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Review article

Adjuvant chemoradiotherapy versus radiotherapy in cervical cancer patients with intermediate-risk factors: A systematic review and meta-analysis

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ABSTRACT

Background: At present, extensive hysterectomy and pelvic lymph node dissection are preferred for early-stage cervical cancer. However, additional adjuvant therapy could be considered if there is a risk for recurrence. Postoperative pelvic radiotherapy plus concurrent platinum-based chemotherapy are recommended for patients with high risk factors. The treatment regimen for patients with intermediate-risk factors, however, remains unclear. We, thus, performed a systematic review and meta-analysis to assess the recurrence-free survival (RFS), overall survival (OS), grade III/IV hematologic toxicity and grade III/IV non-hematologic toxicity in chemoradiotherapy (CRT) versus radiotherapy (RT) groups.

Methods: We systematically searched PubMed, Cochrane, and Embase to identify relevant studies published before November 30, 2018 to compare CRT with RT as a postoperative adjuvant therapy in early-stage cervical cancer patients with intermediate-risk factors. We used Stata (version 14.0) to calculate odds risks (ORs) and 95% confidence intervals (CIs) and pooled data was assessed by the fixed-effects model.

Results: Of the 428 identified studies, only 9 were eligible and included in our analysis (CRT: n = 870; RT: n = 932). CRT significantly prolonged RFS (OR = 3.43, 95% CI 2.08–5.67, P = 0.000) and OS (OR = 1.80, 95% CI 1.30–2.50, P = 0.000). The occurrence rate of grade III/IV hematologic toxicity (OR = 16.07, 95% CI 6.47–39.93, P = 0.000) was significantly higher in CRT, while grade III/IV non-hematologic toxicity was ambiguous for CRT and RT with an OR of 1.91 (95% CI 0.95–3.83, P = 0.069).

Conclusions: For early-stage cervical cancer patients with intermediate-risk factors, CRT can dramatically improve RFS and OS compared with RT. Apart from the increase in grade III/IV hematologic toxicity, CRT was well tolerated and accepted treatment for early-stage cervical cancer.

Contents

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Introduction

At present, extensive hysterectomy and pelvic lymph node dissection are the preferred methods of treatment for early-stage cervical cancer (FIGO (International Federation of Gynecology and Obstetrics) stages I-IIA) [1]. However, additional adjuvant therapy is considered if there are risks for recurrence. The pathological risk factors for recurrence in early-stage cervical cancer after radical hysterectomy were first reported in the 1980s [2]. Parametrial invasion, positive resection margin and pelvic lymph node metastasis are all considered to be high-risk factors [3], and lympho-vascular space invasion (LVSI), deep stromal invasion(DSI) and large tumor size are regarded as intermediate-risk factors for recurrence [4]. While postoperative pelvic radiotherapy plus concurrent platinum-based chemotherapy are recommended for postsurgical patients with high risk factors [5], therapeutic regimen for patients with intermediate-risk factors remains indistinct. Previous phase III studies by Gynecologic Oncology Group (GOG 92) revealed that post-operative radiotherapy after radical surgery, significantly reduced the recurrence risk and improved the recurrence-free survival rate (RFS) in stage IB cervical cancer patients [6]. Nevertheless, a recent review of reports showed that adjuvant radiotherapy (RT) is more likely to have only partial effects, which are not salutary in extra-pelvic recurrence, suggesting that patients with intermediate-risk factors may need chemotherapy in addition to radiotherapy [7]. This combination of radiotherapy and chemotherapy known as chemoradiotherapy (CRT) or chemo-radiation, has been widely used in a variety of malignant tumors. In order to have a better understanding of the advantages of postoperative CRT, we conducted a meta-analysis to provide an overview of all eligible studies comparing CRT with RT alone to treat cervical cancer after radical hysterectomy.

Methods

Search strategy and quality assessment

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [8]. We systematically searched PubMed, Embase and Cochrane to identify relevant articles published before November 30, 2018. Medical Subject Headings (MeSH) terms “Uterine Cervical Neoplasms,” “Chemoradiotherapy,” “Radiotherapy,” and “Risk Factors” were used to search for eligible studies. There were no date or national restrictions in our research. Finally, one randomized controlled trial (RCT) and eight retrospective studies were selected in the present study. The Cochrane Risk of Bias tool [9] and the Newcastle–Ottawa Scale (NOS) [10] were used to assess the methodological quality of RCT and rerospective studies, respectively. Disagreements in the evaluation process were resolved by discussions and consensus between the two reviewers (Mengyang Hu and Yuanjian Wang).

Selection criteria

The inclusion criteria were: (a) pathology certified as cervical neoplasm; (b) FIGO stage I-II cervical cancer with intermediate-risk factors; (c) studies on high-risk factors (parametrial invasion, positive resection margin and pelvic lymph node metastasis) were excluded; (d) English full-text publications; (e) unpublished articles, summaries or comments were excluded.

Data extraction

Based on the inclusion criteria, 2 reviewers (Meng Li and Mengyang Hu) extracted the following data parameters independently from each eligible study: name of the first author, year of publication, country of origin, number of patients, inclusion period, histology types, FIGO stage, surgical procedures, chemotherapy details, and radiotherapy traits. The primary characteristics of the selected publications are shown in Table1. The endpoints for the assessment for early-stage cervical cancer with intermediate-risk factors were: RFS, overall survival (OS), grade III/IV hematologic toxicity and grade III/IV non-hematologic toxicity.

Statistical analysis

We calculated OR (odds risks) and 95% CI (confidence intervals) using the Stata 14.0 (STATA Corporation, College Station, TX, USA) to generate forest plots, determine statistical significance, and to evaluate the heterogeneity of the eligible studies. In the absence of heterogeneity, the fixed-effects model was used to compute the comprehensive risk estimation. Publication bias was evaluated by the Begg and Egger tests, and $p < 0.05$ defined statistically significant publication bias [11]. The Cochran Q test was used to evaluate the heterogeneity between studies [12] and I^2 testing was performed to assess the magnitude of inter-study heterogeneity; an I^2>50% indicated moderate-to-high heterogeneity [13].

Resuits

Study selection

After scanning the electronic databases and performing manual retrieval, a total of 428 records (PubMed 190 records, Embase 199 records, and Cochrane 39 records) were scrutinized for inclusion. Only 9 studies [14–22] met all the inclusion/exclusion criteria for this meta-analysis. The remaining 419 articles, including case reports, non-English studies, meta-analysis, reviews and irrelevant papers were excluded based on titles and abstracts. The flowchart of the selection procedure is shown in Fig. 1.

Study characteristics

A total of 870 patients in the CRT group and 932 in the RT arm were identified in the selected 9 trials and were all published between 2009 and 2018. Squamous cell carcinoma (SCC) was diagnosed in 1348 patients (75%) and 457 cases were histologically other than SCC. In the nine studies, intermediate-risk factors were not exactly the same, but all cases were consistent with the overall study population. Except for two [14,20], the rest of the seven studies clearly specified the radiotherapy (1.8–2.0 Gy/F; total

Table 1
Characteristics of included studies. (RH: radical hysterectomy; RH-PLND: radical hysterectomy and pelvic lymphadenectomy).

Study	Design type	Country	Group	No. of patients	Inclusion period	Histology		Stage	Surgery	Radiotherapy	Concurrent Chemotherapy
						Squamous	Non-squamous				
Kim [14]	Retrospective	Korea	CCRT	55	1997-	42	16	IB-IIB	RH with pelvic/ paraaortic lymphadenectomy	Total dose: 45-50 Gy	Paclitaxel + carboplatin q3-4wks for 2-3cycles
			RT	24	2005	17	16				
Mabuchi [15]	Retrospective	Japan	CCRT	22	1997.4-	13	9	IB-IIA	RH-PLND	Pelvic and the regional of node: 2.0 Gy/F×5 F/wk, total dose:50 Gy	Nedaplatin 40 mg/m2 d1, qwk for 5 cycles
			RT	35	2006.3	27	8				
Ryu [16]	Retrospective	Korea	CCRT	89	2000.1-	71	18	IB-IIA	RH-PLND	Pelvic and the regional of node: 1.8-2.0 Gy/F×5 F/wk, total dose:	cisplatin 40 mg/m2 qwk or cyclophosphamide 500 mg/m2, plus
			RT	49	2006.6	36	13			40-50.4 Gy	cisplatin 50 mg/m2 q3wks
Song [17]	Retrospective	Korea	CCRT	54	1990-	37	17	IB-IIA	Radical surgery	Pelvic and the regional of node: 1.8-2.0 Gy/F× 5 F/wk,	Paclitaxel 135 mg/m2, Carboplatin 4.5 mg min/ml, q4wks for 2-6cycles
			RT	56	2010	47	9			total dose: 45-50.4 Gy	
Okazawa [18]	Retrospective	Japan	CCRT	89	1996.1-	64	25	IB1-IIB	RH-PLND	Pelvic and the regional of node:1.8-2.0 Gy/F×5 F/wk,	Nedaplatin 40 mg/m2 qwk for 5 cycles or Nedaplatin 70 mg/m^2 biweekly for 2 cycles
			RT	40	2009.12	31	9			total dose:45-50.4 Gy	
Sun [22]	RCT	China	CCRT	15	2011.9-	13	2	IB-IIA	RH with pelvic/ paraaortic lymphadenectomy	Pelvic and the regional of node:1.8-2.0 Gy/F× 5 F/wk, total dose:45-50 Gy	topotecan 0.75 mg/m2, followed by cisplatin 25 mg/m2 d1-3 for 3 cycles
			RT	13	2013.8	12	1				
Yu [21]	Retrospective	China	CCRT	44	2010.2-	44	0	IA-IIA	RH-PLND	Pelvic and the regional of node: 1.8-2.0 Gy/F× 5 F/wk,	Carboplatin 150 mg/m2 and paclitaxel 60 mg/m2 qwk for 5-6 cycles
			RT	42	2014.3	42	0			total dose:45-50 Gy	
Mahmoud [20]	Retrospective	United States	CCRT	440	2004-	269	171	IB-IIA	RH-PLND	/	/
			RT	429	2013	280	149				
Sun [22]	Retrospective	China	CCRT	124	2008.1-	123	1	IB-IIA	RH-PLND	Pelvic and the regional of node:5 F/wk,	Cis-diamminedichloro-platinum 40 mg/m2d1, qwk for 4-5 cycles.
			RT	182	2011.12	180	2			total dose:45-54 Gy	

dose: 45–54 Gy) and chemotherapy regimens. Although the chemotherapy doses varied from study to study, all of them were based on platinum compounds. In one study, 17 patients received neoadjuvant chemotherapy for one to four cycles before radical surgery [14]. One RCT [19] was closed ahead of time due to serious hematologic toxicity during adjuvant CRT, hence, only the data on grade III/IV hematologic toxicity and grade III/IV non-hematologic toxicity were used in this meta-analysis.

Effects of CRT vs. RT for different endpoints

The four endpoints assessed were RFS, OS, grade III/IV hematologic toxicity and grade III/IV non-hematologic toxicity in both the adjuvant CRT and RT groups. RFS was reported in seven trials. However, hematologic and non-hematologic system toxicities were available only in five studies, and OS was mentioned only in four studies.

The seven trials containing data for RFS reported 477 patients in the CRT arm and 428 patients in the RT alone arm. It was quite clear that the RFS of the CRT group was higher than the RT group (OR = 3.43, 95% CI 2.08–5.67, P = 0.000), (I^2 = 0%). The analysis indicated that cervical cancer with intermediate-risk factors significantly benefitted from CRT. Analysis of the 4 studies covering 1002 people in CRT group and 640 people in RT group revealed obvious deviations in OS between the groups (OR = 1.80, 95% CI 1.30–2.50, P = 0.000), (I^2 = 0%). Grade III/IV hematologic toxicities including neutropenia, thrombocytopenia, myelosuppression, and anemia were more acute in the CRT group than the RT group (OR = 16.07, 95% CI 6.47–39.93, P = 0.000), (I^2 = 0%). However, there were very few treatment-related deaths. The occurrence rate of grade III/IV non-hematologic system toxicities, including hepatotoxicity, nephrotoxicity, diarrhea, genitourinary toxicity were ambiguous for both CRT and RT groups with an OR of 1.91 (95% CI 0.95–3.83, P = 0.069), (I^2 = 0%) (Fig. 2).

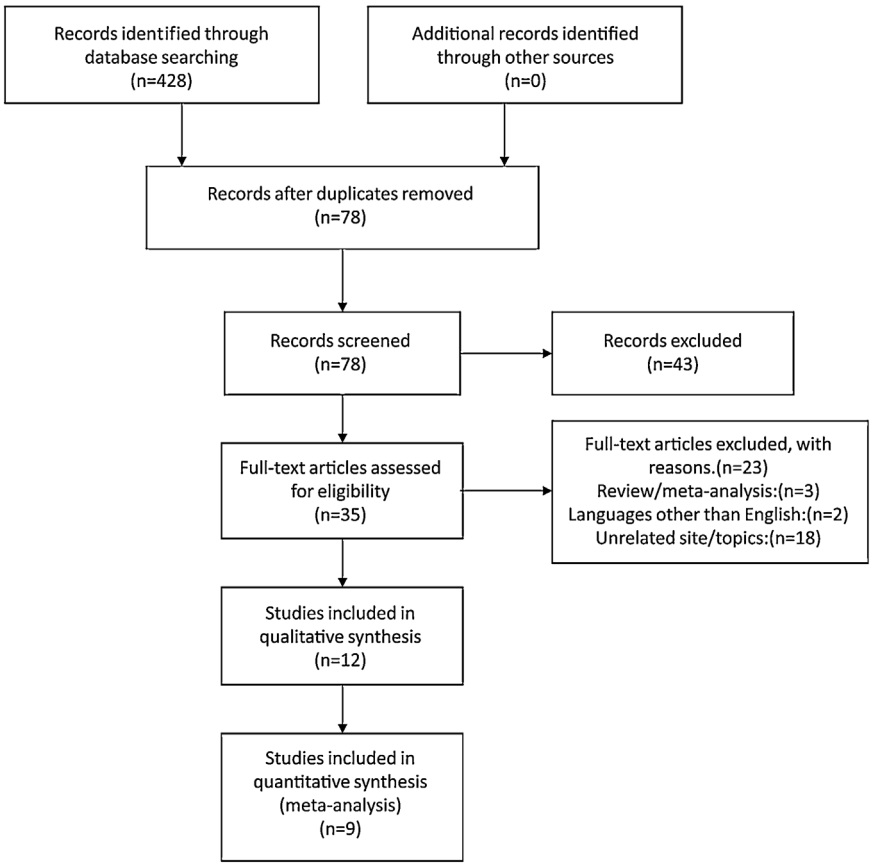

Fig. 1. Study selection process.

Publication Bias

Begg rank correction test and Egger linear regression indicated that no significant publication bias impacted the results of the meta-analysis (Fig. 3).

Discussion

Cervical cancer is the fourth most common cancer in women, with an estimated 570 000 new cases and 311,000 deaths in 2018. Underdeveloped countries carry a significant proportion (more than 85%) of the burden of deaths due to cervical cancer [23]. The therapeutic strategies for early-stage cervical cancer including radical surgery, radiotherapy and chemotherapy are based largely on the FIGO stage, patient's overall physical health and treatment choices, surgeon's experience, and clinical judgment. Factors influencing the prognosis of cervical cancer include pathological stages, degree of differentiation, lymph node metastasis, and resection margins. Postoperative treatment option for patients in early-stage cervical cancer with intermediate-risk factors for recurrence is not well defined.

The proceeding of the National Comprehensive Cancer Network (NCCN) guidelines recommends pelvic radiotherapy as category I treatment in cervical cancer. Owing to the effectiveness, radiotherapy has become the most recommended adjuvant therapy in patients with intermediate-risk factors after radical surgical resection [24]. Nevertheless, nearly half of the patients with early-stage cervical cancer suffer from recurrence in the extrapelvic region [25]. The main objective of adjuvant therapy after radical surgery, however, should be to reduce extrapelvic recurrence rather than local recurrence. To control extra-pelvic recurrence, many studies have debated whether to add chemotherapy as an adjuvant therapy. So far, it is not clear whether chemotherapy with RT is better or safer than RT alone. A previous meta-analysis reported significant survival benefits of CRT only in patients with high risk factors; patients with intermediate-risk factors did not benefit from CRT [26]. The present analysis indicated that cisplatin-based chemotherapy combined with radiation can increase RFS and improve the OS in cervical cancer patients with intermediate-risk factors. Despite the seeming advantages, there is a caveat of the probability of severe treatment-related complications associated with adjuvant chemoradiotherapy in patients with cervical cancer undergoing radical surgery, which may adversely affect the patient's quality of life (QOL). After all, it is prudent to take into account the adverse events as well as the QOL for long-term survivors. In the present study, compared to RT alone, the incidence of grade III/IV hematologic toxicities were higher in the CRT group, which can be mostly managed with conservative treatments. Moreover, we found no distinct difference in grade III/IV non-hematologic toxicity between the CRT and RT groups. Therefore, concomitant adjuvant chemotherapy might improve the efficacy of RT for postoperative cervical cancer.

Previous observations have shown that cervical cancer is moderately chemosensitive. Cisplatin is the most effective antineoplastic agent widely used in cervical cancer. In a cervical cancer preclinical assessment, nedaplatin exhibited obvious antitumor competency equivalent to cisplatin with less-severe nephrotoxicity, neurotoxicity and gastrointestinal complications [27]. Other chemotherapy drugs such as fluorouracil and paclitaxel also are effective in cervical cancer. Although in recent years neoadjuvant chemotherapy (NACT) has been used in patients with locally advanced cervical

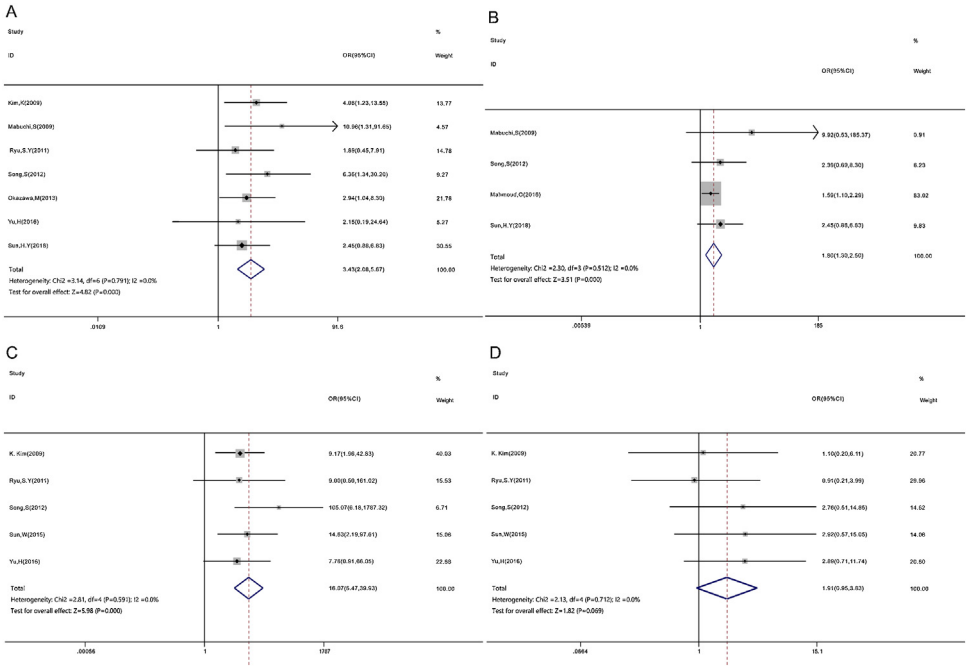

Fig. 2. Forest plots for CRT vs. RT trials for RFS (A), OS (B), grade III/IV hematologic toxicity (C) and grade III/IV non-hematologic toxicity(D).

cancer (FIGO stage IB2–IIB), its efficacy in the context of PFS and OS still is debatable [28,29]. Previous study on chemotherapeutic agents used concurrently with chemoradiotherapy, demonstrated that the combination of cisplatin and 5-fluorouracil increased progression-free survival (PFS) and OS compared with hydroxyurea [30]. Since the report by Rose et al. (1999) showing the effectiveness of adjuvant chemoradiotherapy in locally advanced cervical cancer (improvement in OS and PFS in stage IIB-IVA cervical cancer patient), the National Cancer Institute (NCI) has recommended cisplatin-based chemoradiation as the standard treatment for patients with locally advanced disease [31]. Another study showed that paclitaxel + carboplatin therapy combined with radiotherapy and consolidation chemotherapy improved the 3-year PFS and OS of patients at high risk of lymph node metastasis after radical surgery [32]. Nonetheless, the exact role of adjuvant chemoradiotherapy on patients with intermediate-risk factors remains doubtful. Two important issue that need to be defined are the optimal number of chemotherapy cycles and specific dosage of chemotherapy drugs. Although CRT was not routinely recommended by the NCCN and FIGO in women with intermediate-risk factors for recurrence, an overwhelming number of patients have accepted postoperative CRT in the past few years. An international prospective trial (GOG 263) is currently evaluating the

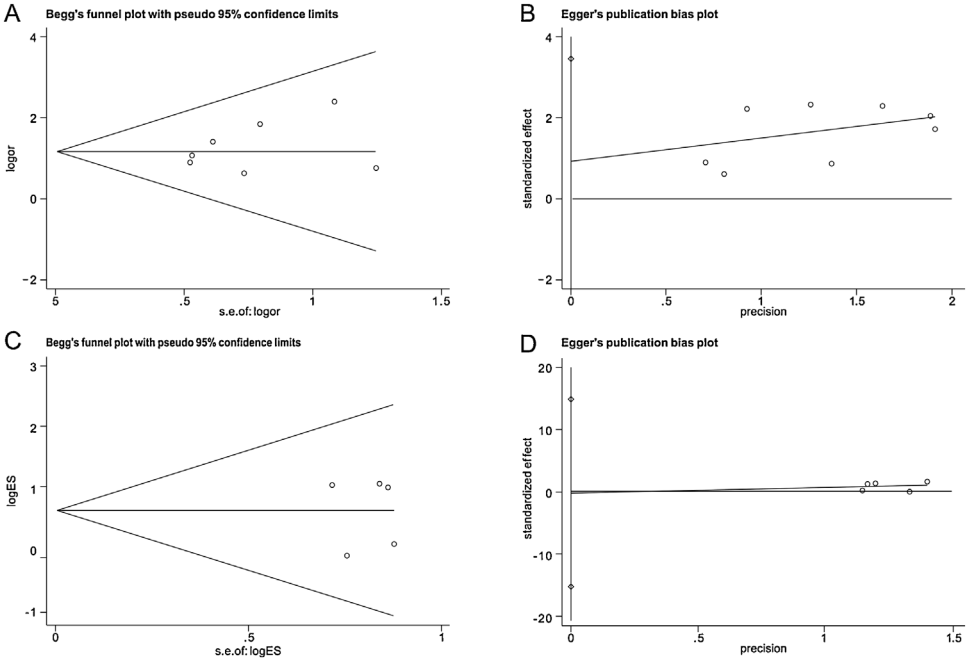

Fig. 3. Publication bias for RFS (A, Begg: P = 0.369 > 0.05; B, Egger: P = 0.382 > 0.05, for grade III/IV non-hematologic toxicity (C, Begg: P = 0.462 > 0.05; D, Egger: P = 0.955 > 0.05).

impact of adjuvant CRT in patients with intermediate-risk factors [33]. The outcome of this trial may help to identify patients who will benefit from CRT rather than RT alone. Multicenter randomized trials with large sample size are needed to determine which regimen is most effective in postoperative early-stage cervical cancer.

Limitations of this study

The potential limitations of the present study are as follows: First, a very small number of papers were included and most papers reported a small series. Second, there was only one RCT in our study; the reliability of retrospective studies is relatively low due to a number of inherent caveats, including patient heterogeneity, selection bias and incomplete data. Third, pathological stages of the disease in every study were not exactly same, and variations in chemotherapy regimens, RT patterns and target volumes could have resulted in distinct differences. Fourth, the search strategy was limited to articles published in English. High quality articles published in other languages could not be included given the difficulty in obtaining accurate translation and data. Fifth, owning to the lack of subgroup analysis by the number of intermediate-risk factors, our research was unable to specifically identify patients who will benefit most from adjuvant chemoradiotherapy.

Conclusions

Currently, with the popularization of cervical cancer screening, the incidence of early-stage cervical cancer has gradually increased and the age of onset of cervical cancer has tended to be younger [34]. With further deepening of research, the treatment of early-stage cervical cancer has also attracted a lot of attention. Additional chemotherapy could dramatically improve RFS and OS in early-stage cervical cancer of intermediate-risk factors. Moreover, adjuvant chemoradiotherapy could be well tolerated and accepted in early-stage cervical cancer. Nevertheless, due to the absence of specific regimens with overwhelming benefits, chemotherapy should be chosen based on the consideration of security and QOL. Above all, large-scale population-based studies are required to get more robust data to validate the present findings.

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