelvic deep hyperthermia as an important treatment for cervical cancer has been widely used in clinics, its therapeutic effect has gained great recognition [5–7], and it has already become a conventional adjuvant therapy for cervical cancer treatment in China. However, the randomized controlled trials (RCTs) are mostly small sample size and single-center studies with much lower reliability, thus hindering the thermotherapy widely used in clinical practice all over the world. Therefore, in this meta-analysis, we systematically evaluated the efficacy and safety of local hyperthermia combined with radio-chemotherapy in treating cervical cancer to provide a more reliable basis in clinical application and research.

Material and methods

Literature inclusion and exclusion criteria

(1) Studies are randomized controlled trials (RCTs). (2) Studies focused on patients with cervical cancer and without radio-chemotherapy and thermotherapy contraindications, and the age of patients is not limited. (3) Comparative studies were between radio-chemotherapy (CRT) and CRT + local hyperthermia (HT). (4) Efficacy determination was conducted according to the solid tumor efficacy evaluation criteria. Outcome index included: a. long-term efficacy (3-year survival rate, 3-year SR); b. short-term efficacy (1-year tumor-free survival rate, 1-year TFSR), complete remission rate (CRR), partial remission rate (PRR), overall effective rate (OER); disease stability rate (SDR); disease progression rate (PDR); c. the acute-care side effect including gastrointestinal reaction, bone marrow suppression and bladder reaction. (5) Studies with sample size < 50 cases, repeat publications, non-original studies, animal tests or preclinical trials, and abstract-only publications were excluded.

Search strategy

We searched for studies comparing HCRT with CRT for the treatment of cervical cancer using Cochrane Library, PubMed and Embase, along with four domestic databases (CBM, VIP, CNKI, and Wan Fang Data). Retrieval time was from 1 January 2000 to 31 December 2016. The combination of subject search with free word examination approach was adopted for retrieval. The search terms were: "cervical cancer", "uterine neoplasms/cancer", "gynecologic cancer", "radiotherapy", "chemotherapy", "drug therapy", "thermotherapy", "hyperthermia", "fever", "heat and randomized controlled trials". The literature was incorporated on radiotherapy and chemotherapy combined with hyperthermia in the treatment of advanced cervical cancer, and the relevant literature was also searched on the Internet.

Data extraction and quality assessment

Two reviewers independently extracted the safety and efficacy indexes into a prospective data extraction form and checked them twice. Disagreements were resolved by discussing or consulting the third author. The methodological quality of the included studies was assessed using the RCT risk-based assessment tool based on the Cochrane System Reviewer's Manual 5.3. The main contents of the data extraction included the first author, publication date, grouping method, Karnofsky score, FIGO stage, pathological type, radiotherapy, and chemotherapy. The outcomes such as survival rate, complete remission rate, partial remission rate, overall effective rate, and the related incidence of adverse reactions were extracted. According to the RECIST (Provide Evaluation Criteria in Solid Tumors) definition, complete remission (CR) means all lesions disappeared completely and no new lesions appeared, and tumor markers dropped to normal levels for 4 weeks. Partial remission (PR) means that the largest diameter of the tumor decreased by > 30%, and was maintained for 4 weeks. Stabilization (SD): lesions increased less than in PD, and decreased less than in PR. Progress (PD): lesion diameter increased > 20%, or the emergence of new lesions. The total effective rate or overall effective rate is (OR) = (CR + PR)/total number of cases × 100%.

Statistical analysis

The meta-analysis was conducted using Review Manager 5.3 (RevMan, The Cochrane Collaboration, Oxford, UK). The Cochrane-Q statistic and the I^2 statistic were used to assess statistical heterogeneity. The χ^2 test was used to analyze the heterogeneity of all the included studies. Inspection level is $\alpha = 0.1$, and p-value ≥ 0.10 and I^2 values ≤ 50% illustrated that the selected studies were consistent with homogeneity, which was suitable for a fixed-effect model for meta-analysis; If p-value < 0.10 as well as I^2 values < 50%, it showed that heterogeneity existed among the studies but within an acceptable range, which also used the fixed-effect model meta-analysis; When the p-value < 0.10 and I^2 values > 50%, it indicated greater heterogeneity among the results, which necessitated further analysis of its sources of heterogeneity. If without obvious clinical heterogeneity, the random-effect model can be used for analysis; if heterogeneity is extremely obvious, descriptive analysis was chosen. Odds ratios (ORs)

and 95% confidence intervals (CIs) were used as the summary variables for final outcomes.

Results

Description of selected studies and quality assessment

A total of 471 articles were related to the initial examination. After reading the abstracts as well as the full texts, irrelevant or non-comparative studies, reviews, abstracts, case reports, repeated and narrative studies, small sample studies, non-RCTs and seriously missing data studies were excluded, and after the first meta-analysis, papers of low quality were removed. Finally, 19 RCTs were included in the study for further analysis. The flow diagram for study selection is shown in Figure 1. The characteristics of the included studies are summarized in Table I [8–26]. Although some missing data were not adequately described in some studies, the results showed that the basic information between the test group and the control group had good comparability, which suggested that the investigations included in this study were of high quality.

Short-term efficacy

For 1-year tumor-free survival rate (1-year TFSR), five studies with a total of 615 patients were included in this analysis. When compared with the CRT group, the HCRT (hyperthermia and radio-chemotherapy) group had significantly improved 1-year TFSR (OR = 2.84, 95% CI: 1.14–7.09, $p = 0.03$) (Figure 2 A). Eighteen studies described the CRR, and the fixed-effects model of meta-analysis showed that CRR was significantly higher in the HCRT group than in the CRT group (OR =2.41, 95% CI: 1.94–3.01, $p < 0.00001$) (Figure 2 B). The partial remission rates (PRR) of both CRT and HCRT groups were statistically similar (OR = 0.92, 95% CI: 0.72–1.17) (Figure 2 C). The benefit to the OER was significantly higher in the HCRT group than in the CRT group (OR = 4.11, 95% CI: 3.11–5.44, $p < 0.00001$) (Figure 3). Additionally, the HCRT group had a significantly lower SDR (OR = 0.44, 95% CI: 0.32–0.62, $p < 0.00001$) (Figure 4 A) and PDR (OR = 0.15, 95% CI: 0.08–0.28, $p < 0.00001$) (Figure 4 B).

Long-term efficacy

The long-term efficacy was evaluated by the 3-year survival rate at the end of the treatment. Only three of the included studies compared the 3-year survival rate between the HCRT group and the CRT group, and the meta-analysis showed that the 3-year survival rate of the HCRT group was similar to that of the CRT group, without statistical significance (OR = 1.17, 95% CI: 0.80–1.72, $p = 0.42$) (Figure 5).

Adverse effects in different groups

Fourteen studies reported the incidences for gastrointestinal disorders and the bone marrow

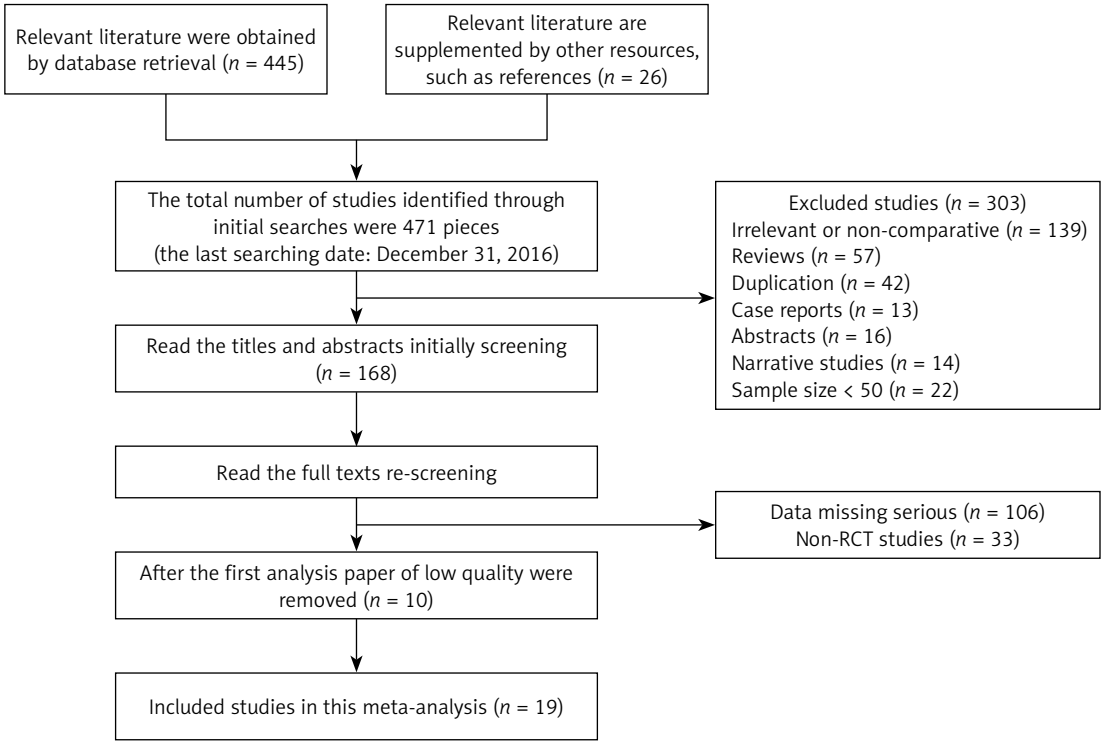


Figure 1. Flow diagram of the literature search and study selection

Table I. Characteristics of included RCTs

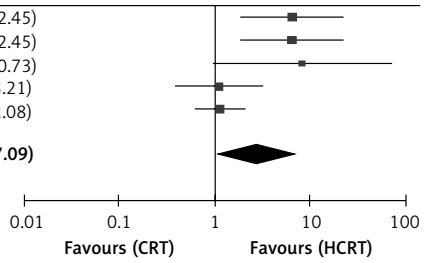
Study (author + year)	KPS score	Cases (T/C)	FIGO stage	Pathological type (S/A/AS)	Radiotherapy	Chemotherapy	Hyperthermia intensity	Outcome index	Adverse reactions
Pang 2016 [8]	Unclear	46/46	Unclear	Unclear	Unclear	DDP 6 times	Twice a week for 12 times	CR, PR, OE, SD, PD	Unclear
Yang 2016 [9]	≥ 70	100/100	IIb–IIIb	187/9/4	Conventional fractionated and endoluminal radiotherapy	DDP 6 times	41.8–42°C once a week for 4 times	CR, PR, OE, SD, PD	Unclear
Lei 2016 [10]	≥ 80	30/30	IIIb	53/6/1	Extracavitary and intracavitary radiotherapy	DDP 6 times	Twice a week for 12 times	CR, PR, OE, SD, PD	GR, BS, BR
Zhang 2016 [11]	≥ 60	149/149	IIb–IIIb	249/49/0	Conventional fractionated radiotherapy	DDP 6 times	40–41.5°C twice a week for 6 times	OE, 1 SR, 3 SR	Unclear
Xiang 2015 [12]	≥ 70	43/42	IIb–IIIb	85/0/0	Extracavitary and intracavitary radiotherapy	DDP 6 times	40–41°C twice a week for 10 times	CR, PR, OE, SD, 3 SR	GR, BS, BR
Li 2015 [13]	≥ 70	43/43	IIIa–IIIb	75/9/2	Pelvic 4 field and intracavitary radiotherapy	DDP 6 times	43°C twice a week for 16 times	CR, PR, OE, SD, PD	Unclear
Yan 2015 [14]	≥ 70	48/49	IIb–IIIb	81/16/0	Conventional fractionated radiotherapy	DDP 6 times	39–41.5°C twice a week for 6 times	CR, PR, OE , 1 SR, 3 SR	Unclear
Wang 2014 [15]	≥ 70	40/40	IIb–IIIb	Unclear	Extracavitary and intracavitary radiotherapy	TAX + DDP 6 times	42–43°C twice a week for 6 times	CR, PR, OE, SD, PD, 1 SR	GR, BS, BR
Tian 2014 [16]	≥ 80	103/103	IIb–IIIb	176/30/0	Intracavitary brachytherapy	DDP 6 times	42–45°C twice a week for 12 times	CR, PR, OE, SD	GR, BS, BR
Wang 2014 [17]	≥ 70	27/27	IIb–IVa	54/0/0	Extracavitary and intracavitary radiotherapy	TAX + DDP 6 times	43–45°C twice a week for 10 times	CR, PR, OE, SD, PD	GR, BS, BR
Liu 2014 [18]	≥ 70	32/30	IIb–IVa	62/0/0	Extracavitary and intracavitary radiotherapy	DDP + 5-FU 4 times	41–42°C twice a week for 10 times	CR, PR, OE, SD, PD	GR, BS, BR
Mao 2014 [19]	≥ 60	30/30	IIb–IIIb	55/5/0	Pelvic 4 field and intracavitary radiotherapy	DDP + 5-FU 4 times	40–42°C twice a week for 8 times	CR, PR, OE, SD, PD	GR, BS, BR
Xu 2014 [20]	≥ 70	23/23	IIb–IIIb	38/1/7	Conventional fractionated radiotherapy	DDP 5 times	40–42°C once a week for 4 times	CR, PR, OE, SD, PD	GR, BS
Yang 2013 [21]	Unclear	50/52	IIb–IIIb	88/9/5	Extracavitary and intracavitary radiotherapy	DDP 6 times	Once a week for 5 times	CR, PR, OE, SD, PD	GR, BS
Du 2013 [22]	≥ 70	39/39	IIb–IIIb	66/10/2	Conventional fractionated radiotherapy	DDP 6 times	42–45°C twice a week for 12 times	CR, PR, OE, SD, PD	GR, BS
Qi 2013 [23]	≥ 70	29/29	IIb–IIIb	Unclear	Conventional fractionated radiotherapy	DDP 6 times	42–45°C twice a week for 12 times	CR, PR, OE, SD, PD	GR, BS
Ma 2011 [24]	≥ 70	35/35	IIIb	66/3/1	Conventional fractionated radiotherapy	DDP 6 times	Once a week for 4 times	CR, PR, OE, SD, PD	GR, BS, BR
Xu 2011 [25]	≥ 70	69/69	IIIa–IIIb	138/0/0	Extracavitary and intracavitary radiotherapy	DDP 6 times	42–44°C twice a week for 12 times	CR, PR, OE, SD, PD	GR, BS, BR
Dong 2011 [26]	≥ 70	35/35	IIb–IIIb	66/3/1	Conventional fractionated radiotherapy	DDP 6 times	Once a week for 4 times	CR, PR, OE, SD, PD	Unclear

RT – test (HCRT) group, C – control (CRT) group, S – squamous cell carcinoma, A – adenocarcinoma, AS – adenosquamous carcinoma, CR – complete remission, PR – partial remission, OE – overall effective rate, SD – disease stability, PD – disease progression, 1SR – 1-year tumor-free survival rate, 3SR – 3-year survival rate, GR – gastrointestinal reaction, BS – bone marrow suppression, BR – bladder reaction, DDP – cisplatin, 5-FU – 5-fluorouracil, TAX – paclitaxel.

A

Study or subgroup	HCRT Events	HCRT Total	CRT Events	CRT Total	Weight (%)	Odds ratio M-H, random, 95% CI
Dong 2011	31	35	19	35	19.7	6.53 (1.90–22.45)
Ma 2011	31	35	19	35	19.7	6.53 (1.90–22.45)
Wang 2014	39	40	33	40	11.4	8.27 (0.97–70.73)
Yan 2015	40	48	40	49	21.9	1.13 (0.39–3.21)
Zhang 2016	124	149	121	149	27.2	1.15 (0.63–2.08)
Total (95% CI)		**307**		**308**	**100**	**2.84 (1.14–7.09)**
Total events	265		232			

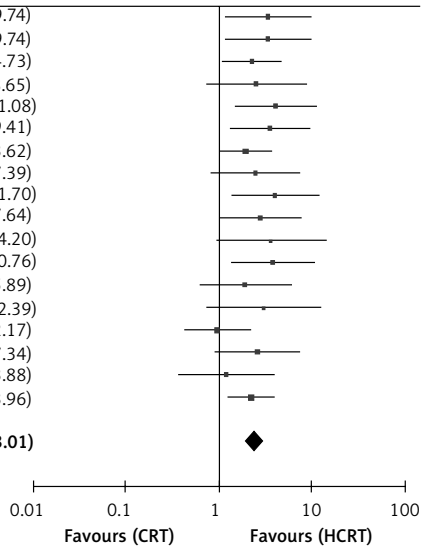
Heterogeneity: $\tau^2 = 0.71$, $\chi^2 = 13.29$, $df = 4$ ($p = 0.010$), $I^2 = 70\%$
Test for overall effect: $Z = 2.24$ ($p = 0.03$)



B

Study or subgroup	HCRT Events	HCRT Total	CRT Events	CRT Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Ma 2011	28	35	19	35	3.6	3.37 (1.16–9.74)
Dong 2011	28	35	19	35	3.6	3.37 (1.16–9.74)
Xu 2011	53	69	41	69	9.1	2.26 (1.08–4.73)
Qi 2013	24	29	19	29	3.1	2.53 (0.74–8.65)
Du 2013	31	39	19	39	3.7	4.08 (1.50–11.08)
Yang 2013	43	50	33	52	4.3	3.54 (1.33–9.41)
Tian 2014	82	103	69	103	13.4	1.92 (1.02–3.62)
Wang 2014	17	27	11	27	3.9	2.47 (0.83–7.39)
Mao 2014	20	30	10	30	3.2	4.00 (1.37–11.70)
Liu 2014	20	32	12	32	4.3	2.78 (1.01–7.64)
Xu 2014	10	23	4	23	2.2	3.65 (0.94–14.20)
Wang 2014	33	40	22	40	3.7	3.86 (1.38–10.76)
Xiang 2015	37	43	32	42	4.3	1.93 (0.63–5.89)
Li 2015	8	43	3	43	2.3	3.05 (0.75–12.39)
Yan 2015	28	48	29	49	11.4	0.97 (0.43–2.17)
Lei 2016	19	30	12	30	4.2	2.59 (0.91–7.34)
Pang 2016	7	46	6	46	4.9	1.20 (0.37–3.88)
Yang 2016	69	100	50	100	14.8	2.23 (1.25–3.96)
Total (95% CI)		**822**		**824**	**100**	**2.41 (1.94–3.01)**
Total events	557		410			

Heterogeneity: $\chi^2 = 11.67$, $df = 17$ ($p = 0.82$), $I^2 = 0\%$
Test for overall effect: $Z = 7.90$ ($p < 0.00001$)



C

Study or subgroup	HCRT Events	HCRT Total	CRT Events	CRT Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Dong 2011	6	35	8	35	4.9	0.70 (0.21–2.28)
Xu 2011	9	69	10	69	6.5	0.89 (0.34–2.33)
Ma 2011	6	35	8	35	4.9	0.70 (0.21–2.28)
Du 2013	5	39	3	39	1.9	1.76 (0.39–7.96)
Qi 2013	3	29	2	29	1.3	1.56 (0.24–10.09)
Yang 2013	5	50	8	52	5.2	0.61 (0.19–2.01)
Xu 2014	12	23	11	23	3.9	1.19 (0.37–3.78)
Liu 2014	11	32	9	30	4.5	1.22 (0.42–3.56)
Wang 2014	9	27	8	27	4.0	1.19 (0.38–3.75)
Mao 2014	6	30	8	30	4.8	0.69 (0.21–2.30)
Tian 2014	13	103	21	103	13.6	0.56 (0.27–1.20)
Wang 2014	4	40	7	40	4.7	0.52 (0.14–1.95)
Yan 2015	8	48	4	49	2.5	2.25 (0.63–8.04)
Xiang 2015	6	43	4	42	2.6	1.54 (0.40–5.91)
Li 2015	14	43	12	43	6.0	1.25 (0.50–3.14)
Yang 2016	28	100	37	100	19.8	0.66 (0.36–1.20)
Pang 2016	39	46	33	46	3.7	2.19 (0.78–6.14)
Lei 2016	7	30	9	30	5.1	0.71 (0.22–2.25)
Total (95% CI)		**822**		**822**	**100**	**0.92 (0.72–1.17)**
Total events	191		202			

Heterogeneity: $\chi^2 = 12.08$, $df = 17$ ($p = 0.80$), $I^2 = 0\%$
Test for overall effect: $Z = 0.71$ ($p = 0.48$)

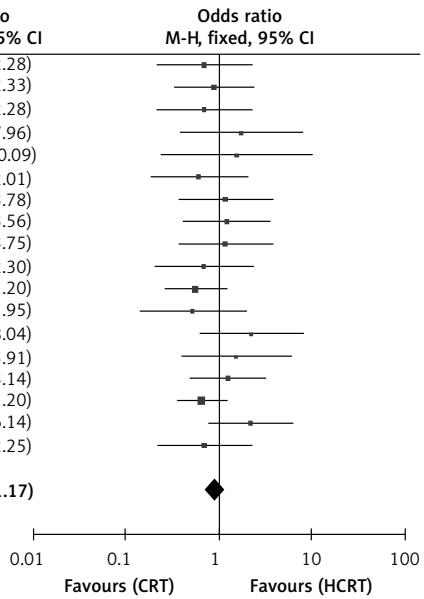


Figure 2. Forest plot for meta-analysis of the short-term efficacy of 1-year tumor-free survival rate (1-year TFSR (**A**)), complete remission rate (CRR (**B**)), and progression rate (PRR (**C**)) between the CRT group and the HCRT group

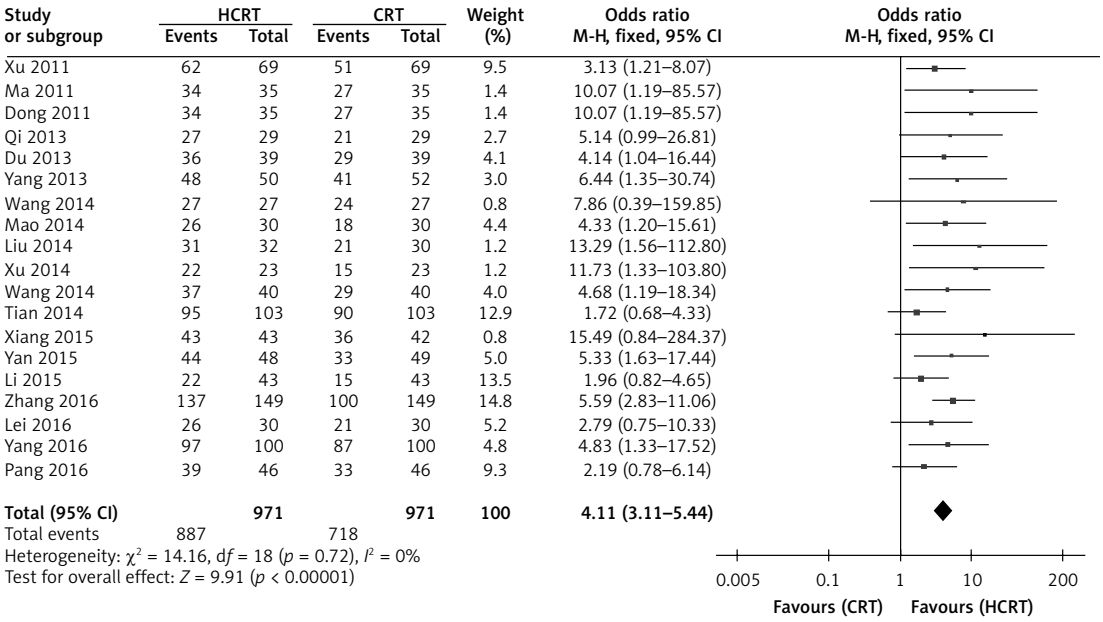


Figure 3. Forest plot for meta-analysis of the overall effective rate (OER) between the CRT group and the HCRT group

suppression and 10 studies reported about bladder problems. The investigations included in this study were without statistical heterogeneity, so the fixed-effect model was used for meta-analysis and the results showed that the CRT and HCRT groups were statistically similar with respect to gastrointestinal disorders, bone marrow suppression and bladder problems (Table II).

Publication bias

The funnel plot analysis of the overall effective rate showed that the symmetry of the funnel plot was better (Figure 6), which suggested that the results were less likely to be affected by publication bias.

Discussion

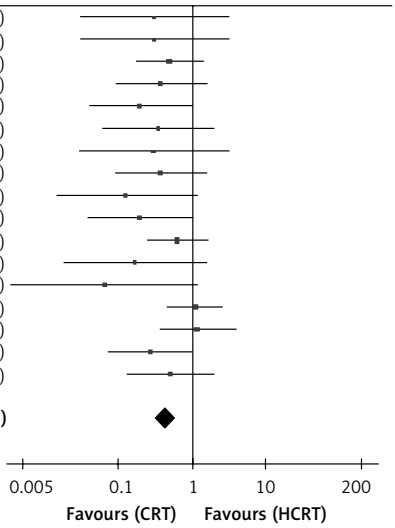
Recently, thermotherapy is widely used in the treatment of advanced cancers and with prospective effect [27]. HT takes advantage of the tumor tissue pathophysiological characteristics that the tumor cells are more sensitive to the heat than normal ones, so when the tumor tissue is heated with a physical temperature of 42.5–43.5°C for 60–120 min, the tumor cells will be destroyed, but not the normal tissue. The main anti-tumor mechanisms of HT include: (1) inhibiting the proliferation of tumor cells and inducing apoptosis [28]; (2) reducing the vascular endothelial growth factor synthesis of tumor tissue, thereby undermining and reducing the tumor angiogenesis [29]; (3) stimulating the body's cellular and humoral immune system to improve the body's anti-tumor immune effect [30]; (4) increasing the sensitivity of the tumor tissue to CRT [31]. The published randomized controlled trials (RCTs) mostly are small sample size and single-center studies, and the methods of HT were various, resulting in lower reliability. Therefore, we performed a comparison of CRT alone with CRT plus HT in this meta-analysis.

This systematic meta-analysis incorporated 19 RCTs which were published in the last 5 years with almost the same method of HT, deep pelvic local hyperthermia, and most of which used the same hyperthermia equipment: an sR-1000-type deep RF hyperthermia machine (Shenzhen Advanced Technology Corporation). In addition, extra-cavitary and intra-cavitary radiotherapy and the conventional fractionated radiotherapy were mostly adopted for radiotherapy and cisplatin (DDP) was always used for chemotherapy. Also, all the patients included in this study were Chinese. As a result, it was without methodological or ethnic heterogeneity. The pooled analysis demonstrated that CRT plus HT was associated with a greater 1-year TFSR, CRR, and OER than CRT alone. Moreover, there was no increase in the incidence of adverse reactions. The results also showed that the HCRT group had significantly lower PRR and SDR compared with the CRT group, which was mainly because the incorporated studies mostly had small sample sizes. When the CR cases notably increased in the HCRT group, the number of PR and SD were bound to decrease, thus contributing to lower PRR and SDR in the HCRT group. Although the PRR decreased, the total effective rate still significantly increased in the HCRT group. As the 3-year survival rate between the HCRT group and the CRT group was compared only by three studies, the outcome showed that

A

Study or subgroup	HCRT Events	HCRT Total	CRT Events	CRT Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Ma 2011	1	35	3	35	2.6	0.31 (0.03–3.17)
Dong 2011	1	35	3	35	2.6	0.31 (0.03–3.17)
Xu 2011	6	69	11	69	9.0	0.50 (0.17–1.44)
Du 2013	3	39	7	39	5.8	0.38 (0.09–1.60)
Yang 2013	2	50	9	52	7.6	0.20 (0.04–0.97)
Qi 2013	2	29	5	29	4.2	0.36 (0.06–2.00)
Xu 2014	1	23	3	23	2.6	0.30 (0.03–3.15)
Wang 2014	3	40	7	40	5.8	0.38 (0.09–1.60)
Liu 2014	1	32	6	30	5.4	0.13 (0.01–1.14)
Mao 2014	2	30	8	30	6.7	0.20 (0.04–1.02)
Tian 2014	8	103	12	103	9.9	0.64 (0.25–1.63)
Wang 2014	1	27	5	27	4.3	0.17 (0.02–1.56)
Xiang 2015	0	43	6	42	5.8	0.06 (0.00–1.18)
Li 2015	18	43	17	43	8.9	1.10 (0.47–2.60)
Pang 2016	7	46	6	46	4.6	1.20 (0.37–3.88)
Yang 2016	3	100	10	100	8.7	0.28 (0.07–1.04)
Lei 2016	4	30	7	30	5.4	0.51 (0.13–1.95)
Total (95% CI)		**774**		**773**	**100**	**0.44 (0.32–0.62)**
Total events	63		125			

Heterogeneity: $\chi^2 = 14.15$, $df = 16$ ($p = 0.59$), $I^2 = 0\%$
Test for overall effect: $Z = 4.83$ ($p < 0.00001$)



B

Study or subgroup	HCRT Events	HCRT Total	CRT Events	CRT Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Ma 2011	0	35	5	35	7.7	0.08 (0.00–1.47)
Xu 2011	1	69	7	69	9.8	0.13 (0.02–1.09)
Dong 2011	0	35	5	35	7.7	0.08 (0.00–1.47)
Qi 2013	0	29	3	29	4.9	0.13 (0.01–2.60)
Du 2013	0	39	1	39	2.1	0.32 (0.01–8.22)
Yang 2013	0	50	2	52	3.4	0.20 (0.01–4.27)
Wang 2014	0	27	3	27	4.9	0.13 (0.01–2.59)
Mao 2014	2	30	4	30	5.3	0.46 (0.08–2.75)
Tian 2014	0	103	1	103	2.1	0.33 (0.01–8.20)
Wang 2014	0	40	4	40	6.3	0.10 (0.01–1.92)
Xu 2014	0	23	5	23	7.6	0.07 (0.00–1.38)
Liu 2014	0	32	3	30	5.0	0.12 (0.01–2.44)
Xiang 2015	0	43	0	42		Not estmable
Li 2015	3	43	11	43	14.5	0.22 (0.06–0.85)
Pang 2016	0	46	7	46	10.5	0.06 (0.00–1.02)
Yang 2016	0	100	3	100	4.9	0.14 (0.01–2.72)
Lei 2016	0	30	2	30	3.5	0.19 (0.01–4.06)
Total (95% CI)		**774**		**773**	**100**	**0.15 (0.08–0.28)**
Total events	6		66			

Heterogeneity: $\chi^2 = 3.52$, $df = 15$ ($p = 1.00$), $I^2 = 0\%$
Test for overall effect: $Z = 6.01$ ($p < 0.00001$)

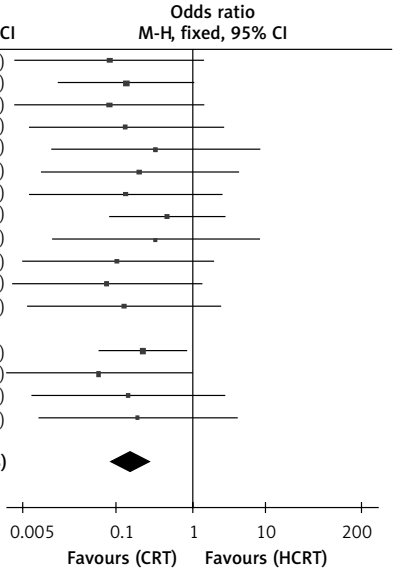


Figure 4. Forest plot for meta-analysis of disease stability rate (SDR (**A**)) and partial remission rate (PDR (**B**)) between CRT alone and CRT combined with HT

Study or subgroup	HCRT Events	HCRT Total	CRT Events	CRT Total	Weight (%)	Odds ratio M-H, fixed, 95% CI
Xiang 2015	36	43	33	42	10.7	1.40 (0.47–4.19)
Yan 2015	28	48	27	49	22.0	1.14 (0.51–2.55)
Zhang 2016	87	149	82	149	67.3	1.15 (0.72–1.81)
Total (95% CI)		**240**		**240**	**100**	**1.17 (0.81–1.70)**
Total events	151		142			

Heterogeneity: $\chi^2 = 0.12$, $df = 2$ ($p = 0.94$), $I^2 = 0\%$
Test for overall effect: $Z = 0.83$ ($p = 0.40$)

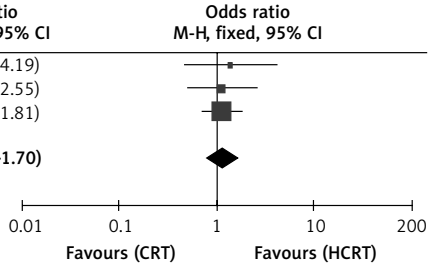


Figure 5. Forest plot for long-term efficacy 3-year SR between the CRT group and the HCRT group

the 3-year survival rate of the HCRT group was similar to that of the CRT group, without statistical significance. In short, radiotherapy and chemotherapy combined with hyperthermia in treatment of advanced cervical cancer is a reasonable, effective and safe treatment therapy. However, its long-term efficacy remains to be verified by more large-scale, high-quality RCTs. In addition, improv-

Table II. Safety comparison meta-analysis results of the HCRT group and CRT group

Adverse reactions	Incorporated studies	HCRT		CRT		Heterogeneity test		Analytical method	Meta-analysis results	
		n	*N*	*n*	*N*	I^2 (%)	*P*-value		OR (95% CI)	*P*-value
Gastrointestinal reaction	14	225	597	228	599	0	0.97	Fixed-effect model	0.99 (0.76–1.29)	0.35
Bone marrow suppression	14	280	598	293	598	39	0.42	Fixed-effect model	0.90 (0.70–1.16)	0.91
Bladder reaction	10	118	457	126	455	39	0.07	Fixed-effect model	0.79 (0.56–1.07)	0.05

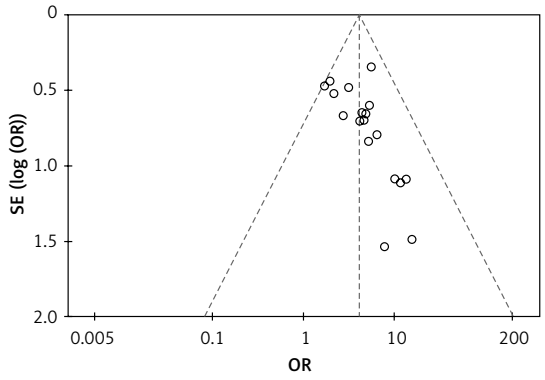


Figure 6. Funnel plot analysis of overall effective rate (OER) between the CRT group and the HCRT group

ing the efficacy as well as reducing toxicity is the most important issue to focus on in the future clinical research.

As HT in clinical practice has not been universally used in western countries, and some HT methods are not consistent with the methods in this study, the included literature was mainly Chinese literature, which may lead to the results of the analysis lacking great significance internationally. On the other hand, because it is advantageous to avoid racial heterogeneity, the results at least in China possess greater clinical significance. Due to the lack of adequate clinical data from the investigations, long-term efficacy of the two groups could not be evaluated exactly, and thus could not achieve comprehensive evaluation of the treatment model of HCRT and CRT, so it is proposed that the clinical trials should increase the observation indicators of long-term efficacy.

In conclusion, HCRT is comprehensive treatment method for cervical cancer and it has a promising future. However, this method remains associated with many problems in clinical practice. These problems include non-destructive testing temperature technology, implementation frequency, duration of HT sessions, the route and dose of radiotherapy, the choice and compatibility of chemotherapy drugs, and the sequence of HT, radiotherapy and chemotherapy. Further research is required to determine the best way to achieve optimal efficacy of HCRT and reduce its side effects.

Conflict of interest

The authors declare no conflict of interest.

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