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Adjuvant Therapy in Early-Stage Cervical Cancer Patients with Intermediate-Risk Factors, Comparing Between Chemotherapy and Radiotherapy: A Systematic Review and Meta-Analysis

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Abstract

BACKGROUND: Patients with early-stage cervical cancer (ESCC) after radical hysterectomy surgery usually need additional adjuvant treatment, but it depends on the presence or absence of certain risk factors. Factors, such as large tumor size, deep stromal invasion, and lymphovascular space involvement, are classified as intermediate risks. Therefore, postoperative adjuvant concurrent chemo-radiotherapy (CRT) or radiotherapy (RT) is recommended for ESCC with risk factors. However, it remains controversial whether CRT is superior to RT as an adjuvant regimen for postoperative with risk factors.

METHODS: A systematic search was performed within PubMed, Cochrane, Science Direct, and Google Scholar databases to research the outcome between CRT and RT in ESCC. Three reviewers independently reviewed titles, abstracts, and full article text to identify studies meeting inclusion and exclusion criteria. If there are any discrepancies, it will be resolved by discussion. In this analysis, the Newcastle–Ottawa scale was used to assess the risk of bias of non-randomized studies. We used review manager 5.4 to calculate the result of 95% CI for the outcomes using odds ratio (OR), random effect model was also used if there is heterogeneity. The primary endpoints of interest are recurrence-free survival (RFS) and overall survival (OS).

RESULTS: A total of 14 studies included in qualitative synthesis and meta-analysis with a total of 5.294 patients were identified. Patients who had RT after radical hysterectomy was found to significantly have a more favorable RFS rate with OR 0.57 95% CI (0.38–0.84), p = 0.005; I^2 = 63%. Nine studies were found comparing the OS between adjuvant RT and adjuvant CRT in a patient with ESCC with intermediate risk, the result is quite similar favoring adjuvant RT with significantly better OS outcome OR 0.69 95% CI (0.54–0.87), p = 0.002; I^2 =34%. 1.526 had hematologic toxicities, 797 were RT and 729 had CRT. The study showed RT had better outcomes with lesser toxicities (OR 0.11, 95% CI [0.03–0.44] p = 0.002; I^2 = 91%). Non-hematological toxicity, with a total of 1.463 patients, 799 were RT and 664 had CRT. Random models were used due to heterogeneity. RT is significantly associated with lesser non-hematologic toxicities with OR 0.34, 95% CI (0.18–0.66) p = 0.001; I^2 = 65%.

DISCUSSION: During the last two decades, there were significant changes in practice to cure uterine cervical cancer. Based on the consistent results generated in several previous randomized controlled trials, cisplatin-based CCRT has become the standard treatment for advanced cervical cancer. A randomized prospective studies by Sedlis *et al*., randomized FIGO IB patients without residual tumor or involved lymph nodes but with two or more intermediate-risk factors later named the "Sedlis criteria" to receive observation or RT following radical surgery. Adjuvant RT led to a reduction of recurrence rates at the cost of an approximately 4% higher rate of grade 3/4 adverse events. There was no increase in OS but an improvement of long-term RFS. On the other hand, a study found that RFS and OS were significantly improved in the addition of chemotherapy, especially in patients with clinical-stage IA2, IB, and IIA with para-metric invasion, residual tumor and/or lymph node involvement. This study found that RT had better outcomes in RFS and OS, RT also had lesser hematologic toxicity and non-hematologic toxicity. After all, it is prudent to take into account the adverse events as well as the QOL for long-term survivors.

CONCLUSION: Adjuvant RT shows a better outcome in RFS and OS. CRT is often associated with greater hematological and non-hematological toxicities. Further high-quality randomized clinical trials with larger sample size comparing the efficacy and toxicity of adjuvant CRT with RT are recommended.

Introduction

Cervical cancer is the fourth-most common cancer among women worldwide and the second-most diagnosed cancer in developing countries [1]. Most patients with stage IB–IIA cervical cancer, according to the International Federation of Gynaecology and Obstetrics (FIGO) staging system, are treated by radical hysterectomy with pelvic lymph node dissection (PLND). Radical hysterectomy with pelvic lymphadenectomy has been a primary treatment in women with stage IB cervical cancer, and the procedure is associated with a 5-year survival rate of 87–92% [2].

After surgical treatment, adjuvant radiotherapy (RT) or chemo-radiotherapy (CRT) is recommended according to the presence of risk factors on histopathologic examination [3]. These risk factors,

including parametrial invasion, positive resection margin, and lymph node metastasis, are defined as high-risk factors. These factors are associated with a higher rate of recurrence (35–40%), requiring adjuvant CRT [4], [5]. RT was also a feasible technique that provides similar outcomes as radical hysterectomy. Surgery enables pathological examination by surgeons, permitting the identification of risk factors for cancer recurrence [6], [7].

On the other hand, isolated intermediate-risk factors such as lymphovascular space involvement (LVSI), large tumor size, or deep stromal invasion (DSI) do not significantly increase the recurrence rate. When those risks are combined, the risk of recurrence increases to 15–20%. In consequence, the prognostic significance of intermediate-risk factors and the appropriate management of these patients remain controversial [5].

In 2000, a study from America reported a significant survival benefit associated with CCRT rather than RT alone in patients with high-risk factors, such as parametrial invasion, lymph node metastasis, and positive surgical margin [7]. Until now, CCRT has been considered a primary postoperative therapy for high-risk cervical cancer. However, the treatment regimen for patients with intermediate risk factors, including deep stromal invasion (DSI), lymph vascular space involvement (LVSI), low differentiation, and tumor diameters ≥4 cm remains unclear [8].

According to a phase 3 trial of the Gynecologic Oncology Group (GOG 92), the stage IB cervical cancer patients with intermediate-risk factors showed improved recurrence-free survival (RFS) and reduced risk of recurrence when treated with adjuvant post-surgical RT [2]. However, some studies suggest the need for chemotherapy in addition to RT because RT alone is showing extra pelvic recurrence. The need for CRT is still debatable for the presence of hematological, gastrointestinal, hepatic, genitor-urinary, and lymphatic toxicities, and it always exists with fear for over-treatment [9].

Adjuvant RT therapy was associated with a 47% reduction in the risk of recurrence. Some follow-up data published in 2006 confirmed that there is an improvement of progression-free survival (PFS) in patients with adjuvant RT. Other publications reported similar improved outcomes after adjuvant RT, but the study suffered from limitations such as small sample size, and heterogeneity of patient population. It should be noted that from today's perspective the original GOG trial also had many limitations [2].

Since no randomized prospective trials have been reported that compare outcomes of adjuvant RT with those of CCRT in patients with intermediate-risk factors, no standard criteria are universally accepted to define distinct risk groups among these patients. The aim of this systematic review and meta-analysis is to identify the comparative studies assessing the survival rate and complications of early-stage cervical cancer (ESCC) patients with intermediate-risk factors who have undergone radical hysterectomy and using post-surgical adjuvant RT versus CRT.

Methods

Literature search

This systematic review and meta-analysis were taken on according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P). The literature search was conducted in Pubmed, Cochrane Library, Science Direct, and Google Scholar from January 2002 until September 2022 using the following terms: "Uterine Cervical Neoplasms," "cervical cancer," "Early stage," "Hysterectomy," "Radiotherapy, Adjuvant,' "Chemotherapy, Adjuvant," "survival, complication" with all studies must be comparative, in English and full-text publication. Further manual search was performed by scanning the references of all included and relevant studies. Our study design is provided in supplement Table 1.

Table 1: Supplement for study design

Patients	Cervical cancer patients with intermediate risk who had adjuvant radiotherapy or chemo radiotherapy after radical hysterectomy
Literature search	Keyword search in PubMed, Cochrane, Science Direct, and Scholar
Limits	Only comparable studies, January 2002–September 2022 In English
Keywords	Uterine cervical neoplasm, cervical cancer, hysterectomy Early stage cervical cancer, intermediate risk Radiotherapy, chemo radiotherapy, adjuvant Survival or complication
Eligibility criteria	Article in full text No duplicate articles Reported each of the interested outcomes: type of publication (prospective and retrospective trial), patient characteristics (total population, age, intermediate risk definition, histology type, intervention given and pathological stage), duration of follow-up, intervention given (radiotherapy type and chemo-radiotherapy type), Recurrence free survival, overall survival, adverse event (hematological toxicity, non hematological toxicity) Outcome reported in a usable form (each surgical approach was reported as a separate cohort, no missing or unreliable data)
Exclusion criteria	Duplicate patient population, where some or all of the same patients were included in a different study reporting on the same parameters (prevents double counting) Total sample size less than 10
Data extraction	Articles needed to report and contain each of outcome of interest to be included in the analysis. Three reviewers independently reviewed titles of full article text to identify studies meeting inclusion and exclusion criteria. Discrepancies were resolved by discussion before data analysis. All primary outcomes were then double checked and any discrepancies resolved.
Primary outcomes	Recurrence free survival Overall survival (OS) rate
Secondary outcomes	Hematological toxicity Non hematological toxicity

The following PICO criteria were considered to identify the study:

- Patients (P): ESCC patients with intermediate-risk factors who had a radical hysterectomy.
- Intervention (I): Adjuvant radiotherapy
- Comparison (C): Adjuvant chemotherapy.
- Outcome (O): overall survival (OS), disease recurrence, complications, and toxicities.

Eligible criteria and study selection

The population was women diagnosed with ESCC that underwent radical hysterectomy who then had adjuvant therapy post-operative and the types of publication were prospective or retrospective. Three reviewers independently reviewed titles, abstracts, and full article text to identify studies meeting inclusion and exclusion criteria, if there are any discrepancies, it will be resolved by discussion. The Newcastle–Ottawa scale was used to assess the risk of bias of non-randomized studies in this analysis (Table 2).

Outcome measures

The study's primary outcome was the OS and disease recurrence. Secondary outcomes were complications from hematological toxicities and non-hematological toxicities. The data from all the included studies were extracted using an Excel spreadsheet (Microsoft, USA). Data regarding the baseline characteristics are country, the study design, FIGO stage of cervical cancer, intermediate-risk factors definitions of each study, sample size, histology cell type, mean follow-up period, interventional characteristics from types RT dose and frequency, a chemotherapeutic agent used, dose and frequency of administration and finally outcome characteristics from OS, disease recurrence, hematological and non-hematologic toxicities were retrieved from all included studies.

Statistical analysis

The retrieved data were subjected to both qualitative and quantitative analysis. The demographic and interventional characteristics were tabulated for all included. Data were pooled using the Mantel-Haenszel fixed-results fashions with risk ratio (RR) because of the impact degree with the associated 95% confidence interval (CI). The dichotomous outcomes such as OS, disease recurrence, and toxicities were expressed as risk ratio (RR) with CI and subjected to meta-analysis. Statistical heterogeneity among companies becomes measured by the usage of Higgins I^2 statistic. Specifically, an $I^2 = 0$ indicated no heterogeneity even as we have taken into consideration excessive heterogeneity primarily based totally on the values of I^2 as above 50%. If the heterogeneity with a $p < 0.05$, random model was used. Publication bias becomes evaluated in step with evaluation of the funnel plot asymmetry. All analyses had been done by Review Manager 5.4.1 (the Nordic Cochrane Centre, The Cochrane Collaboration, 2020). A $p < 0.05$ (two-sided) was considered statistically significant.

Results

Search outcomes and study selection process

3.080 records were identified during the initial search (2.950 from Scholar, 51 from Science Direct, 58 from Pubmed, and 31 from Cochrane), 21 records were removed due to duplicates. 2.673 records were removed due to the following reasons, 1.169 because of irrelevant titles, 728 were because it was not a comparative study, 638 studies were excluded because not a trial, 109 studies were not relevant intervention, and lastly, 29 studies were excluded because of not relevant subject. Finally, after we further undertook a complete assessment, 72 studies were excluded and 14 studies were included in qualitative synthesis and meta-analysis, with a total of 5.294 patients were identified. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram Figure 1 [7], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [22], [23], [24], [25], [26], [27], [28] shows the entire review process from the original search to the final selection of studies. The included studies were

Table 2: Supplement risk of bias assessment

Checklist	Cao	Kim	Mabuchi	Mahmoud	Okazawa	Ryu	Sun	Schral	Song
Selection									
Representativeness of exposed cohort	*	*	*	*	*	*	*	*	*
Selection of nonexposed cohort	*	*	*	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*	*	*	*
Non presence of outcome at beginning	*	*	*	*	*	*	*	*	*
Comparability									
Comparability of cohorts	**	**	**	**	*	*	*	**	*
Outcome									
Assessment of outcome	*	*	*	*	*	*	*	*	*
Enough follow-up time	*	*	*	*	*	*		*	*
Adequacy of follow up	*	*	*	*	*	*		*	*

Checklist	Huang	Hosaka	Kim H	Sun HY	Matsuo	Nie
Selection						
Representativeness of exposed cohort	*	*	*	*	*	*
Selection of nonexposed cohort	*	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*	*
Non presence of outcome at beginning	*	*	*	*	*	*
Comparability						
Comparability of cohorts	*	*	**	**	**	**
Outcome						
Assessment of outcome	*	*	*	*	*	*
Enough follow-up time	*		*	*	*	*
Adequacy of follow up	*		*	*	*	*

carried out in China, South Korea, Japan, Germany, and the US, thus making this meta-analysis have wide geographic diversity, the base characteristics of each study are provided in Table 3.

Main characteristics and quality assessment of included studies

The data quality of the studies was assessed using the Newcastle-Ottawa quality assessment form for Cohort studies, which was divided into three quality. Three or four stars in the selection domain and 1 or 2 stars in the comparability domain and 2 or 3 stars in the outcome/exposure domain was concluded in good quality. Fair quality was 2 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the outcome/exposure domain. The poor quality was 0 or 1 star in the selection domain odds ratio (OR) 0 stars in comparability domain OR 0 or 1 stars in the outcome/exposure domain. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram reveals the entire review process from the original search to the final selection of the citations in this study. Most of our selected study is fall into good quality studies, each of the study assessment summary is provided in Table 2.

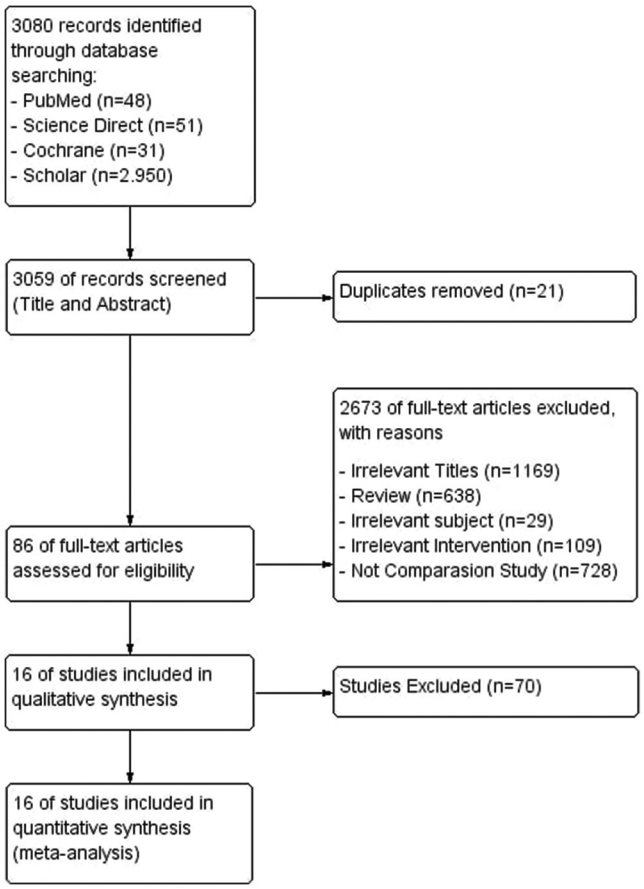

Figure 1: Flow chart of study selection

This systematic review and meta-analysis included twelve retrospective studies and two randomized clinical trials. All the included population studies were ESCC patients with FIGO stage ranging from IA to IIB with intermediate risk factors. The intermediate risk factors to classify these ESCC patients included large tumor size from 2 to 4 cm, deep stromal invasion with invasion depth more than half into the thickness of the cervical wall with lymphovascular space invasion; each of the study definition of intermediate-risk is provided in Table 4. From of 5.294 total patients, 4.232 patients were Asian [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [27], [28] and 1.062 were non-Asian [21], [22]. Thus, this study's total population was mostly Asians, 2.765 received adjuvant CRT and 2.178 patients received adjuvant RT after radical hysterectomy. These patients were follow-up until a maximum of 93.5 months and a minimum of 16 months.

Pooled analysis for clinical outcomes

All the patients were treated by radical hysterectomy with or without pelvic lymph node dissection. The patients receiving adjuvant RT were mostly exposed to pelvic RT with a daily fraction of 1.8–2 Gy for a total dose ranging from 45 to 50 Gy for around four to six weeks. In the patients receiving adjuvant CRT, CRT was administered a range of chemotherapeutic agents for a definite dose and specified frequency duration. Cisplatin with a dose ranging from 30 to 40 mg/m^2 was the most common

Table 3: Base characteristics of the study

Author	Year	Study design	Country	Figo stage	Total		Mean age	Cell type		Follow-up (month)
					CRT	RT		Squamous	Non	
Cao *et al*.	2020	Retrospective study	China	IB1-IIA2	493	283	47	861	0	63
Kim *et al*.	2008	Retrospective study	South Korea	IB1-IIB	55	24	NA	59	23	51
Mabuchi *et al*.	2009	Retrospective study	Japan	IA2-IIB	22	35	49.7	40	17	36
Mahmoud *et al*.	2016	Retrospective study	US	IB-IIA	440	429	46	549	320	48
Okazawa *et al*.	2013	Retrospective study	Japan	IB1-IIB	89	40	50	95	34	58.7
Ryu *et al*.	2011	Retrospective study	South Korea	IB1-IIA	89	49	49.8	107	21	44.6
Huang *et al*.	2021	RCT	China	IB1-IIA2	345	350	48	600	95	56
Sun *et al*.	2015	RCT	China	IB1-IIA2	13	15	NA	26	2	16
Scharl *et al*.	2021	Retrospective study	Germany	IB-IIA	119	74	NA	143	50	93.6
Song *et al*.	2011	Retrospective study	South Korea	IB1-IIA	54	56	NA	84	26	NA
Sun *et al*.	2018	Retrospective study	China	IB-IIA	124	182	NA	303	3	61
Yu *et al*.	2016	Retrospective study	China	IA-IIA	44	42	NA	86	0	30
Matsuo *et al*.	2017	Retrospective study	Japan	IB-IIB	502	253	48.7	597	158	64.5
Nie *et al*.	2021	Retrospective study	China	I-IIA	275	61	NA	485	86	62
Kim *et al*.	2020	Retrospective study	Korea	IB-IIA	73	243	49	232	84	70
Hosaka *et al*.	2008	Retrospective study	Japan	IB1-IIB	493	283	47	861	0	63

RCT: Randomized controlled trials; CRT: Concurrent chemo-radiotherapy; RT: Radiotherapy; NA: Not available.

chemotherapeutic agent used and it was administered in six included studies, nedaplatin at a dose of 40 mg/m^2 was administered in two included studies, the rest of the studies used 5-fluorouracil, cyclophosphamide (500 mg/m^2), carboplatin (150 mg/m^2), cis-diammine-dichloro-platinum (40mg/m^2), bleomycin, topotecan (0.75 mg/m^2) or in combination of above chemotherapeutic agents. The intervention given in each study is provided in Table 5.

Thirteen studies [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20], [21], [27], [28] comparing the RFS rate between adjuvant RT and adjuvant CRT in a patient with ESCC with intermediate risk, pool analysis were used to pool the odds of association for RFS patients. We further analyzed using a random model due to heterogeneity. Patients who had RT after radical hysterectomy was found to significantly had a more favorable RFS rate with OR 0.57 95% CI (0.38–0.84), p = 0.005; I^2 = 63% (Figure 2). Nine studies [9], [10], [11], [12], [18], [19], [20], [21], [27] were found comparing the OS between adjuvant RT and adjuvant CRT in a patient with ESCC with intermediate risk, the result are quite similar favoring adjuvant RT with significantly better OS outcome OR 0.69 95% CI (0.54–0.87), p = 0.002; I^2 = 34% (Figure 3).

For the adverse event during therapy, we divide them into hematologic toxicities and nonhematologic toxicities. In hematologic toxicities there were seven studies included with a total of 1.526 patients, 797 underwent RT and 729 had CRT. After using random model because of heterogeneity, the study showed between patients receiving post-surgical adjuvant RT and adjuvant CRT showed RT had more better outcomes with lesser toxicities (OR 0.11, 95% CI [0.03–0.44] p = 0.002; I^2 = 91%) (Figure 4).

Eight studies reported for non-hematological toxicity, with a total of 1.463 patients, 799 of those were RT patients and 664 had CRT. We also underwent random model due to heterogeneity in patients with non-hematologic toxicity. RT is significantly associated with lesser non-hematologic toxicities with OR = 0.34, 95% CI (0.18–0.66) p = 0.001; I^2 = 65% (Figure 5).

Table 4: Definition of intermediate risk factors of the study

Author	Year	Intermediate risk factor
Cao *et al*.	2020	A tumor with positive LVSI with one of deep 1/3 stromal invasion, middle 1/3 stromal invasion and tumor diameter ≥2 cm, superficial 1/3 stromal invasion and tumor diameter ≥5 cm, or with no LVSI but with deep or middle 1/3 stromal invasion and tumor diameter ≥4 cm
Kim *et al*.	2008	Large tumor size (longest diameter on surgical specimen 4 cm), DSI (invasion depth 1/2 of the cervical wall), and LVSI
Mabuchi *et al*.	2009	Large tumor size >4 cm, LVSI, and DSI
Mahmoud *et al*.	2016	NA
Okazawa *et al*.	2013	Large tumor >4 cm in diameter, LVSI, or DSI
Ryu *et al*.	2011	Lymphovascular space involvement, greater than one-third stromal invasion, or tumor size >2 cm
Huang *et al*.	2021	Large tumor size (longest diameter on surgical specimen 4 cm), DSI (invasion depth 1/2 of cervical wall), and LVSI
Sun *et al*.	2015	Apillary lymphatic space involvement, stromal invasion depth, and tumor size >4 cm in diameter
Scharl *et al*.	2021	Large tumor size (longest diameter on surgical specimen 4 cm), DSI (invasion depth 1/2 of cervical wall), and LVSI
Song *et al*.	2011	DSI, defined as an invasion into >half the thickness of the cervical wall; LVSI; tumor size ≥4 cm
Sun *et al*.	2018	LVSI, depth of cervical stromal invasion >1/2, and tumor size >4 cm. Patients with high- or low-risk factors were excluded
Yu *et al*.	2016	DSI, LVSI, tumor diameters >4 cm, and low differentiation
Matsuo *et al*.	2017	NA
Nie *et al*.	2021	LVSI, DSI and tumor size >4 cm
Kim *et al*.	2020	LVSI, over one-half stromal invasion, or tumor size ≥4 cm
Hosaka *et al*.	2008	DSI (>2/3 thickness), LVSI, PI, LNM, and BT

LVSI: lympho-vascular space invasion; DSI: deep stromal invasion; PI: Parametrial invasion; LNM: Lymph node metastasis; BT: Bulky tumor (tumor diameter>4 cm).

Table 5: Types of intervention given

Author	Year	Radiotherapy	Chemotherapy	Frequency	Duration (weeks)
Cao *et al*.	2020	25 to 28 fractions for a total dose of 45 to 50.4 Gray	Cisplatin in a single weekly dose of 40 mg/m^2 for 5–6 doses concomitant with pelvic radiation	1 cycles/week	5–6
Kim *et al*.	2008	Radiation dose ranged from 4500 to 5100 cGy	5-fluorouracil + cisplatin or 5-fluorouracil + carboplatin + interferon gamma, epirubicin + cisplatin, paclitaxel + carboplatin, UFT þ cisplatin, etoposide + cisplatin	2–3 cycles	3–4
Mabuchi, *et al*.	2009	Pelvic RT was delivered using a 10 mega-volt (MV) 2 Gy per fraction for 5 fractions per week, a total of 25 fractions (50 Gy)	Nedaplatin 40mg/m^2	1 cycles/week	5
Mahmoud *et al*.	2016	Pelvic RT: 40 Gy in 23 fractions to 50.4 Gy in 28 fractions (five fractions weekly). Each patient was to be given daily fractions of 1.80–2.00 Gy within 4.5–6 weeks	Cisplatin (40 mg/m^2) or cyclophosphamide (500 mg/m^2)	1 cycles/week	5–7
Okazawa *et al*.	2013	Pelvic RT: 2 Gy per fraction in 5 fractions per week for a total of 25 fractions (50 Gy)	Nedaplatin 40 mg/m^2 Nedaplatin 70 mg/m^2	1 cycle, 2 cycle	5, 2
Ryu *et al*.	2011	Pelvic RT: 40 Gy in 23 fractions to 50.4 Gy in 28 fractions	Cisplatin (40 mg/m^2) or cyclophosphamide (500 mg/m^2) + cisplatin (50 mg/m^2)	1 cycle/week	3
Huang *et al*.	2021	Pelvic RT: total dose of 45.0–50.0 Gy was administered over 5–6 weeks with 1.8–2 Gy per fraction, five fractions per week.	Cisplatin, 30–40 mg/m^2, for a maximum of 6 doses during radiation	1 cycle/week	6
Sun *et al*.	2015	Pelvic RT: total dose of 45.0–50.0 Gy was administered over 5–6 weeks with 1.8–2 Gy per fraction, five fractions per week.	Topotecan 0.75 mg/m^2 IV 30 min, cisplatin 25 mg/m^2 IV for days 1, 2 and 3	Topotecan: 3 cycles/week	14
Scharl *et al*.	2021	NA	NA	NA	NA
Song *et al*.	2011	Pelvic RT: 1.8 or 2.0 Gy per fraction once daily, 5 days per week	Cisplatin, fluorouracil + cisplatin, paclitaxel + carboplatin	2–6 cycles	4
Sun *et al*.	2018	4,500–5,400 cGy for a total of 25–28 fractions, 5 days/week	Cis-diamminedichloroplatinum 4–5 cycles, at a dose of 40 mg/m^2	4–5 cycles	5
Yu *et al*.	2016	A total dose of 45.0–50.0 Gy was administered over 5–6 weeks with 1.8–2 Gy per fraction	Carboplatin (150 mg/m^2) and paclitaxel (60 mg/m^2)	1 cycles/week	5–6
Matsuo *et al*.	2017	NA	NA	NA	NA
Nie *et al*.	2021	45–50 Gy was delivered in 25 fractions using three dimentional conformal RT or intensity modulated RT	Cisplatin/Lobaplatin/Carboplatin + paclitaxel (135mg/m), docetaxel, paclitaxel liposomes	1 cycles/3 weeks	12
Kim *et al*.	2020	Median radiation dose was 50.4 Gy, ranging from 44.0 Gy in 22 fractions to 50.4 Gy in 28 fractions (daily fractions of 1.8–2.0 Gy over 4.5–6 weeks, 5 fractions per week)	Cisplatin or cisplatin 5-fluorouracil	1 cycles/week or 2–3 cycles/3 week	6
Hosaka *et al*.	2008	50 Gy for 25 fractions	Bleomycin (7 mg/body from days 1–5), vincristine (0.7 mg/m^2 on day 5), mitomycin C (7 mg/m2 on day 5), and cisplatin (14 mg/m^2 from days 1–5)	3 cycles/4 week	NA

NA: Not available

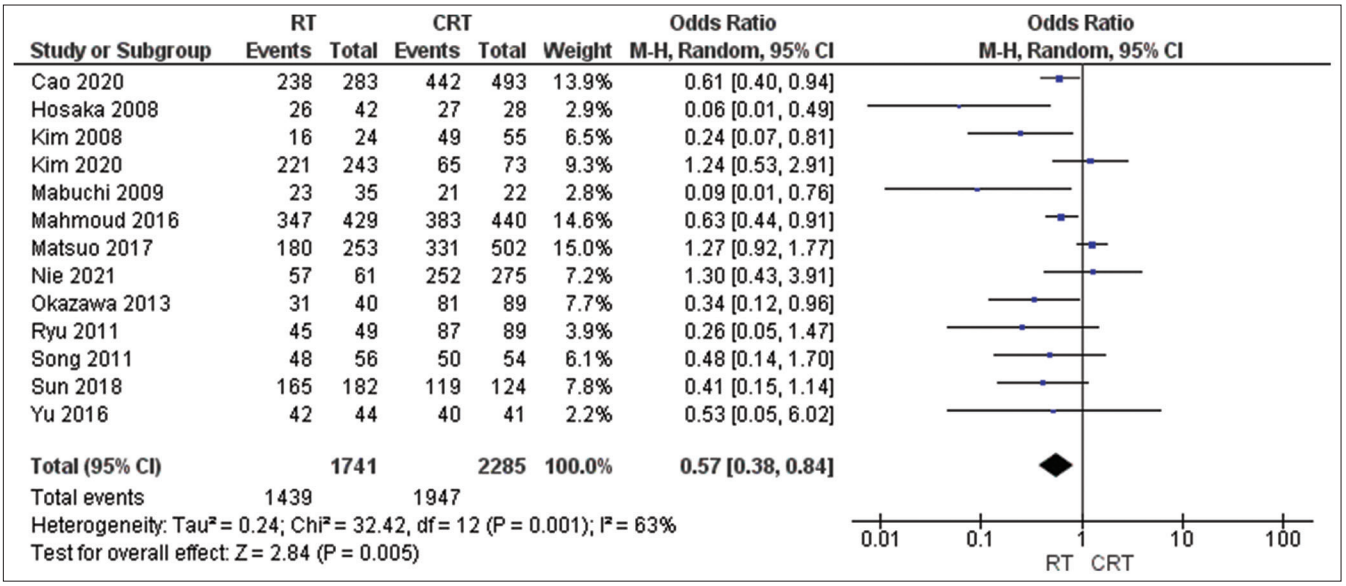

Figure 2: Forest and funnel plot for recurrence-free survival using random model

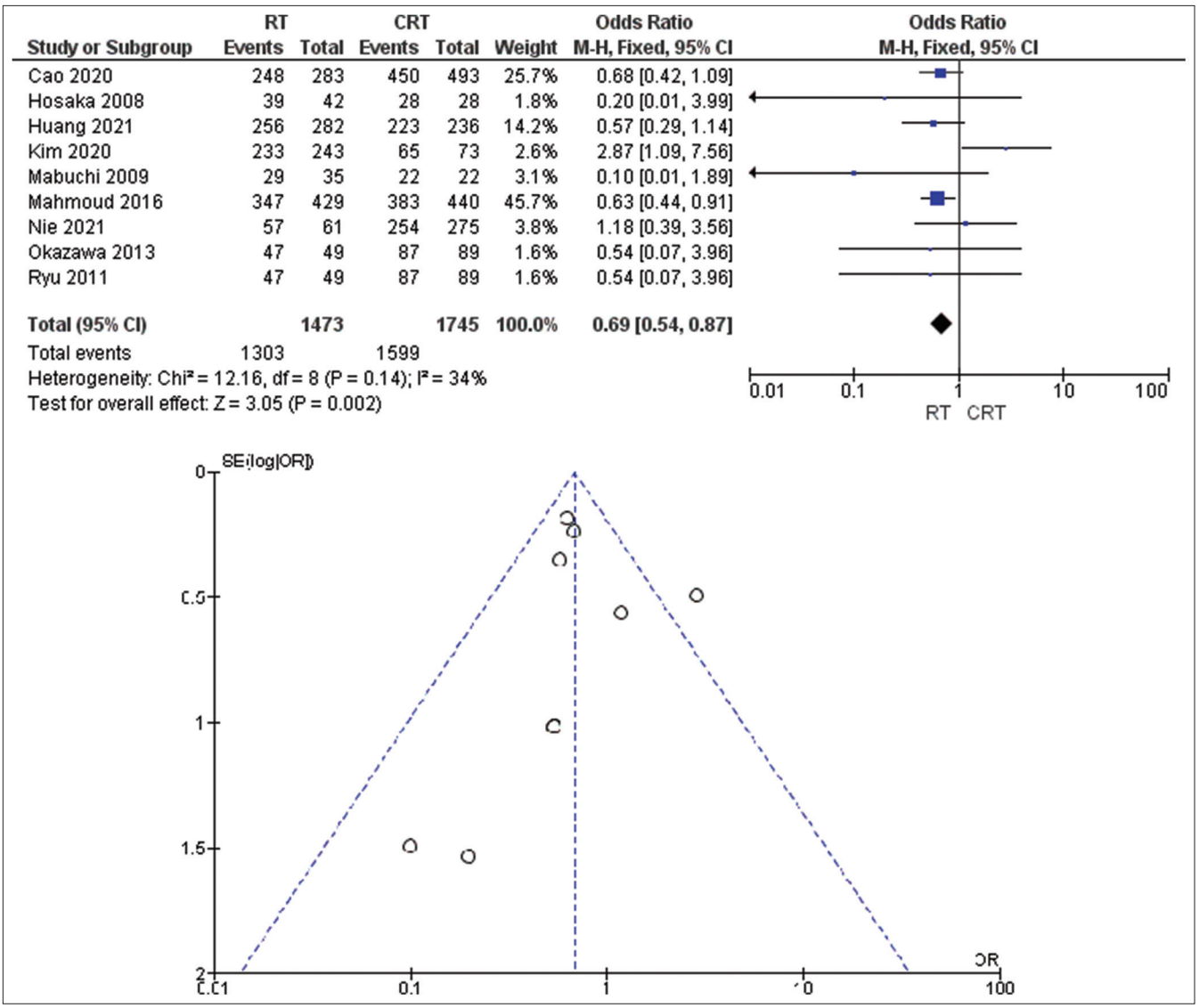

Figure 3: Forest and funnel plot for overall survival

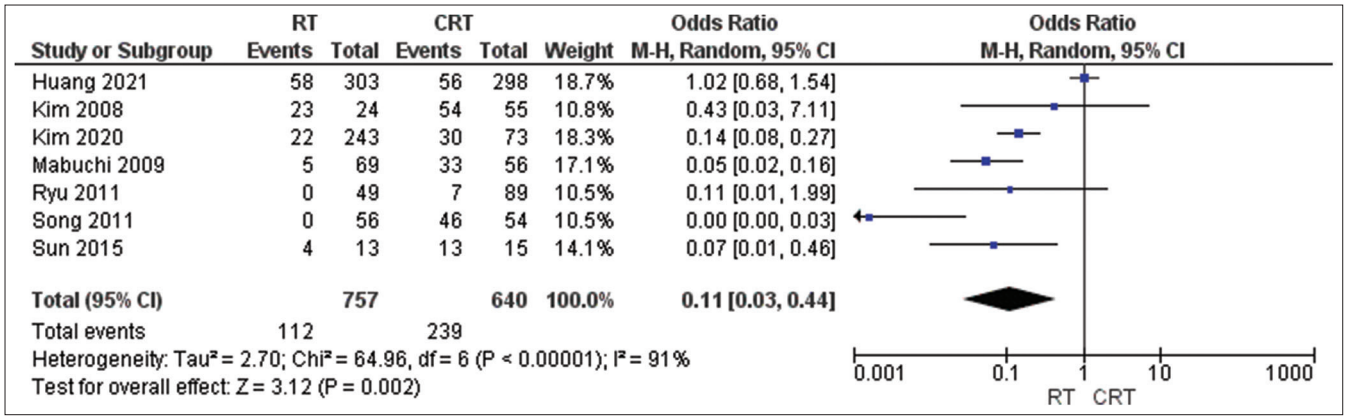

Figure 4: Forest for hematologic toxicities using random model

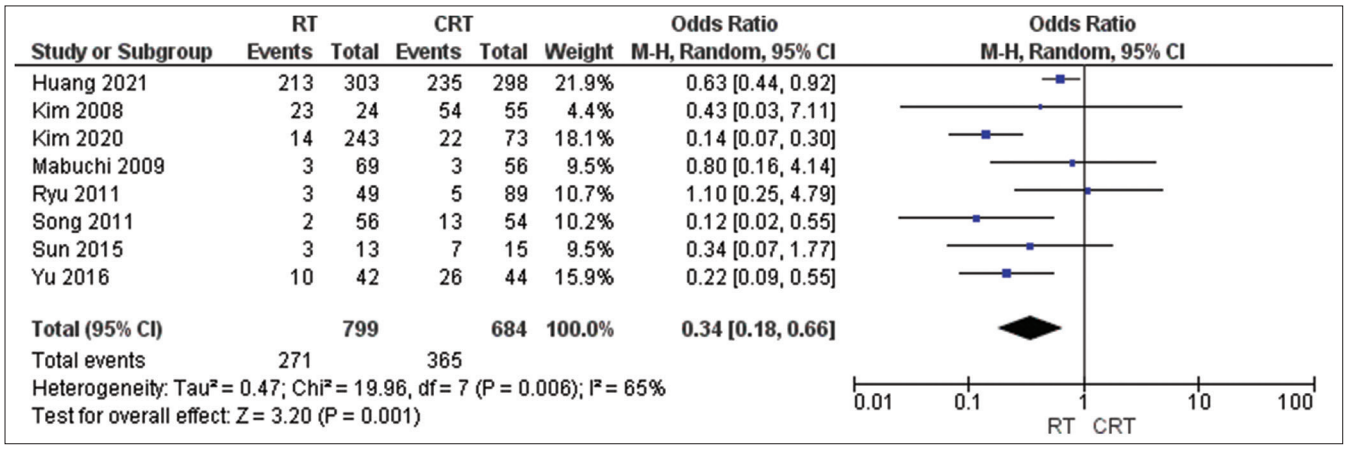

Figure 5: Forest for non-hematologic toxicities using random model

Discussion

Cervical cancer is still the fourth-most common cancer in women, with an estimated 570.000 new cases and 311,000 deaths in 2018. In underdeveloped countries carry a significant proportion which was more than 85% of the burden of death due to cancer [23]. The therapeutic strategies for ESCC, including radical surgery, RT, and chemotherapy are based largely on the FIGO stage, the patient's overall physical health, treatment choices, surgeon's experience, and clinical judgment. However, postoperative treatment option for patients in ESCC with intermediate-risk factors for recurrence is not well defined and the outcome of surgery with or without adjuvant RT or CRT in patients with ESCC has been debated by many researchers. A study suggests it may be more favorable to go for RT for adjuvant treatment in patients with intermediate-risk factors after radical surgical resection.

The main goal of adjuvant therapy should be to reduce extra pelvic recurrence rather than local recurrence. This specific goal had led to many studies debating whether to add chemotherapy as an adjuvant therapy. Earlier meta-analysis suggest for patients with high-risk factor have better outcomes for CRT only, but it was contradicted in patients with intermediate-risk factors, which the study found intermediate risk factor patients did not gain benefit from CRT. Earlier analysis demonstrated that cisplatin-based chemotherapy, if combined with radiation, may present with better RFS and improve OS outcome in cervical cancer with intermediate-risk factors [24]. Despite greater outcome with CRT, it has some drawbacks of severe treatment-related complications associated with adjuvant chemo-radiotherapy, which may affect the patient's quality of life (QOL).

Qin *et al*., in 2016, showed that there was no survival benefit found in CCRT combined with RT treatment after surgery for cervical cancer with intermediate risk factors. This makes RT alone might be recommended for postoperative patients with intermediate risk factors. However, the efficacy of CRT might be associated with the number of intermediate risk factors. The Okazawa *et al*. trial suggest in patients with 2 or more intermediate-risk factors, CCRT was superior to RT as assessed by recurrence rates. If compared to RT alone, no survival benefit from CCRT was gained for patients with only 1 intermediate risk factor. Further studies still needed with larger samples to address which group with intermediate risk factors gain more survival benefit from CRT.

The result of this study demonstrates that RT patients had better RSF outcome and also better OS.

Unfortunately, our study cannot provide information regarding the presence effect of single or multiple intermediate risk factors. It would have been interesting to see the effect of particular risk factors. A study by Sedlis *et al*. randomized FIGO IB patients without residual tumors or involved lymph nodes but with two or more intermediate risk factors, which were later named the "Sedlis criteria" to receive observation or RT following radical surgery. The study found adjuvant RT led to a reduction of recurrence rates at the cost of an approximately 4% higher rate of grade 3/4 adverse events. There was no increase in OS but an improvement in long-term RFS [25]. On the other hand, a study found that RFS and OS were significantly improved in the addition of chemotherapy, especially in patients with clinical-stage IA2, IB and IIA with parametric invasion, residual tumor and/or lymph node involvement [7].

Owing to the advantage of using adjuvant CRT in managing ESCC patients with multiple risk factors, there is a high incidence of grade 3 or 4 hematological and non-hematological toxicity with the use of adjuvant CRT. Hematological toxicities such as neutropenia, thrombocytopenia, or anemia are regularly reported with the included studies. Non-hematological toxicities like gastro-intestinal, hepatic, genito-urinary, and lymphatic toxicities are shown to be associated with both treatment regimens, which may affect the patient's QOL. After all, it is prudent to take into account the adverse events as well as the QOL for long-term survivors. This study shows RT had lesser hematologic toxicity and non-hematologic toxicity. However, this study cannot provide a subgroup analysis of all individual toxicities.

Limitations

The potential limitations of the study were there is a small number of papers included, the reliability of retrospective studies being relatively low and high patient heterogeneity. Different pathological stages of the disease in every study, and variations in chemotherapy regimens, RT patterns, and target volumes could have resulted in distinct differences [26]. The search strategy was limited to articles published in English which may impact that high-quality articles published in other languages did not include.

Conclusion

Despite the limitation in this review, we could conclude that overall adjuvant RT shows a better outcome in RFS and OS. CRT is often associated with greater hematological and non-hematological toxicities. Further high-quality randomized clinical trials with larger sample sizes comparing the efficacy and toxicity of adjuvant CRT with RT are recommended to strengthen the available evidence.

References

1. Bermudez A, Bhatla N, Leung E. Cancer of the cervix uteri. Int J Gynaecol Obstet. 2015;131(Suppl 2):S88-95. https://doi.org/10.1016/j.ijgo.2015.06.004
   PMid:26433680
2. Rotman M, Sedlis A, Piedmonte MR, Bundy B, Lentz SS, Muderspach LI, *et al*. A phase III randomized trial of postoperative pelvic irradiation in stage IB cervical carcinoma with poor prognostic features: Follow-up of a gynecologic oncology group study. Int J Radiat Oncol Biol Phys. 2006;65(1):169-76. https://doi.org/10.1016/j.ijrobp.2005.10.019
   PMid:16427212
3. Lahousen M, Haas J, Pickel H, Hackl A, Kurz C, Ogris H, *et al*. Chemotherapy versus radiotherapy versus observation for high-risk cervical carcinoma after radical hysterectomy: A randomized, prospective, multicenter trial. Gynecol Oncol. 1999;73(2):196-201. https://doi.org/10.1006/gyno.1999.5343
   PMid:10329034
4. Ho CM, Chien TY, Huang SH, Wu CJ, Shih BY, Chang SC. Multivariate analysis of the prognostic factors and outcomes in early cervical cancer patients undergoing radical hysterectomy. Gynecol Oncol. 2004;93(2):458-64. https://doi.org/10.1016/j.ygyno.2004.01.026
   PMid:15099962
5. Van de Putte G, Lie AK, Vach W, Baekelandt M, Kristensen GB. Risk grouping in stage IB squamous cell cervical carcinoma. Gynecol Oncol. 2005;99(1):106-12. https://doi.org/10.1016/j.ygyno.2005.05.026
   PMid:16137752
6. Gray HJ. Primary management of early stage cervical cancer (IA1-IB) and appropriate selection of adjuvant therapy. J Natl Compr Canc Netw. 2008;6(1):47-52. https://doi.org/10.6004/jnccn.2008.0005
   PMid:18267058
7. Peters WA 3rd, Liu PY, Barrett RJ 2nd, Stock RJ, Monk BJ, Berek JS, *et al*. 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. 2000;18(8):1606-13. https://doi.org/10.1200/JCO.2000.18.8.1606
   PMid:10764420
8. Mabuchi S, Morishige KI, Isohashi F, Yoshioka Y, Takeda T, Yamamoto T, *et al*. Postoperative concurrent nedaplatin-based chemo-radiotherapy improves survival in early-stage cervical cancer patients with adverse risk factors. Gynecol Oncol. 2009;115(3):482-7. https://doi.org/10.1016/j.ygyno.2009.09.002
   PMid:19783286
9. Zaghloul MS, Christodouleas JP, Smith A, Abdallah A, William H, Khaled HM, *et al*. Adjuvant sandwich chemotherapy plus radiotherapy vs adjuvant chemotherapy alone for locally advanced bladder cancer after radical cystectomy. JAMA Surg. 2018;153(1):e174591. https://doi.org/10.1001/jamasurg.2017.4591
   PMid:29188298
10. Okazawa M, Mabuchi S, Isohashi F, Suzuki O, Yoshioka Y, Sasano T, *et al*. 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. 2013;23(3):567-75. https://doi.org/10.1097/IGC.0b013e31828703fd
PMid:23385284

11. Ryu SY, Park SI, Nam BH, Cho CK, Kim K, Kim BJ, *et al*. Is adjuvant chemoradiotherapy overtreatment in cervical cancer patients with intermediate risk factors? Int J Radiat Oncol Biol Phys. 2011;79(3):794-9. https://doi.org/10.1016/j.ijrobp.2009.11.019
PMid:20421158
12. Huang H, Feng YL, Wan T, Zhang YN, Cao XP, Huang YW, *et al*. Effectiveness of sequential chemoradiation vs concurrent chemoradiation or radiation alone in adjuvant treatment after hysterectomy for cervical cancer. JAMA Oncol. 2021;7(3):361-9. https://doi.org/10.1001/jamaoncol.2020.7168
PMid:33443541
13. Sun W, Wang T, Shi F, Wang J, Wang J, Hui B, *et al*. Randomized phase III trial of radiotherapy or chemo-radiotherapy with topotecan and cisplatin in intermediate-risk cervical cancer patients after radical hysterectomy. BMC Cancer. 2015;15(1):353. https://doi.org/10.1186/s12885-015-1355-1
PMid:25935645
14. Song S, Song C, Kim HJ, Wu HG, Kim JH, Park NH, *et al*. 20 year experience of postoperative radiotherapy in IB-IIA cervical cancer patients with intermediate risk factors: Impact of treatment period and concurrent chemotherapy. Gynecol Oncol. 2012;124(1):63-7. https://doi.org/10.1016/j.ygyno.2011.09.033
PMid:22004904
15. Sun HY, Tang Q, Chen JH, Lv XJ, Tu YQ, Yan DD. Cisplatin concurrent chemo-radiotherapy vs adjuvant radiation in stage IB/IIA cervical cancer with intermediate risk factors, treated with radical surgery: A retrospective study. Onco Targets Ther. 2018;11:1149-55. https://doi.org/10.2147/OTT.S158214
PMid:29563803
16. Yu H, Zhang L, Du X, Sheng X. Postoperative adjuvant chemotherapy combined with intracavitary brachytherapy in early-stage cervical cancer patients with intermediate risk factors. Onco Targets Therapy. 2016;9:7331-5. https://doi.org/10.2147/OTT.S107146
PMid:27942225
17. Matsuo K, Shimada M, Aoki Y, Sakamoto M, Takeshima N, Fujiwara H, *et al*. Comparison of adjuvant therapy for node-positive clinical stage IB-IIB cervical cancer: Systemic chemotherapy versus pelvic irradiation. Int J Cancer. 2017;141(5):1042-51. https://doi.org/10.1002/ijc.30793
PMid:28524247
18. Nie J, Wu Q, Yan A, Wu Z. Impact of different therapies on the survival of patients with stage I-IIA cervical cancer with intermediate risk factors. Ann Transl Med. 2021;9(2):142-2. https://doi.org/10.21037/atm-20-7679
PMid:33569444
19. Kim H, Park W, Kim Y, Kim Y. Chemoradiotherapy is not superior to radiotherapy alone after radical surgery for cervical cancer patients with intermediate-risk factor. J Gynecol Oncol. 2020;31(3):e35. https://doi.org/10.3802/jgo.2020.31.e35
PMid:31912685
20. Hosaka M, Watari H, Takeda M, Moriwaki M, Hara Y, Todo Y, *et al*. Treatment of cervical cancer with adjuvant chemotherapy versus adjuvant radiotherapy after radical hysterectomy and systematic lymphadenectomy. J Obstet Gynaecol Res. 2008;34(4):552-6. https://doi.org/10.1111/j.1447-0756.2008.00739.x
PMid:18937708
21. Mahmoud O, Hathout L, Shaaban SG, Elshaikh MA, Beriwal S, Small W Jr. Can chemotherapy boost the survival benefit of adjuvant radiotherapy in early stage cervical cancer with intermediate risk factors? A population based study. Gynecol Oncol. 2016;143(3):539-44. https://doi.org/10.1016/j.ygyno.2016.10.022
PMid:27769525
22. Scharl S, Becher C, Gerken M, Scharl A, Anapolski M, Ignatov A, *et al*. Is there a benefit for adjuvant radio (chemo) therapy in early cervical cancer? Results from a population-based study. Arch Gynecol Obstet. 2021;304(3):759-71. https://doi.org/10.1007/s00404-021-05989-w
PMid:33575846
23. Li M, Hu M, Wang Y, Yang X. Adjuvant chemo-radiotherapy versus radiotherapy in cervical cancer patients with intermediate-risk factors: A systematic review and meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2019;238:1-6. https://doi.org/10.1016/j.ejogrb.2019.04.039
PMid:31082737
24. Qin AQ, Liang ZG, Ye JX, Li J, Wang JL, Chen CX, Song HL. Significant efficacy of additional concurrent chemotherapy with radiotherapy for postoperative cervical cancer with risk factors: A systematic review and meta-analysis. Asian Pac J Cancer Prev. 2016;17(8):3945-51.
PMid:27644643
25. Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: A Gynecologic Oncology Group Study. Gynecol Oncol. 1999;73(2):177-83. https://doi.org/10.1006/gyno.1999.5387
PMid:10329031
26. Sagi-Dain L, Abol-Fol S, Lavie O, Sagi S, Arie AB, Segev Y. Cervical cancer with intermediate risk factors: Is there a role for adjuvant radiotherapy? A systematic review and a meta-analysis. Gynecol Obstet Invest. 2019;84(6):606-15. https://doi.org/10.1159/000501683
PMid:31344705
27. Cao L, Wen H, Feng Z, Han X, Zhu J, Wu X. Role of adjuvant therapy after radical hysterectomy in intermediate-risk, early-stage cervical cancer. Int J Gynecol Cancer. 2020;31(1):52-8. https://doi.org/10.1136/ijgc-2020-001974
PMid:33303568
28. Kim K, Kang SB, Chung HH, Kim JW, Park NH, Song YS. Comparison of chemoradiation with radiation as postoperative adjuvant therapy in cervical cancer patients with intermediate-risk factors. Eur J Surg Oncol (EJSO). 2009;35(2):192-6. https://doi.org/10.1016/j.ejso.2008.04.004
PMid:18490129