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Primary radical hysterectomy vs chemoradiation for IB2-IIA cervical cancer
A systematic review and meta-analysis

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Abstract

Background: To compare the clinical outcomes of radical hysterectomy (RH) with chemoradiotherapy (CRT) in women with stage IB2-IIA cervical cancer.

Methods: Based on articles published up to December 2017, a literature search of PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Chinese National Knowledge Infrastructure (CNKI) databases was conducted to identify eligible studies. Overall survival (OS), progression-free survival (PFS) with hazard ratios (HRs), and toxicities with odds ratios (ORs) were analyzed.

Results: In total, 7 studies comprising 687 patients were identified for this meta-analysis. RH showed a significant trend toward improved survival outcomes compared with those of CRT, regardless of OS (HR = 0.49, 95% confidence interval [CI] 0.36–0.67, $P < .001$); or PFS (1.61, 95% CI 1.15–2.26, $P = .005$) for IB2-IIA cervical cancer. Subgroup analysis revealed that stage IB2 cervical cancer patients obtained better OS (HR = 0.36, 95% CI 0.23–0.56, $P < .001$; heterogeneity: $P = .32$, $I^2 = 13\%$). However, a higher incidence of grade 3/4 genitourinary abnormalities was evident with RH (OR = 2.3, 95% CI 1.42–3.87, $P = .021$).

Conclusion: Our study suggested that RH had distinct advantages over CRT for carcinoma of the uterine cervix with FIGO stage IB2-IIA, especially for IB2 cervical cancer.

Abbreviations: BRT = brachytherapy, CRT = chemoradiotherapy, EBRT = pelvic external-beam radiotherapy, HR = hazard ratio, OR = odds ratio, RH = radical hysterectomy.

Keywords: chemoradiation, cervical cancer, radical hysterectomy, meta-analysis

1. Introduction

Despite the increased development of preventative methods such as screening programs and human papillomavirus vaccination,

cervical cancer still accounted for an estimated 528,000 new cancer cases and 266,000 fatalities worldwide during 2012.[1] It has become a major challenge across the globe, yet there is controversy regarding the best management options in the treatment of stage IB2-IIA cervical cancer. At present, radical hysterectomy (RH) with or without tailored adjuvant therapy and CRT are the most frequent treatment modalities for affected women. Several studies have demonstrated that both treatments are equally effective for patients with early stage cervical cancer.[2–6] However, some larger scale trials have suggested patients undergoing RH achieved better survival outcomes compared to those undergoing CRT.[2,7] Additionally, there is concern that patients treated with RH plus adjuvant therapy may be at a higher risk of complications compared to CRT. Therefore, it is necessary to clarify which is the most effective treatment modality in stage IB2-IIA cervical cancer.

Consequently, we performed a meta-analysis of all eligible studies to compare the clinical treatment outcomes and toxicities of RH and CRT for stage IB2-IIA cervical cancer patients, with the hope of providing valuable evidence to inform treatment guidelines and suggestions for future trials.

2. Materials and methods

2.1. Literature search strategy

The systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines.[8] The following electronic databases were systematically searched for relevant

literature: PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Chinese National Knowledge Infrastructure databases (CNKI). The last search was performed on December 2017, without nationality restrictions. The following terms and their combinations were applied: (chemoradiation OR concomitant radiochemotherapy OR concurrent radiochemotherapy) AND (surgery OR operations OR operative therapy) AND (uterine cervical neoplasms OR cervical cancer OR cancer of cervix). We also searched previous systematic reviews and examined the references which were included in our analysis.

2.2. Selection criteria

Studies were considered eligible for the meta-analysis if they met the following criteria: included untreated patients with histologically proven cervical cancer; involved randomized or nonrandomized controlled clinical trials that compared RH vs CRT in stage IB2-IIA cervical cancer patients, where the CRT group was designed as a control group and the experimental group was treated with RH; time to event data, including overall survival (OS) and progression-free survival (PFS), could be acquired from the paper to calculate hazard ratios (HRs) with a 95% confidence interval (CI); sufficient information should be available to evaluate odds ratios (ORs) with a 95% CI for instances of grade 3/4 adverse events; patients who received neoadjuvant chemotherapy before RH were excluded; and abstracts, conferences, reviews, letters, and case reports were excluded. The eligibility assessment was performed independently in a standardized manner by 2 reviewers. Disagreements between reviews were resolved by discussion or intervention by a 3rd reviewer.

2.3. Data extraction and quality assessment

All eligible studies were assessed and evaluated by 2 investigators working independently. During the data abstraction, a 3rd reviewer was consulted by discussion to reach a consensus when disagreement occurred. We included information regarding the name of the first author, date of publication, country, stage of cancer, number of patients in the CRT group and the RH group, details of radical hysterectomy and primary chemoradiation, follow-up time, and quality of the trials. The endpoints for evaluation were OS and PFS. OS was defined as the time from diagnosis until death, or the latest day the patient was known to be alive. The duration of time to distant metastasis or recurrence was counted from the initiation of treatment to treatment failure. Grade 3/4 complications were also assessed in 2 groups. Additionally, the methodological quality of included retrospective studies was evaluated using the 9-star Newcastle–Ottawa scale.[9] The quality of each retrospective study was scored from 0 to 9, and studies with scores of 6 or above were considered high quality.

2.4. Statistical analysis

The OS and PFS were assessed by HRs and a 95% CI, and the results were pooled using STATA 14 (STATA Corporation, College Station, TX). For each study, the HRs for OS and RFS were extracted directly from the original report. If not available, we obtained the data by reading off Kaplan–Meier survival curves to estimate the HRs of survival or by the indirect method

which was suggested by Parmar and colleagues.[10] Additionally, the results of grade 3/4 complications were calculated as ORs and presented with a 95% CI. The Cochrane Q test and I^2 statistic were used to assess statistical heterogeneity among trials. If a P-value was <.1 or the $I^2 > 50\%$, results were reported using a random-effects model. If not, a fixed-effects model was used.

Sensitivity analysis was applied by excluding the trials that potentially biased the results. The Egger test was conducted to assess potential publication bias in the meta-analysis, and a P-value of >.1 was considered to have no potential publication bias.[11,12]

3. Results

3.1. Study selection and characteristics

The baseline characteristics of eligible studies are summarized in Table 1. A total of 1026 records were identified from the databases and references. After excluding 208 duplicate publications, 781 nonrelevant studies were discarded by screening their titles and/or abstracts. Of the 37 full-text articles assessed for eligibility, 4 were abandoned for no matched comparison, 12 for not involving RH modality, and 13 for including patients with III or IV stages of cervical cancer. The flow diagram is presented in Figure 1. Consequently, a total of 7 studies were identified for inclusion in the meta-analysis.[13–19] Of 683 total patients included in our meta-analysis, 411 received RH and 272 received CRT. Most of studies were performed in Korea and all trials were retrospective studies. Four studies[13,17–19] only recruited stage IB2 cervical cancer patients and 3 studies[14–16] included a small fraction of stage IIA patients. The general quality of the 7 studies was evaluated, and 6 were classified as high quality.

3.2. Survival outcomes

The meta-analysis of OS was based on 7 trials with 683 patients. No obvious heterogeneity was observed among these trials ($P = .137$, $I^2 = 38\%$). Analysis using a fixed-effects model showed that the RH group had improved OS compared with that of the CRT group (HR = 0.49, 95% CI 0.36–0.67, $P < .001$; Fig. 2A). Six trials with 629 patients reported PFS (Fig. 3). The merge HR was 1.61 (95% CI 1.15–2.26, $P = .005$; heterogeneity: $P = .89$, $I^2 = 0\%$), indicating that the RH group did demonstrate improved PFS in comparison to the CRT group. Four studies that only included IB2 stage cervical cancer patients reported OS. Figure 2B shows that stage IB2 cervical cancer patients can obtain a better OS (HR = 0.36, 95% CI 0.23–0.56, $P < .001$; heterogeneity: $P = .32$, $I^2 = 13\%$).

A sensitivity analysis was performed to identify whether the survival results were sharply influenced by certain trials. As showed in Table 2, the survival outcomes remained stable after separately excluding three trials that recruited <90 patients,[17–19] 2 low-quality studies,[17,18] 1 trial without the median follow-up time and enough information about the treatment of RH or CRT group,[17] and 1 trial that enrolled a small number of cervical cancer patients and had a median follow-up time of <40 months.[18] As we all know, the weight assigned to each study was influenced by the number of patients. One trial[16] received the largest weight in this analysis. After we removed this largest study and analyzed a combined HR estimate from the remaining papers, the combined HRs for OS and PFS were 0.47 (95% CI

Table 1

Characteristics of the included studies.

Study and year	Country	Accrual period	Stage	No. of patients		RH treatment details			Concurrent or sequential	CCRT treatment details	Median follow-up, mo	Quality
				RH	CCRT	Surgery	Adjuvant RT	Adjuvant CT				
Jang 2007[15]	Korea	2002–2011	IB2–IIA	64	49	Hysterectomy type C with lymphadenectomy level 2 or 3	EBRT, 4500–5400 cGy over 5 wk	Until 2007, P/C or cisplatin/C or 5-FU/cisplatin since 2008, cisplatin (40 mg/m^2) over 6 wk	Concurrent	EBRT: 4500–5400 cGy BRT: 3000–3500 cGy CT: until 2007, P/C or P/cisplatin or 5-FU/cisplatin since 2008, cisplatin (40 mg/m^2)	66	8
Bradbury 2015[13]	UK	1991–2013	IB2	67	25	Radical hysterectomy and/or Para-aortic node sampling	EBRT, 4400–4500 cGy over 5 wk	Cisplatin 40 mg/m^2 over 5 wk	Concurrent	EBRT: 4400–5000 cGy BRT: 1400–2100 cGy CT: cisplatin 40 mg/m^2 over 5 wk	57.5	7
Kim 2009[18]	Korea	1995–2007	IB2	28	35	Radical hysterectomy with bilateral pelvic lymphadenectomy with or without para-aortic lymphadenectomy	EBRT, 4500 cGy	Cisplatin (70 mg/m^2) on day 1 + 5-FU (1000 mg/m^2/d) from days 2–5	Concurrent	EBRT: 4500 cGy BRT: 2800 cGy booster dose: 400 cGy CT: cisplatin (70mg/m^2) on day 1 + 5-FU (1000 mg/m^2) on days 2–5	37	5
Park 2012[16]	Korea	2001–2010	IB2–IIA	147	68	Piver-Rutledge type 3 hysterectomy with pelvic and/or para-aortic lymphadenectomy	EBRT: 4010–5040 cGy	Cisplatin or 5-FU/ cisplatin or P/cisplatin	Concurrent	EBRT: 4140–5040 cGy BRT: 3000–3500 cGy parametrial booster dose: 540–1200 cGy CT: cisplatin weekly or 5-FU or P/cisplatin	40	8
Ryu 2007[17]	Korea	1995–2005	IB2	304	52	Radical hysterectomy	NM	NM	NM	NM	NM	4
Zivanovic 2008[19]	USA	1982–2006	IB2	27	20	Piver-Rutledge type III radical hysterectomy with or without bilateral salpingo-oophorectomy	EBRT: 3780–6000 cGy	Weekly cisplatin (40 mg/m^2) or cisplatin (75 mg/m^2) and bleomycin (20 IU/m^2/d)	Concurrent	EBRT + BRT: 7770 cGy CT: weekly cisplatin (40 mg/m^2)	42	6
Kong 2016[14]	Korea	2000–2015	IB2–IIA	54	54	Radical hysterectomy with pelvic and/or para-aortic lymphadenectomy	EBRT: 4510–6100 cGy over 6 wk	Cisplatin + 5-FU	Concurrent	EBRT + BRT: total pelvic dose 8150 cGy (range, 6840–9100 cGy) CT: cisplatin + 5-FU	NM	8

The quality of retrospective trials was evaluated by the 9-star Newcastle–Ottawa scale.
BRT = brachytherapy, C = carboplatin, CRT = chemoradiotherapy, CT = chemotherapy, EBRT = pelvic external-beam radiotherapy, NM = not mentioned, P = paclitaxel, RH = radical hysterectomy.

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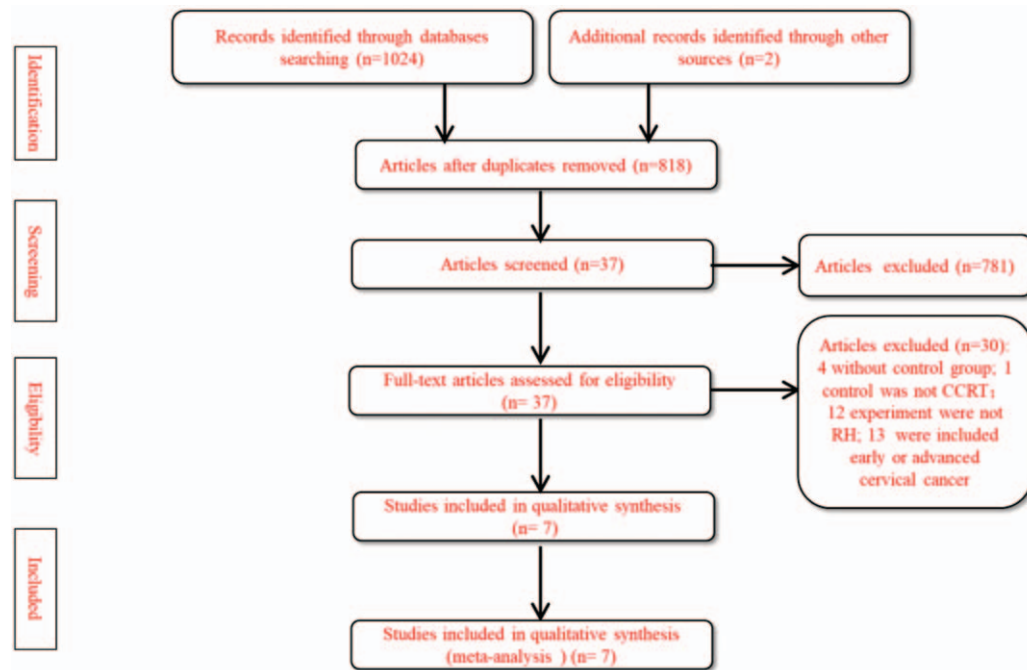
Figure 1. A flowchart showing the selection procedure of relevant studies in this meta-analysis.

0.32–0.68, $P < .001$) and 1.57 (95% CI 1.07–2.32, $P = .021$), suggesting a similar result as the main meta-analysis. Generally speaking, the survival results of RH vs CRT were of high stability. We performed Egger tests and no obvious publication bias was observed in OS or PFS (Egger test, $P = .197, .196$).

3.2.1. Grade 3/4 complication. The grade 3/4 adverse events that were available for pooled analysis are presented in Table 3. No significant difference was observed between the 2 arms in terms of the incidence of hematologic abnormality (OR = 0.43, 95% CI 0.56–2.45, $P = .669$) or gastrointestinal abnormality (OR = 0.25, 95% CI 0.33–2.33, $P = .805$). However, compared with CRT, RH notably increased the risk of genitourinary abnormality (OR = 2.3, 95% CI 1.42–3.87, $P = .021$).

4. Discussion

At present, the 1st strategy for FIGO stage IB2 and IIA cervical cancer has been CRT, which is classified as category 1 level of evidence according to the NCCN guidelines.[20,21] However, surgery has also been proven a highly effective method for early stage disease.[22–25] In our systematic review and meta-analysis, we compared the survival outcomes of primary radical hysterectomy and chemoradiation. The results reported that the RH group obtained better survival conditions for stage IB2-IIA cervical cancer, especially for IB2 patients.

Several large-scaled studies have revealed that RH facilitated improved rates of survival compared to CRT in early stage patients with bulky disease. One study demonstrated a 49% improvement in survival with an RH group, consistent with our meta-analysis.[2,3,17] There are several possible explanations for the significant difference in survival. First, a bulky and especially barrel-shaped disease has a poor radiation dose

distribution, which may lead to increased local failure and decreased survival outcomes.[26,27] However, surgery can remove the part of the disease which is too far from the radium system to receive an effective dose. Therefore, women with this type of tumor may benefit from radical hysterectomy.[20,28] Next, surgery can confidently permit the status of lymph node and parametrial invasion, the most dependent factor associated with survival outcomes. A retrospective study[16] reported that lymph node failure rate was higher in the CRT group compared to the RH group, although it was not statistically significant (14.7% vs 8.2%). Delpech et al[29] observed a high rate of positive para-aortic nodes (18%) in patients with stage IB2/II cervical cancer. All these data were in good agreement. In addition, several studies[30,31] reported that performing a pelvic lymphadenectomy along with removal of the primary disease could reduce the rate of lymph node recurrence in patients with a bulky, early stage disease. This may be the reason for better PFS in the RH group. Our subgroup analysis found that stage IB2 cervical cancer patients can achieve better OS from radical surgery with tailored therapy. In our study, at least half of stage IB2 patients received adjuvant to promote local control. The greatest concern for bulky stage IB2 cervical cancer is poor local control rate; therefore, radical surgery with adjuvant therapy is strongly recommended compared to chemoradiation.

There is concern that patients treated with radical hysterectomy, followed by adjuvant therapy, may be at higher risk of complication incidences. However, the pooled analysis showed no significant difference between the 2 arms regarding the incidence of grade 3/4 toxicity reactions, except for genitourinary abnormalities (OR = 2.3, 95% CI 1.42–3.87, $P = .021$). A retrospective study conducted by Park et al[16] found that the incidence of grade 3/4 early complications is similar between RH with radiation therapy and the CRT group. More interestingly,
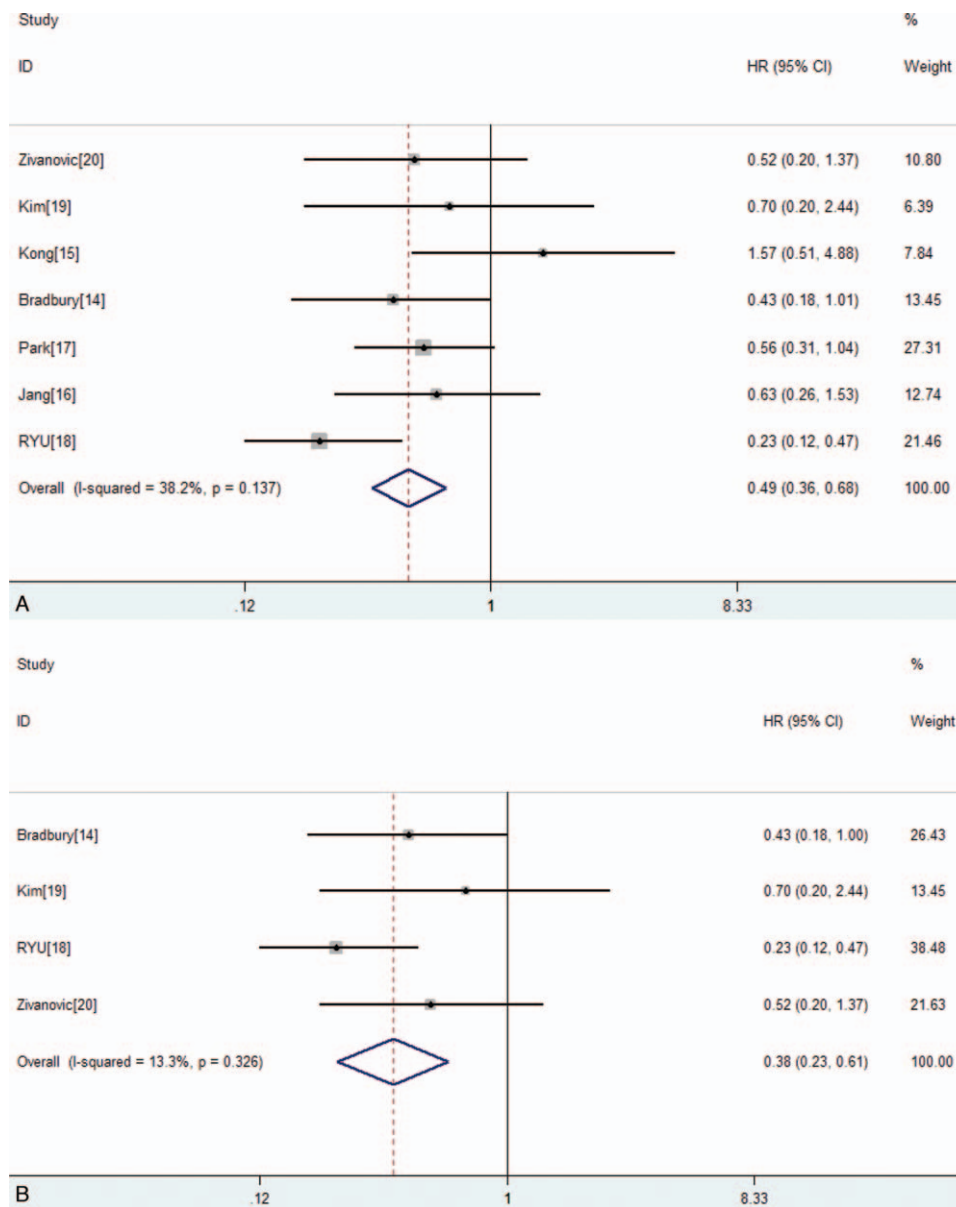
Figure 2. (A) Forest plot of the hazard ratios of overall survival (OS) between the radical hysterectomy (RH) group and chemoradiotherapy (CRT) group in all papers. (B) Forest plot of the hazard ratios of OS between the RH group and CRT group in stage IB2 patients. CI = confidence interval, HR = hazard ratio.

they also suggest that the rate of grade 3/4 late complications is lower in the RH group. In addition, several recent trials[32,33] have reported similar results in terms of grade 3/4 complications. However, considering the genitourinary complications, the management of RH should be considered with caution.

This systematic review and meta-analysis had several limitations. First, the included trials were retrospective, which made biases inevitable. Second, our meta-analysis evaluated the differences in survival outcomes between RH and CRT. We must admit that the RH group had a lower risk for recurrence, which may have influenced our final conclusions. Third, the included studies were performed in Korea, which may be attributed to the epidemiologic characteristics of cervical cancer. Undeniably, the generalization of our conclusions must be carefully considered. Despite these drawbacks, this meta-analysis

may provide some significant guidance and reference in identifying the optimal treatment strategies for stage IB2-IIA cervical cancer patients.

5. Conclusion

This was the 1st meta-analysis to provide conservative estimates of the clinical treatment effectiveness of radical hysterectomy compared with chemoradiation, in bulky early stage cervical cancer patients. Our study revealed that the RH group had significant superiority over the CRT group among the IB2-IIA patients, especially for IB2 cervical cancer. However, considering the evidence of genitourinary complications, the management of RH should proceed with caution. Prospective, randomized controlled clinical trials with large sample sizes are still required.
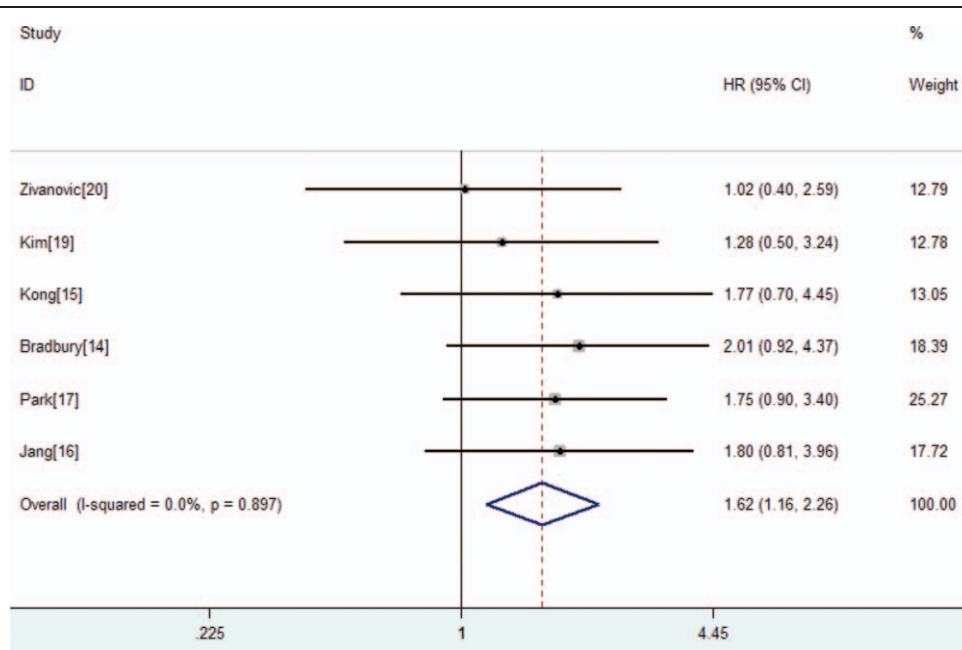
Figure 3. Forest plot of the hazard ratios of progression-free survival between the radical hysterectomy group and chemoradiotherapy group in all papers. CI = confidence interval, HR = hazard ratio.

Table 2

Sensitivity analysis for the comparison of RH group with CRT group.

Outcome	Patients		Effect		Heterogeneity			
	RH	CRT	HR (95% CI)	P-value	χ^2	df	I^2, %	P-value
Sample size >90 patients								
OS	332	196	0.61 (0.41–0.92)	.019	3.41	3	12	.33
PFS	333	197	1.82 (1.23–2.68)	.002	0.07	3	0	.99
High-quality studies								
OS	359	216	0.60 (0.42–0.87)	.007	3.51	4	0	.47
PFS	360	222	1.67 (1.17–2.39)	.005	1.34	4	0	.85
Median follow-up time >40								
OS	158	94	0.52 (0.31–0.86)	.013	0.37	2	0	.83
PFS	158	94	1.61 (1.0–2.6)	.049	1.29	2	0	.53

CI = confidence interval, CRT = chemoradiotherapy, df = degrees of freedom, HR = hazard ratio, OS = overall survival, PFS = progression-free survival, RH = radical hysterectomy.

Table 3

Grade 3/4 adverse events of RH vs CRT for stage IB2-IIA cervical cancer.

Grade 3/4 adverse events	Number		Effect		Heterogeneity			
	RH (events/total)	CRT (events/total)	OR (95% CI)	P-value	χ^2	df	I^2, %	P-value
Hematological abnormality	18/146	15/129	0.43	.669	2.35	2	15	.308
Gastro-intestinal abnormality	9/146	9/129	0.25	.805	1.65	2	0	.439
Genitourinary	10/118	0/103	2.3	.021	0.59	1	0	.442

CI = confidence interval, CRT = chemoradiotherapy, df = degrees of freedom, OR = odds ratio, RH = radical hysterectomy.

Author contributions

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Writing – review & editing: Fang Liu, Han-lin Gong, Lei Liu.

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