

RESEARCH ARTICLE

Significant Efficacy of Additional Concurrent Chemotherapy with Radiotherapy for Postoperative Cervical Cancer with Risk Factors: a Systematic Review and Meta-analysis

Ai-Qiu Qin^{1&}, Zhong-Guo Liang^{2&}, Jia-Xiang Ye^{3*}, Jing Li¹, Jian-Li Wang¹, Chang-Xian Chen¹, Hong-Lin Song^{1*}

Abstract

Background: Whether concurrent chemotherapy treatment is superior to radiotherapy alone as an adjuvant regimen for postoperative cervical carcinoma with risk factors remains controversial. **Materials and Methods:** A literature search strategy examined Pubmed, Embase, the Cochrane Library, the China National Knowledge Internet Web, the Chinese Biomedical Database and the Wanfang Database. Article reference lists and scientific meeting abstracts were also screened. Controlled trials comparing concurrent chemoradiotherapy versus radiotherapy alone in postoperative cervical cancer were included. The methodological quality of non-randomized controlled trials was evaluated using the Newcastle-Ottawa Scale. Randomized controlled studies were evaluated with the Cochrane handbook. A meta-analysis was performed with RevMan 5.3. **Results:** A total of 1,073 patients from 11 clinical trials were analysed, with 582 patients in the concurrent chemoradiotherapy group and 491 patients in the radiotherapy group. Hazard ratios (HR) of 0.47 (95% CI 0.31-0.72) and 0.50 (95% CI 0.35-0.72) were observed for overall survival and progression-free survival, indicating a benefit from the additional use of concurrent chemotherapy. Subgroup analyses demonstrated that cervical cancer with high risk factors significantly benefitted from concurrent chemotherapy when examining overall survival (HR 0.44, 95% CI 0.28-0.67) and progression-free survival (HR 0.48, 95% CI 0.33-0.70), but patients with intermediate risk factors showed no benefit from concurrent chemotherapy in overall survival (HR 1.72, 95% CI 0.28-10.41) and progression-free survival (HR 1.09, 95% CI 0.19-6.14). No significant differences were observed for grade 3-4 anaemia (risk ratio (RR) 3.87, 95% CI 0.69-21.84), grade 3-4 thrombocytopenia (RR 3.04, 95% CI 0.88-10.58), grade 3-4 vomiting or nausea (RR 1.71, 95% CI 0.27-10.96), or grade 3-4 diarrhoea (RR 1.40, 95% CI 0.69-2.83). Significant differences were observed for grade 3-4 neutropenia in favour of the radiotherapy group (RR 7.23, 95% CI 3.94-13.26). **Conclusions:** In conclusion, concurrent chemoradiotherapy improves survival in postoperative cervical cancer with high risk factors but not in those with intermediate risk factors.

Keywords: Cervical cancer - concurrent chemoradiotherapy - radiotherapy - meta-analysis

Asian Pac J Cancer Prev, 17 (8), 3945-3951

Introduction

Cervical cancer is endemic in sub-Saharan Africa, Latin America and the Caribbean, and Melanesia. According to a survey from the International Agency for Research on Cancer, there were an estimated 527,600 new cases of cervical cancer and 265,700 related deaths in 2012, which was the fourth leading cause of cancer death in women worldwide (Torre et al., 2015). According to the National Comprehensive Cancer Network (version 1, 2016), radical hysterectomy or primary radiotherapy (RT) is recommended as the primary treatment for early-stage cervical cancer. For early stage cervical cancer with radical surgery and/or RT, the 5-year survival has been reported as 62.0-87.0% (Ariga et al., 2015; Kim et al., 2015; Wang

et al., 2015; Derks et al., 2016).

For patients with early stage cervical cancer after radical surgery, the necessity of additional adjuvant treatment depends on the presence or absence of certain risk factors. These risk factors include positive surgical margins, positive pelvic nodes, and parametrial invasion and are associated with a high risk of recurrence, whereas factors such as large tumour size, deep stromal invasion, and lymphovascular space involvement are classified as intermediate risk (Bidus and Elcas, 2007; Sadalla et al., 2015). Postoperative adjuvant concurrent chemotherapy (CCRT) or RT is recommended for early stage cervical cancer with risk factors, although it remains controversial whether CCRT is superior to RT as an adjuvant regimen for postoperative cervical carcinoma with risk factors

¹Department of Gynecology Oncology, ²Department of Radiation Oncology, ³Department of Medical Oncology, the Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China &Equal contributors *For correspondence: honglingxmu@hotmail.com

(Kobayashi *et al.*, 2009; Mabuchi *et al.*, 2011; Ryu *et al.*, 2011; Okazawa *et al.*, 2013). In 2013, Okazawa *et al.* (Okazawa *et al.*, 2013) conducted a retrospective study examining the impact of additional CCRT together with pelvic RT after surgery for stage IB1-IIB cervical cancer exhibiting intermediate-risk or high-risk factors. They concluded that postoperative CCRT improved the prognosis of stage IB1-IIB cervical cancer patients with high risk factors and patients that displayed 2 or more intermediate risk factors. However, Kobayashi *et al.* (Kobayashi *et al.*, 2009) observed no survival benefit from the additional use of CCRT with RT for high-risk patients.

However, none of these studies was large enough to show a statistically significant effect. Here, we conducted a meta-analysis to provide an overview of all eligible randomized controlled trials (RCTs) and non-RCTs comparing concomitant chemotherapy with RT alone to treat cervical cancer after radical hysterectomy.

Materials and Methods

Literature search strategy

The following electronic databases were systematically searched for relevant literature without language restrictions: Pubmed, Embase, the Cochrane Library, the Chinese periodical databases of the China National Knowledge Internet Web (CNKI), the Chinese Biomedical Database (CBM), and Wanfang. The text search terms were as follows: cervical cancer OR cervical carcinoma OR cervical tumour OR cervical neoplasms OR carcinoma of cervix OR uterine cervix cancer, radiotherapy, chemotherapy, operation OR surgery OR hysterectomy, and clinical trial. The terms were searched in the listed databases up to January 2016. In addition, our search was supplemented by scanning the reference lists of all identified articles and by searching major academic conferences of the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the European Society for Therapeutic Radiation Oncology. The Ethics Committee of the Affiliated Tumor Hospital of Guangxi Medical University approved this meta-analysis.

Inclusion and exclusion criteria

Inclusion criteria were as follows: (1) Participating patients were all postoperative for cervical cancer. (2) Studies comparing CCRT to RT alone. (3) Controlled clinical trials, including RCT and non-RCT.

Studies were excluded using the following criteria: (1) No controlled clinical trials. (2) Important information was not available. (3) Reviews, letters, case reports, or commentaries. The eligibility assessment was performed independently in a blinded and standardized manner by two reviewers. Disagreements between reviewers were resolved by discussion or intervention by a third reviewer.

Quality assessment

The quality of the included trials was independently evaluated by two reviewers. Retrospective studies were assessed and quantified following the 9-star Newcastle-Ottawa Scale (Wells *et al.*, 2011), and RCT quality was assessed using the Cochrane handbook (5.1.0) (Julian and

Sally, 2011). The bias risks of the RCTs were evaluated with the following criteria: random sequence generation, allocation concealment, binding of participants and personnel, binding of outcome assessment, incomplete outcome data, selecting reporting and other biases. High risk, low risk, or unclear were applied to assess the bias risk. Any discrepancies were resolved by consensus using this procedure.

Data extraction

Two reviewers independently extracted relevant data from the selected trials, including the first author, the publication year, the type of included studies, the country, the inclusion period, the number of patients in the CCRT arm and the RT arm, the pathological type, the tumour stage according to the Federation Internationale of Gynecologie and Obstetrique (FIGO), and the regimen of RT and chemotherapy. The outcomes included overall survival (OS), progression-free survival (PFS), relapse-free survival (RFS), distant metastasis failure-free survival (DMFS), hazard ratio (HR) with corresponding 95% confidence interval (CI) and haematological and non-haematological adverse events. When the HRs could not be directly extracted from the original studies, they were extracted from Kaplan-Meier curves as reported by Tierney *et al.* (Tierney *et al.*, 2007).

Statistical analysis

The HR and 95% CI were calculated using RevMan 5.3 to evaluate the correlation between the CCRT group and the RT alone group in terms of OS and PFS. Additionally, the risk ratio (RR) and the 95% CI were used to assess the correlation between the CCRT group and the RT alone group in terms of toxicity. The I^2 statistic was applied to evaluate heterogeneity, and $I^2 \geq 50\%$ indicated a substantial level of heterogeneity. When $I^2 < 50\%$, the fixed-effect model was applied to a pool analysis. Otherwise, the following methodologies were used: (1) Sensitivity analysis was applied by excluding the trials that potentially biased the results. (2) A subgroup analysis might be conducted. (3) The random effect model was employed after evaluating the reasons for the heterogeneity.

Results

Study selection and characteristics

After scanning electronic databases and performing manual retrieval, a total of 2,180 records were searched. After data de-duplication, 1,982 records remained. Next, 1,966 citations were excluded as irrelevant after reviewing the titles and abstracts. In addition, four studies were removed after reviewing the text in its entirety. In the Stehman *et al.* trial (Stehman *et al.*, 2007), patients did not receive surgery, whereas in the Kunos *et al.* trial (Kunos *et al.*, 2010), chemoradiotherapy or RT was applied before surgery. In another three studies (Kim *et al.*, 2009; Lin *et al.*, 2009; Dai *et al.*, 2014), the regimens in the control group did not include RT alone. A total of 11 studies were identified for inclusion in the meta-analysis (Peters *et al.*, 2000; Park *et al.*, 2001; Monk *et al.*, 2005; Huang *et al.*, 2007; Shibata *et al.*, 2008; Kobayashi *et al.*, 2009;

Significant efficacy of additional concurrent chemotherapy with radiotherapy for postoperative cervical cancer with risk factors

Mabuchi et al., 2009; Mabuchi et al., 2011; Ryu et al., 2011; Okazawa et al., 2013; Sun et al., 2015). In these 11 studies, partial data from the same patients was used in both the Peters et al. (Peters et al., 2000) and the Monk et al. (Monk et al., 2005) reports. In addition, partial data in another two studies were from the same participants (Mabuchi et al., 2009; Mabuchi et al., 2011). Finally, a total of 1,073 patients from 11 clinical trials were available for analysis, with 582 patients in the CCRT arm and 491 patients in the RT alone arm. The selection process is depicted in Figure 1.

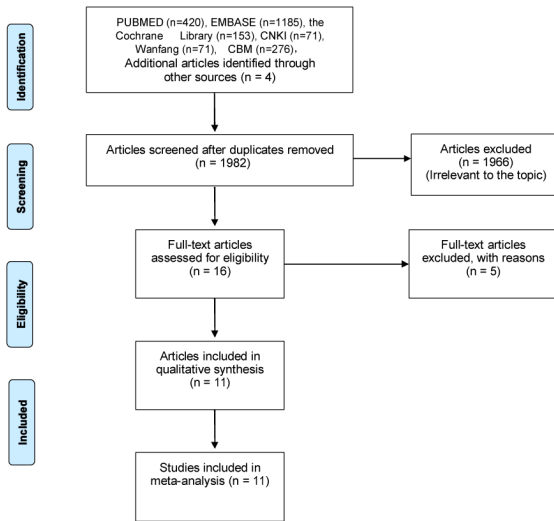


Figure 1. A Flow Chart Showing the Selection of Relevant Studies in This Meta-analysis

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Huang 2007	?	?	+	+	+	-	?
Peters 2000	?	?	+	+	+	+	?
Sun 2015	?	?	+	+	+	-	?

Figure 2. Risk of Bias Summary: Review Authors' Judgements about Each Risk of Bias Item for Three Randomized Controlled Trials

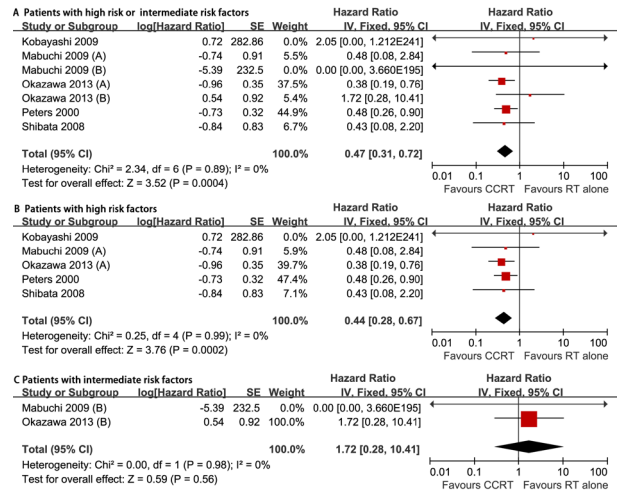


Figure 3. Forest Plot of the Hazard Ratio of Overall Survival between the CCRT group and the RT Alone Group

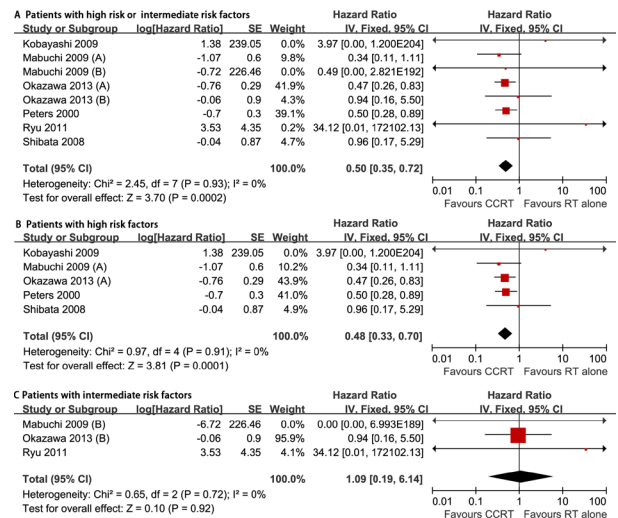


Figure 4. Forest Plot of the Hazard Ratio of Progression-free Survival between the CCRT Group and the RT Alone Group

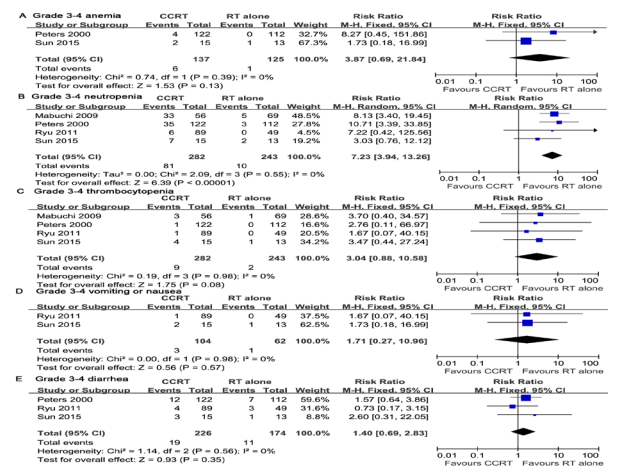


Figure 5. Forest Plot of the Risk Ratio of Grade 3-4 Anaemia, Grade 3-4 neutropenia, grade 3-4 Thrombocytopenia, grade 3-4 Vomiting or Nausea, and Grade 3-4 Diarrhoea

Table 1. Inclusion Criteria of Eligible Trials

Study	Design type	Country	Group	No. of patients	Inclusion period	Histology		Stage	Radiotherapy	Concurrent Chemotherapy	Quality
						Squamous	Non-squamous				
Park, 2001	Retrospective	Korea	CCRT	23	1979-	/	/	IB-IIA	Pelvic and the regional of node: 1.8Gy/F×5F/wk, total dose:45 Gy	Cisplatin 100mg/m ² d1 or Paraplatin, 350 mg/m ² d1 + 5-Fu 1000mg/m ² d1-5 or PAC	5
			RT	19	1998	/	/				
Shibata, 2008	Retrospective	Japan	CCRT	37	2001.7-	29	8	IB1-IIB	Pelvic and the regional of node: 1.8 Gy/F×5F/wk,total dose:45 Gy	Cisplatin 70mg/m ² d1, 5-fluorouracil 700mg/m ² , d1-4,q3wks for 2 cycles	8
			RT	52	2005.9	43	9				
Kobayashi, 2009	Retrospective	Japan	CCRT	13	1995.1-	12	1	IB2-II	Pelvic and the regional of node: 1.8Gy/F×5F/wk,total dose:45-50Gy	Nedaplatin 70mg/m ² d1, biwk for 2-3 cycles	6
			RT	17	2005.12	16	1				
Mabuchi, 2009	Retrospective	Japan	CCRT	56	1997.4-	38	18	IA2-IIB	Pelvic and the regional of node: 2.0Gy/F×5F/wk,total dose:50Gy	Nedaplatin 40mg/m ² d1, qwk for 5 cycles	8
			RT	69	2006.3	48	21				
Mabuchi, 2011	Retrospective	Japan	CCRT	29	1997.4-	25	4	IA2-IIB	Pelvic and the regional of node: 2.0Gy/F×5F/wk,total dose:50Gy	Nedaplatin 40mg/m ² d1, qwk for 5 cycles or Nedaplatin 70 mg/m ² biweekly for 2 cycles	6
			RT	26	2008.3	18	8				
Ryu, 2011	Retrospective	Korea	CCRT	89	2000.1-	71	18	IB-IIA	Pelvic and the regional of node: 1.8-2.0Gy/F×5F/wk,total dose: 40-50.4 Gy	cisplatin 40 mg/m ² qwk or cyclophosphamide 500 mg/m ² , plus cisplatin 50 mg/m ² q3wks	8
			RT	49	2006.6	36	13				
Okazawa, 2013	Retrospective	Japan	CCRT	192	1996.1-	147	45	IB1- IIB	Pelvic and the regional of node: 1.8-2.0Gy/F×5F/wk, total dose:45-50.4 Gy	Nedaplatin 40 mg/m ² qwk for 5 cycles or Nedaplatin 70 mg/m ² biweekly for 2 cycles	9
			RT	124	2009.12	91	33				
Monk, 2005	Retrospective	America	CCRT	127	1991-	98	29	IA2-IIA	Pelvic and the regional of node: 1.7Gy/F×5F/wk, total dose:45-49.3Gy	Cisplatin 70mg/m ² d1, 5-fluorouracil 1000mg/m ² d1-4,q3wks for 4 cycles	8
			RT	116	1996	95	21				
Peters, 2000	RCT	America	CCRT	127	1991-	97	30	IA2-IIA	Pelvic and the regional of node: 1.7Gy/F×5F/wk, total dose:45-49.3Gy	Cisplatin 70mg/m ² d1, 5-fluorouracil 1000mg/m ² , d1-4,q3wks for 2 cycles	/
			RT	116	1996	96	20				
Huang, 2007	RCT	China	CCRT	30	2001.5-	/	/	IB-IIB	Pelvic and the regional of node: 2.0Gy/F×5F/wk, total dose:45-50Gy	Cisplatin 30mg/m ² d1, qwk for 5 cycles.	/
			RT	32	2003.5	/	/				
Sun, 2015	RCT	China	CCRT	15	2011.9-	13	2	IB1-IIA2	Pelvic and the regional of node: 1.8-2.0Gy/F×5F/wk, total dose:45-50Gy	Topotecan 0.75mg/m ² d1 + Cisplatin 25mg/m ² d1-3 for one cycle	/
			RT	13	2013.8	12	1				

The quality of retrospective trials was evaluated by the 9-star Newcastle-Ottawa Scale. RCT: Randomized controlled trial; CCRT: Concurrent chemoradiotherapy. RT: Radiotherapy; PAC: Cisplatin 70 mg/m² d1 or Paraplatin 350 mg/m² d1+ Adriamycin 45 mg/m² d2-3 + Cytosax 250 mg/m² d2-3.

Table 1 shows the inclusion criteria for each trial, including first author, publication year, the type of included studies, treatment regimen, patient number, inclusion period, pathological type, tumour stage according to FIGO, and the regimen of RT and chemotherapy administered in the studies.

Quality assessment of included studies

Of the 11 studies, 8 were retrospective controlled trials, and 3 were RCTs. The scales for the retrospective studies

were assessed according to the 9-star Newcastle-Ottawa Scale and are recorded in Table 1. The three RCTs were judged as “unclear” for random sequence generation, allocation concealment, and other biases (Peters et al., 2000; Huang et al., 2007; Sun et al., 2015). Two studies were evaluated as high risk due to selective reports (Huang et al., 2007; Sun et al., 2015). All studies were assessed as low risk for the complete outcome data, the binding of participants and personnel, and the binding of outcome assessment criteria (Peters et al., 2000; Huang et al., 2007;

Significant efficacy of additional concurrent chemotherapy with radiotherapy for postoperative cervical cancer with risk factors Sun et al., 2015) (Figure 2).

OS

Five trials contained data for OS that included 425 patients in the CCRT group and 378 patients in the RT alone group (Peters et al., 2000; Shibata et al., 2008; Kobayashi et al., 2009; Mabuchi et al., 2009; Okazawa et al., 2013). No apparent heterogeneity was detected ($I^2=0\%$, $P=0.89$), so a fixed-effects model was used. There was a significant difference in favour of the CCRT group (HR 0.47, 95% CI 0.31-0.72) (Figure 3A).

A subgroup analysis indicated that cervical cancer with high risk factors significantly benefitted from CCRT (HR 0.44, 95% CI 0.28-0.67, heterogeneity $P=0.99$, $I^2=0\%$) (Figure 3B), but patients with intermediate risk factors did not benefit from CCRT (HR 1.72, 95% CI 0.28-10.41, heterogeneity $P=0.98$, $I^2=0\%$) (Figure 3C).

PFS

Six studies presented data on PFS that included 514 patients in the CCRT group and 427 patients in the RT alone group (Peters et al., 2000; Shibata et al., 2008; Kobayashi et al., 2009; Mabuchi et al., 2009; Ryu et al., 2011; Okazawa et al., 2013). Significant differences were observed in favour of the CCRT group (HR 0.50, 95% CI 0.35-0.72, heterogeneity $P=0.93$, $I^2=0\%$) (Figure 4A).

A subgroup analysis indicated that cervical cancer with high risk factors significantly benefitted from CCRT (HR 0.48, 95% CI 0.33-0.70, heterogeneity $P=0.91$, $I^2=0\%$) (Figure 4B). However, patients with intermediate risk factors did not benefit from CCRT (HR 1.09, 95% CI 0.19-6.14, heterogeneity $P=0.72$, $I^2=0\%$) (Figure 4C).

Grade 3-4 anaemia

Two trials (Peters et al., 2000; Sun et al., 2015) included data examining grade 3-4 anaemia that included 137 patients in the CCRT group and 125 patients in the RT alone group. No significant differences were found between the two groups (RR 3.87, 95% CI 0.69-21.84, heterogeneity $P=0.39$, $I^2=0\%$).

Grade 3-4 neutropenia

Four trials (Peters et al., 2000; Mabuchi et al., 2009; Ryu et al., 2011; Sun et al., 2015) included data regarding grade 3-4 neutropenia that included 282 patients in the CCRT group and 243 patients in the RT alone group. Significant differences were exhibited favouring the RT alone group (RR 7.23, 95% CI 3.94-13.26, heterogeneity $P=0.55$, $I^2=0\%$).

Grade 3-4 thrombocytopenia

Four trials (Peters et al., 2000; Mabuchi et al., 2009; Ryu et al., 2011; Sun et al., 2015) contained data for grade 3-4 thrombocytopenia that included 282 patients in the CCRT group and 243 patients in the RT alone group. No significant differences were observed between the two groups (RR 3.04, 95% CI 0.88-10.58, heterogeneity $P=0.98$, $I^2=0\%$).

Grade 3-4 vomiting or nausea

Two trials (Ryu et al., 2011; Sun et al., 2015) included

data regarding grade 3-4 vomiting or nausea that included 104 patients in the CCRT group and 62 patients in the RT alone group. Significant differences were found in favour of the RT alone group (RR 1.71, 95% CI 0.27-10.96, heterogeneity $P=0.98$, $I^2=0\%$).

Grade 3-4 diarrhoea

Three trials (Peters et al., 2000; Ryu et al., 2011; Sun et al., 2015) provided data regarding grade 3-4 diarrhoea that included 226 patients in the CCRT group and 174 patients in the RT alone group. There were no significant differences in grade 3-4 diarrhoea between the two groups (RR 1.40, 95% CI 0.69-2.83, heterogeneity $P=0.56$, $I^2=0.0\%$).

Discussion

To our knowledge, this study is the first meta-analysis to evaluate the efficacy and toxicity of CCRT addition to RT for the treatment of postoperative cervical cancer with risk factors. A total of 1,073 patients from 11 studies were analysed, with 582 patients in the CCRT group and 491 patients in the RT alone group. A significant survival benefit from CCRT was observed only in patients with high risk factors. In addition, patients in the CCRT group experienced more significant toxicity with grade 3-4 neutropenia.

CCRT can sensitize cervical cancer cells to RT by inhibiting DNA repair in tumour cells damaged from RT. Moreover, chemotherapy can induce apoptosis and limit tumour resistance. Therefore, concomitant chemotherapy might improve the efficacy of RT as an adjuvant treatment for postoperative cervical cancer. In 2000, Peters et al. (Peters et al., 2000) reported the first prospective controlled trial comparing the efficacy of combining CCRT with RT to treat cervical cancer with high risk factors after surgery, in which 127 patients were randomly selected to receive CCRT, whereas 116 patients received RT alone. After a median follow-up time of 42 months, the projected 4-year PFS and OS were 80% compared to 63% ($P=0.003$) and 81% compared to 71% ($P=0.007$), respectively. CCRT is recommended as a standard regimen to treat postoperative cervical cancer with high risk factors. However, it is unclear whether every cervical cancer patient with high risk factors would benefit from additional CCRT in addition to RT following surgery. In the Monk et al. study (Monk et al., 2005), 116 patients received RT alone, and 127 received CCRT. Significant benefits were gained in 5-year survival for cervical cancer patients with two or more positive lymph nodes but not for those with only one positive lymph node. In addition, the number of high-risk factors might affect the efficacy of CCRT. In 2015, Matsuo et al. reported the clinical implications of surgically treated early-stage cervical cancer with multiple high-risk factors (Matsuo et al., 2015). In this retrospective trial, 109 patients had a single high-risk factor, 68 patients had multiple high-risk factors, and 10 had three high-risk factors. After a median follow-up time of 56.8 months, the 5-year cumulative locoregional recurrence and distant recurrence rates of CCRT were significantly lower than those for RT alone

for cervical cancer with a single high-risk factor. However, for patients with multiple high-risk factors, the 5-year cumulative locoregional recurrence and distant recurrence rates were similar between the two groups receiving CCRT or RT alone. They concluded that CCRT was beneficial only for tumours with a single high-risk factor but not for patients with multiple high-risk factors. Choi et al. (Choi et al., 2011) conducted a matched-case comparison to explore the efficacy of consolidation chemotherapy with cisplatin and 5-fluorouracil after CCRT in 78 stage IIB-IVA cervical cancer patients. The rate of distant metastasis was significantly higher for patients without consolidation therapy than for those who received consolidation therapy (23.1% compared to 7.7%, $p=0.06$). Dueñas-González et al. (Dueñas-González et al., 2011) observed that the additional use of consolidation chemotherapy after CCRT significantly improved OS and PFS for stage IIB to IVA cervical carcinoma patients. Consolidation chemotherapy might be an optional regimen for postoperative cervical cancer with multiple high-risk factors after CCRT.

The present meta-analysis showed that no survival benefit was found for CCRT combined with RT treatment after surgery for cervical cancer with intermediate risk factors. Therefore, RT alone might be recommended for postoperative patients with intermediate risk factors. However, the efficacy of concomitant chemotherapy might be associated with the number of intermediate risk factors. In the Okazawa et al. trial (Okazawa et al., 2013), for patients with 2 or more intermediate-risk factors, CCRT was superior to RT as assessed by recurrence rates and PFS. However, compared to RT alone, no survival benefit from CCRT was gained for patients with only 1 intermediate risk factor.

Thus, it is essential to conduct prospective trials with large samples to address which group of postoperative cervical cancer patients with intermediate risk factors might gain a survival benefit from CCRT.

Most studies used cisplatin with or without 5-fluorouracil as the concomitant chemotherapy regimen for postoperative cervical cancer. In the Sun et al. trial (Sun et al., 2015), the CCRT regimen was topotecan 0.75 mg/m² for days 1, 2 and 3, followed by cisplatin 25 mg/m² for days 1, 2 and 3. The incidence of grade 3-4 neutropenia in the RT alone group was 15.4%, although it was 46.7% in the CCRT group. However, no significant differences were found for grade 3-4 non-haematologic toxicity between the two groups. This study was closed ahead of schedule due to severe toxicity. In the Mabuchi et al. trial (Mabuchi et al., 2009), nedaplatin was chosen as the regimen for concomitant chemotherapy. The frequencies of acute grade 3-4 toxicities were significantly higher in patients treated with CCRT than those treated with RT alone. However, there were no statistically significant differences in severe late toxicities. In all, compared to RT alone, the frequencies of acute grade 3-4 toxicities were higher during CCRT, but these toxicities can be mostly managed with conservative treatment. Multi-centre randomized trials with large samples are needed to determine which regimens are most effective as concomitant chemotherapies for postoperative cervical cancer.

There were several limitations to our meta-analysis. First, limitations of the data from publications and selection bias might occur because individual patient data could not be obtained, which might affect the quality of the evidence used for our analyses. Second, the quality of the included trials might not be high. Nine of the studies were retrospective studies, and patients were included only if they met specific selection criteria. Thus, selection bias might have occurred. Moreover, two of the three RCTs did not satisfy criteria regarding selective reports. Third, the articles used for our analyses did not provide all available data such as OS, PFS, RFS and DMFS, leaving us with a small sample size.

In conclusion, compared to RT alone, CCRT might improve survival in postoperative cervical cancer patients with high risk factors but not in those with intermediate risk factors. However, it is essential to conduct prospective controlled clinical trials to explore the relationship between the number of intermediate risk or high risk factors and the efficacy of CCRT addition to RT treatment. Additionally, after hysterectomy of cervical cancer patients with multiple high-risk factors, it remains unclear whether consolidation chemotherapy after CCRT should be applied as an optional regimen. Moreover, future studies to address which CCRT regimens are most efficient and least toxic are required.

Competing interests, The authors declare no financial or personal relationships with other people or organizations that inappropriately influenced this work.

References

- Ariga T, Toita T, Kato S, et al (2015). Treatment outcomes of patients with FIGO Stage I/II uterine cervical cancer treated with definitive radiotherapy: a multi-institutional retrospective research study. *J Radiat Res*, **56**, 841-8.
- Bidus MA, Elcas JC (2007). Cervical and vaginal cancer. In: Berek & Novak's gynecology. 14th ed. Philadelphia: Lippincott Williams & Wilkins, 1403-1456.
- Choi CH, Lee YY, Kim MK, et al (2011). A matched-case comparison to explore the role of consolidation chemotherapy after concurrent chemoradiation in cervical cancer. *Int J Radiat Oncol Biol Phys*, **81**, 1252-7.
- Dai JL, Li J, Zhang HF, et al (2014). Observation of the curative efficacy and adverse reaction in vascular cancer embolus positive patients with postoperative chemoradiotherapy of the cervical cancer. *Clin Med*, **36**, 346-50.
- Derks M, Biewenga P, van der Velden J, et al (2016). Results of radical surgery in women with stage IB2/IIA2 cervical cancer. *Acta Obstet Gynecol Scand*, **95**, 166-72.
- Dueñas-González A, Zarbá JJ, Patel F, et al (2011). Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol*, **29**, 1678-85.
- Huang D-N, Li G-S, Huang H-X, et al (2007). The effect of concurrent chemoradiotherapy on postoperative early stage cervical cancer with high-risk factors. *Youjiang Med J*, **35**, 20-1.
- Julian PTH, Sally G. (2011). Cochrane handbook for systematic review of interventions version 5.0.1. The cochrane collaboration. Available: <http://www.cochranehandbook.org>.

- Kim HJ, Rhee WJ, Choi SH, et al (2015). Clinical outcomes of adjuvant radiation therapy and prognostic factors in early stage uterine cervical cancer. *Radiat Oncol J*, **33**, 126-33.
- Kim K, Kang SB, Chung HH, et al (2009). Comparison of chemoradiation with radiation as postoperative adjuvant therapy in cervical cancer patients with intermediate-risk factors. *Eur J Surg Oncol*, **35**, 192-6.
- Kobayashi Y, Ohara T, Wada Y, et al (2009). Concurrent chemoradiotherapy with nedaplatin after radical hysterectomy in patients with stage IB and II cervical cancer. *J Obstet Gynaecol Res*, **35**, 490-4.
- Kunos C, Ali S, Abdul-Karim FW, et al (2010). Posttherapy residual disease associates with long-term survival after chemoradiation for bulky stage 1B cervical carcinoma: A Gynecologic Oncology Group study. *Am J Obstet Gynecol*, **203**, 351 1-.8.
- Lin G-S, Cheng H-H, Li D-S (2009). Compare the effect of concurrent chemoradiotherapy with sequential treatment on early stage postoperative cervical carcinoma with high-risk factors. *Chin Clin Oncol*, **14**, 541-3.
- Mabuchi S, Morishige K, Isohashi F, et al (2009). Postoperative concurrent nedaplatin-based chemoradiotherapy improves survival in early-stage cervical cancer patients with adverse risk factors. *Gynecol Oncol*, **115**, 482-7.
- Mabuchi S, Okazawa M, Isohashi F, et al (2011). Postoperative whole pelvic radiotherapy plus concurrent chemotherapy versus extended-field irradiation for early-stage cervical cancer patients with multiple pelvic lymph node metastases. *Gynecol Oncol*, **120**, 94-100.
- Matsuo K, Mabuchi S, Okazawa M, et al (2015). Clinical implication of surgically treated early-stage cervical cancer with multiple high-risk factors. *J Gynecol Oncol*, **26**, 3-11.
- Monk BJ, Wang J, Im S, et al (2005). Rethinking the use of radiation and chemotherapy after radical hysterectomy: A clinical-pathologic analysis of a gynecologic oncology group/southwest oncology group/radiation therapy oncology group trial. *Gynecol Oncol*, **96**, 721-8.
- Okazawa M, Mabuchi S, Isohashi F, et al (2013). Impact of the addition of concurrent chemotherapy to pelvic radiotherapy in surgically treated stage IB1-IIB cervical cancer patients with intermediate-risk or high-risk factors: a 13-year experience. *Int J Gynecol Cancer*, **23**, 567-75.
- Park TK, Kim SN, Kwon JY, et al (2001). Postoperative adjuvant therapy in early invasive cervical cancer patients with histopathologic high-risk factors. *Int J Gynecol Cancer*, **11**, 475-82.
- Peters WA, Liu PY, Barrett RJ, et al (2000). Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol*, **18**, 1606-13.
- Ryu SY, Park SI, Nam BH, et al (2011). Is adjuvant chemoradiotherapy overtreatment in cervical cancer patients with intermediate risk factors? *Int J Radiat Oncol Biol Phys*, **79**, 794-9.
- Sadalla JC, Andrade JM, Genta ML, et al (2015). Cervical cancer: what's new? *Rev Assoc Med Bras*, **61**, 536-42.
- Shibata K, Kajiyama H, Terauchi M, et al (2008). Feasibility and effectiveness of postoperative adjuvant concurrent chemoradiation therapy in Japanese patients with high-risk early-stage cancer of the uterine cervix. *Int J Clin Oncol*, **13**, 233-8.
- Stehman FB, Ali S, Keys HM, et al (2007). Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a Gynecologic Oncology Group trial. *Am J Obstet Gynecol*, **197**, 503 e1-6.
- Sun W, Wang T, Shi F, et al (2015). Randomized phase III trial of radiotherapy or chemoradiotherapy with topotecan and cisplatin in intermediate-risk cervical cancer patients after radical hysterectomy. *BMC Cancer*, **15**, 353.
- Tierney JF, Stewart LA, Ghersi D, et al (2007). Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials*, **8**, 16.
- Torre LA, Bray F, Siegel RL, et al (2015). Global cancer statistics, 2012. *CA Cancer J Clin*, **65**, 87-108.
- Wang JQ, Wang T, Shi F, et al (2015). A randomized controlled trial comparing clinical outcomes and toxicity of lobaplatin-versus cisplatin-based concurrent chemotherapy plus radiotherapy and high-dose-rate brachytherapy for FIGO stage II and III cervical cancer. *Asian Pac J Cancer Prev*, **16**, 5957-61.
- Wells GA, Shea B, O'Connell D, et al (2011). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses, Ottawa:Ottawa Hospital Research Institute.