RESEARCH ARTICLE

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Unveiling The Impact of Prophylactic Para-Aortic Lymph Nodes Irradiation in Cervical Cancer: Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective: This study assessed the impact of prophylactic para-aortic lymph node (PALN) irradiation with extended-field radiotherapy (EF-RT) in individuals with locally advanced cervical cancer. The principal objective was overall survival (OS), whereas the secondary outcomes included PALN metastases, full remission, pelvic recurrence, distant metastasis, and mortality attributable to cervical cancer. **Methods:** A thorough search was performed in Pubmed, Cochrane Central Register of Controlled Trials, and Science Direct in November 2023, following PRISMA procedures. Randomized trials comparing EF-RT to pelvic-only radiation for locally advanced cervical cancer without PALN involvement were incorporated. A meta-analysis was conducted using RevMan software to evaluate the Hazard Ratio (HR) for overall survival (OS) and the Odds Ratio (OR) for additional outcomes. **Result:** Six Randomized Controlled Trials involving 1,028 patients (508 in EF-RT group and 520 in pelvic-only radiotherapy group) were analyzed. EF-RT significantly reduced para-aortic lymph node metastases compared to standard pelvic radiotherapy (OR = 0.23, 95% CI [0.12;0.44], p-value<0.00001, 4 studies), but not significantly improve overall survival (HR = 0.97, 95% CI [0.82;1.16], p-value>0.05, 6 studies) nor other outcomes. EF-RT was also associated with increased gastrointestinal but not urological or gynecological complications. **Conclusion:** EF-RT as a prophylactic treatment for cervical cancer patients with negative PALN metastasis significantly reduces para-aortic lymph node metastatic events, nonetheless, it is improbable to offer any advantages regarding overall survival, managed pelvic illness, or distant metastatic sites. Furthermore, its adverse effects on gastrointestinal problems were observed to exceed those of conventional pelvic irradiation, necessitating further consideration.

Keywords: Para-aortic lymph nodes irradiation- Cervical cancer- Outcome- Side effects

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Introduction

Globally, cervical cancer ranks as the third most common malignancy in women, with more than 569,000 new cases reported each year [1]. Less developed countries experience disproportionately greater burden of disease due to constrained access to screening programs, medication, and the substantial cost associated with HPV vaccines [2]. Treatment options for cervical cancer are tailored according to the International Federation of Gynaecology and Obstetrics (FIGO) stage of the disease. For FIGO stages IA-IIA, surgery or radiotherapy are typically used, both offering high five-year survival rates. Surgery generally encompasses the excision of the uterus and cervix (simple hysterectomy) for FIGO stage IA1 cervical cancer, whereas radical hysterectomy (excision of the uterus, cervix, upper vagina, and adjacent tissues) is frequently employed for FIGO stage IA2 to IB1 cervical cancers owing to higher prevalence of lymph node involvement (3.4% to 15.3%). However, for FIGO stage IA2 and above, radical hysterectomy alone does not provide adequate oncologic control. Pelvic lymph node dissection is crucial in conjunction with radical hysterectomy for precise evaluation of nodal status, given that hidden pelvic lymph node metastases are prevalent and can greatly influence prognosis and treatment strategies. This surgical staging procedure facilitates personalized adjuvant therapies and minimizes the risk of residual disease, emphasizing that pelvic lymphadenectomy is an essential complement rather than a simply optional adjunct to radical hysterectomy. For intermediate-stage and locally advanced cervical cancer (FIGO stages IIB-IVA), concomitant chemotherapy and radiotherapy serves as the principal treatment, with

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recurrence rates between 29% and 38%. Pelvic radiation has historically been employed for advanced cervical cancer due to the elevated incidence of positive pelvic lymph node metastases (22.7% to 71.4%) [3, 4].

Para-aortic lymph node (PALN) metastases are a prevalent occurrence of recurrence following treatment for locally advanced cervical cancer [5]. Certain studies indicate that PALN metastases serves as a significant prognostic indicator for cervical cancer, correlating with an elevated risk of recurrence and mortality [3, 5, 6]. PALN metastases which identified through surgical lymph node staging and [18F] fluorodeoxyglucose (FDG)-PET imaging, were detected in 20% - 60% of FIGO stage IIA-IVA patients. These patients exhibited a 6-fold higher risk of disease recurrence compared to those without PALN metastases [5]. Negative evidence of PALN metastasis shown in PET or PET-CT scans does not exclude the diagnosis. Several studies have demonstrated that 4% to 15% of cases with negative PALN metastasis on PET or PET-CT scans still harbor occult PALN metastasis [7].

The reasoning for conducting PALN irradiation originates from the existence of hidden micrometastases that remain undetectable by current imaging techniques. These small-volume metastases, although clinically silent, can play a substantial role in disease relapse if left untreated. The progression of cervical cancer occurs through various mechanisms, such as direct extension, spread through pelvic lymphatics, hematogenous dissemination, and involvement of PALN. Prophylactic EF-RT is designed to specifically target the para-aortic nodal basin, aiming to eliminate microscopic disease in this area that may not be adequately treated by standard pelvic radiotherapy alone. Understanding the complexities of metastatic heterogeneity highlights the specific function of EF-RT in the wider framework of cervical cancer spread and points to its potential in decreasing para-aortic recurrences, despite the ambiguity surrounding overall survival advantages [3, 5, 6].

Standard pelvic radiotherapy fields that used to treat cervical cancer do not encompass the para-aortic region, making it insufficient for women at elevated risk of hidden cancer in para-aortic lymph nodes [6, 8]. Despite the progress in concurrent chemoradiotherapy (CRT), para-aortic lymph node metastasis continues to be a significant concern, affecting roughly 7% to 15% of patients receiving CRT for cervical cancer [9]. Extended-field radiotherapy (EF-RT) targets pelvic and PALN, potentially reducing the risk of distant metastases and enhancing survival outcomes for women with locally advanced cervical cancer. EF-RT is delivered simultaneously with standard whole-pelvis external-beam radiotherapy, employing an identical treatment regimen and total radiation dosage while encompassing a wider area, specifically focusing on the para-aortic region, which includes the lymph nodes adjacent to the aorta and vena cava, the principal blood vessels situated in the middle and upper abdomen [10, 11].

The effectiveness of prophylactic para-aortic lymph node irradiation by EF-RT for cervical cancer without PALN metastasis remains uncertain. The potential benefits of prophylactic PALN irradiation, including enhanced survival rates, diminished risk of PALN metastasis, and decreased likelihood of cancer recurrence, must be considered alongside the potential risks and adverse effects, such as gastrointestinal, gynecological, and urological radiation reactions. A thorough meta-analysis of the current evidence will yield critical insights into the clinical relevance of prophylactic PALN irradiation in patients with locally advanced cervical cancer exhibiting negative PALN metastasis on pretreatment CT/MRI, thereby aiding in the formulation of evidence-based guidelines for cervical cancer management.

Materials and Methods

Research Methodology and Eligibility Criteria

This study was carried out in line with the standards recommended by the PRISMA statement for systematic reviews and meta-analyses. This study also have been registered in PROSPERO with ID : CRD42024496429. The eligibility criteria for this meta-analysis encompassed randomized controlled trials that explicitly demonstrate the efficacy of prophylactic para-aortic lymph node irradiation with EF-RT under the specified conditions: 1) Histologically confirmed FIGO stage IB1-IVA cervical cancer, encompassing squamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma; 2) Absence of PALN metastasis verified by PET/PET-CT scan or MRI; 3) Age ≥18 years; 4) No distant metastases, including to the lung, liver, or bone; 5) Both treatment arms included all patients receiving identical systemic therapy or no systemic therapy. Studies involving pediatric patients and treatment arms that included chemotherapy-based treatments were excluded from this review. All participating centers obtained ethical approval from their respective institutional review boards before enrolling patients in the included studies. During the initial selection phase, four reviewers (C.T.S., M.F.B.G., B.G.L., and P.E.D) conducted the literature search and data extraction. Studies that evidently failed to satisfy the inclusion criteria were eliminated, and the remaining papers were thoroughly reviewed in full text to assess their eligibility. In case of any disagreements, a fifth reviewer (I.N.G.B.) was consulted. The PICOS (Population, Intervention, Comparison, Outcome, and Study design) approach was employed to determine the inclusion and exclusion criteria, as outlined in Table 1.

Literature Review and Selection

An extensive database search was carried out through PubMed, Cochrane CENTRAL, and Science Direct in November 2023. We used Medical Subject Headings and Boolean terms as follows : ((Cervical Cancer) OR (Cervical Carcinoma)) AND (((Para-aortic Lymph Node) OR (Para-Aortic) OR PALN)) AND ((Radiation) OR (Irradiation) OR (Radiotherapy)) OR (Extended Field Radiotherapy) AND ((Pelvic Radiotherapy) OR (Standard Pelvic Radiotherapy)) AND ((Outcome) OR (Survival) OR (Survival Rate) OR (Recurrence) OR (Metastasis) OR (Remission) OR (Death)) AND ((Side Effects) OR (Adverse Effects) OR (Complications) OR (Morbidity)).

Table 1. PICOS Structure

PICOS	Inclusion criteria	Exclusion criteria
Population (P)	Women ≥18 years old with histologically confirmed FIGO stage IB1-IVA cervical cancer	PALN metastasis Other distant metastases, including lung, liver, or bone
Intervention (I)	Prophylactic Para-Aortic Irradiation	-
Comparison (C)	Standard Pelvic Radiotherapy	-
Outcome (O)	Overall survival (OS) PALN metastasis Complete remission Pelvic recurrence Distant metastasis Death due to cervical cancer Digestive complications Gynecology complications Urology complications	-
Study design (S)	Randomized Controlled Trial (RCT)	Unavailable full-text article Uncompleted article

Quality Evaluation of Included Studies

The second edition of the Cochrane Risk of Bias tool (RoB 2.0), designed for randomized studies was used in a methodical and complete evaluation of possible bias. Using the RoB 2.0 tool, two review authors—C.T.S. and M.F.B.G.—each separately assessed the risk of bias. Disagreements were resolved by further discussion or referral to a third reviewer (B.G.L.).

Data Extraction

Data extraction of demographic, baseline clinical, treatment guideline, and outcome data from the included trials was conducted. The gathered information included the number of trial centers and participants age, FIGO stage, treatment protocols in both arms including procedural details such as external beam dose and area covered by irradiation, time to last follow-up, PALN metastasis, complete remission, pelvic recurrence, distant metastasis, death due to cervical cancer, overall survival, grade III-IV digestive, gynecological, and urological complications.

Statistical Analysis

A thorough statistical methodology was employed to assess the data obtained from the included research, ensuring the reliability and accuracy of our conclusions. In order to standardize the effect estimates across studies, Hazard Ratios (HRs) of overall survival and their associated 95% confidence intervals (CIs) were standardized based on the within-study standard deviation. This standardization accounts for variations in the absolute magnitude of the HRs across studies. For other binary outcomes, such as PALN metastasis, complete remission, pelvic recurrence, distant metastasis, death due to cervical cancer, digestive complication, gynecology complication and urology complication, odd ratios (ORs) with 95% CI were measured. The Mantel-Haenszel technique was used to evaluate heterogeneity, and the ORs were compiled using a random-effects model, specifically the Restricted Maximum Likelihood (REML). In order to effectively and clearly convey the data, forest plots were developed to provide a clear representation of the effect estimates and their corresponding confidence intervals for each study. The I^2 statistic was employed to evaluate the heterogeneity of the studies. If the I^2 value was less than 50%, which indicates homogeneity, a fixed-effects model was employed; otherwise, a random-effects model was employed. The Review Manager software version 5.4.1 was employed to conduct all statistical analyses, with a significance threshold of p-value<0.05.

Treatment Protocol

The treatment protocols outlined in the RCTs consistently involved the use of EBRT, focusing on either the standard pelvic field or an extended field that included both the pelvis and PALN. The treatment protocols outlined in the RCTs consistently involved the use of EBRT, focusing on either the standard pelvic field or an extended field that included both the pelvis and PALN. The definition of standard pelvic radiotherapy fields has shown variability, but they generally include the pelvic brim, with superior borders extending from the L3/L4 vertebral junction to the L4/L5 intervertebral space. The lateral borders were typically established around 2 cm lateral to the pelvic brim, while the inferior border reached the most distal extent of vaginal involvement [3,5,6,8,10,11]. The radiation dose for pelvic-only EBRT varied from 39.6 to 50.4 Gy, administered through fractionation schedules of either five fractions per week or twice weekly, with doses per fraction ranging from 1.5 to 2.0 Gy based on specific trial protocols.

Prophylactic PALN irradiation was delivered using extended-field radiotherapy techniques, which encompassed Extended-Field Concurrent Chemoradiation Therapy (EF-CCRT), computed tomography (CT)-guided Extended-Field Irradiation External Beam Radiotherapy (EFI-EBRT), and Extended-Field Intensity Modulated Radiation Therapy (EF-IMRT). The EF-RT fields were defined to include the para-aortic nodal basin, maintaining a 5 mm margin in front of the inferior vena cava and abdominal aorta, with the posterior limit set by the anterior vertebral body, and laterally constrained by the medial edge of the psoas muscles. The superior borders were extended to the T12-L1 intervertebral space to guarantee adequate coverage of the upper para-aortic nodes [3,5,6,8]. The radiation doses and fractionation schedules in the EF-RT arms were designed to align with those of the pelvic-only arms, ensuring dose equivalence across the groups.

The chemotherapy protocols utilized primarily consisted of platinum-based agents, which were administered either before or alongside radiotherapy. The regimen of cisplatin at 40 mg/m² administered weekly for six cycles was the most frequently utilized approach, although one study did not provide specific details regarding the chemotherapy protocol [3,5,6]. Furthermore, brachytherapy was integrated as a follow-up treatment in the majority of studies, usually commencing three weeks after the conclusion of external beam radiotherapy, to provide a targeted enhancement to the cervical tumor and surrounding tissues [3,10,11].

The descriptions provided here represent the data extracted from the included randomized controlled trials and aim to elucidate the range and consistency of the interventions evaluated in this meta-analysis. This information is crucial for the comparative assessment of prophylactic PALN irradiation in relation to pelvic-only radiotherapy.

Results

Selection of Studies

An initial search using keywords and Boolean operators across the selected databases yielded 2,038 citations. These records were subjected to title and abstract screening, during which 1,375 were excluded due to duplication, irrelevance to the research objective, or unsuitable article types. The remaining studies underwent a full-text eligibility review, narrowing the selection to 11 citations that met the inclusion criteria. Of these, six studies were ultimately included in the quantitative synthesis, as depicted in Figure 1.

Potential for Bias in Selected Studies

Evaluation performed by RoB 2.0 indicated that the majority of research exhibited a low risk of bias across

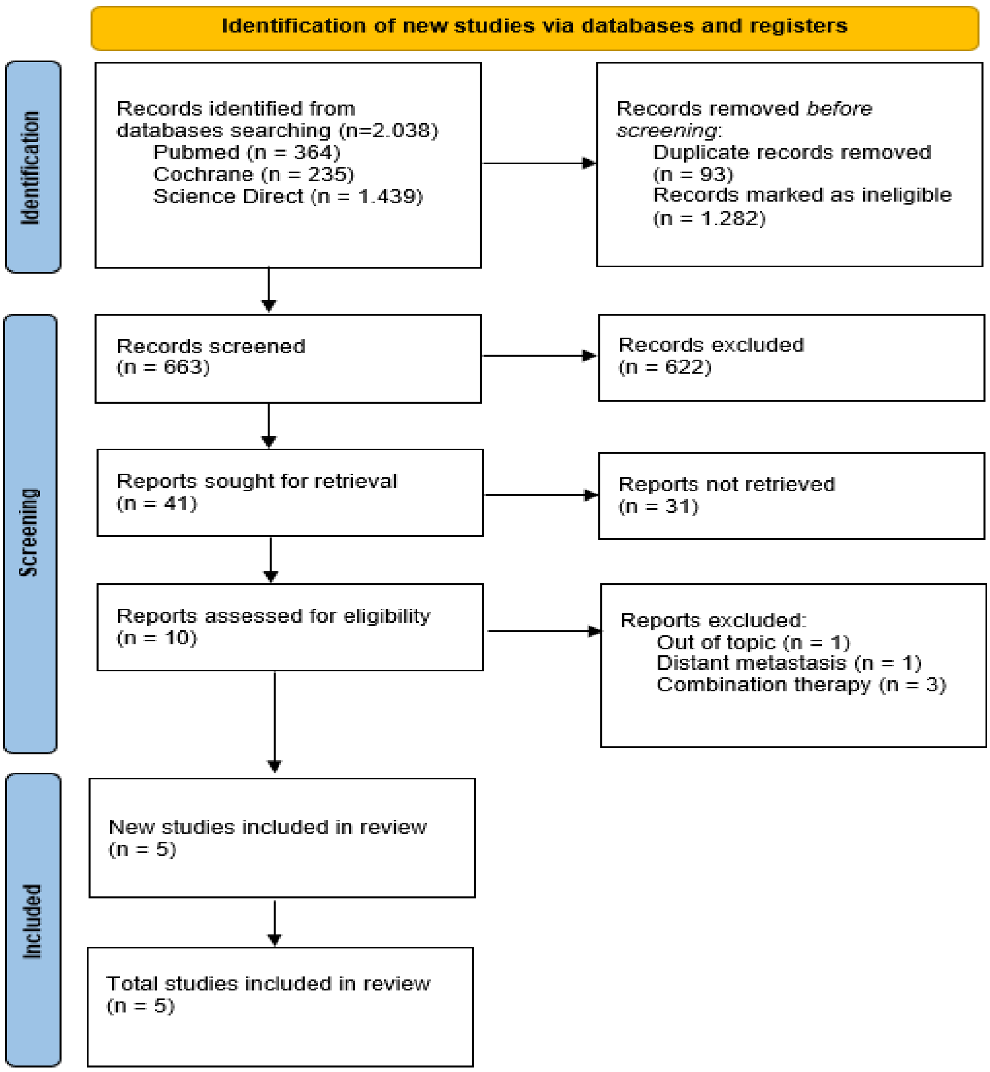

Figure 1. PRISMA Chart of the Study

most domains, thereby ensuring a rigorous assessment of the quality of evidence in the included studies, as illustrated in Figure 2 and Table 2.

Baseline Characteristics

Six Randomized Controlled Trials (RCTs) fulfilled the inclusion criteria, encompassing a total of 1,028 patients in this research. A total of 508 patients underwent prophylactic para-aortic lymph node irradiation with EF-RT, while 520 individuals received normal pelvic radiotherapy. The participants in both the control and intervention groups had a mean average age of 53.1 years, ranging from 42.1 to 64.5 years, and the follow-up periods in these studies had a mean average of 70 months, ranging from 6.8 to 120 months, allowing for a thorough examination of long-term outcomes. A comprehensive overview of the patients' characteristics is well displayed in Table 3 and Table 4.

Efficacy of Prophylactic Para-Aortic Lymph Node Irradiation

Primary Outcomes

Prophylactic PALN irradiation by EF-RT did not significantly improve overall survival (HR = 0.97, 95% CI [0.82;1.16], p-value>0.05, 6 studies) as shown in Figure 3.

Secondary Outcomes

Prophylactic PALN irradiation by EF-RT was found to significantly reduce the incidence of PALN metastases (OR = 0.23, 95% CI [0.12;0.44], p-value<0.00001, 4 studies) compared to standard pelvic radiotherapy, as seen in Figure 4.

Furthermore, prophylactic PALN irradiation did not significantly reduce the incidence of distant metastasis (OR = 0.79, 95% CI [0.55;1.14], p-value>0.05, 5 studies), pelvic recurrence (OR = 0.86, 95% CI [0.58;1.29], p>0.05, 5 studies), complete remission (OR = 1.11, 95% CI [0.61;2.03], p-value >0.05, 3 studies), or mortality due to

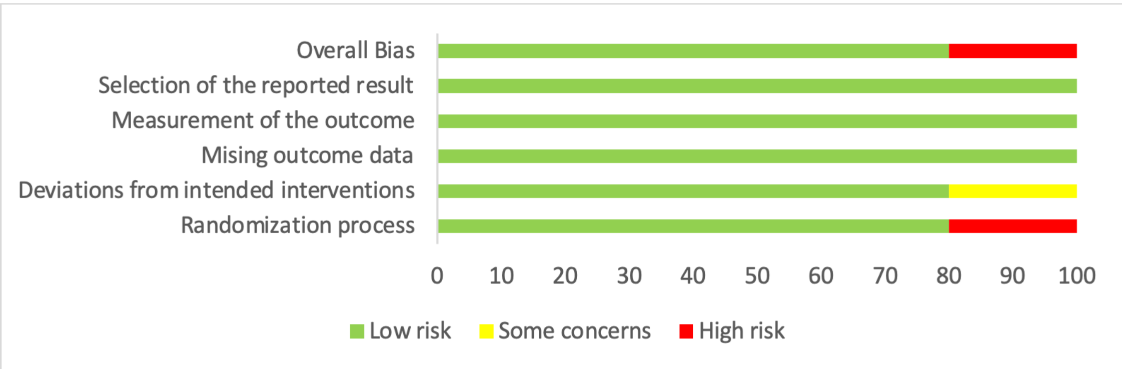

Figure 2. Risk of Bias Graph

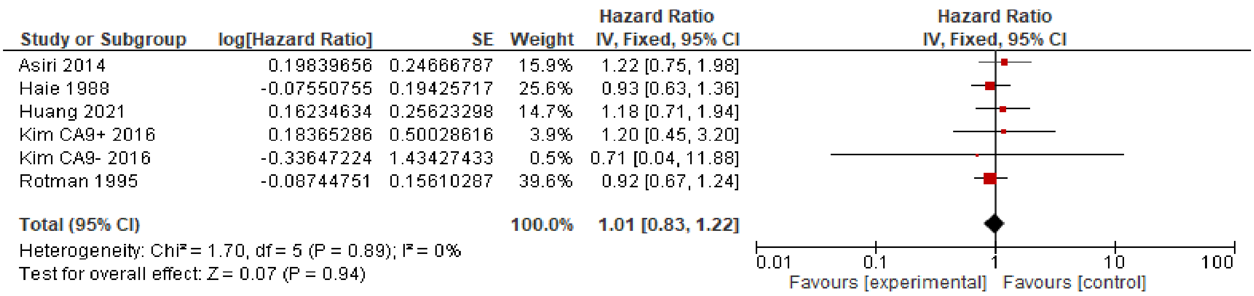

Figure 3. Forest Plot HR of OS

Table 2. Risk of Bias Summary

Study	Randomization process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall	Interpretation	
Asiri 2014	-	!	+	+	+	-	+	Low risk
Haie 1988	+	+	+	+	+	+	!	Some concerns
Huang 2021	+	+	+	+	+	+	-	High risk
Kim 2016	+	+	+	+	+	+		
Rotman 1995	+	+	+	+	+	+		

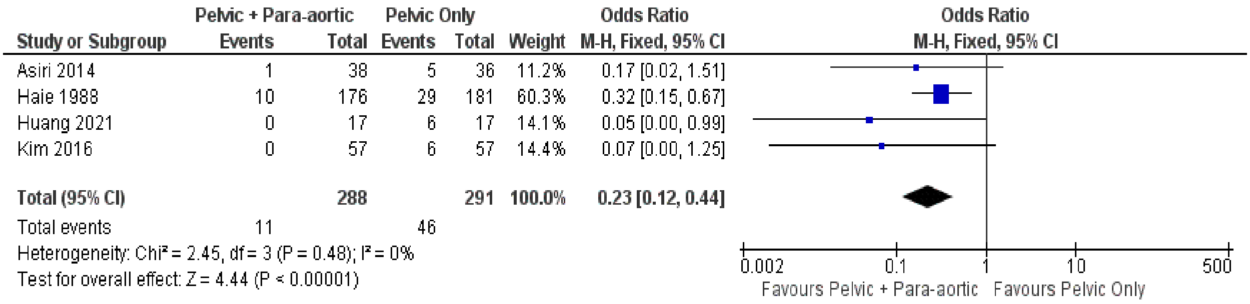

Figure 4. Forest Plot of OR of PALN Metastasis

Table 3. Baseline Characteristics of Included Studies

Author	Year	Participants (n)		Age (mean)		FIGO Stage
		Control Arm	Intervention Arm	Control Arm	Intervention Arm	
Asiri	2014	50	52	51:06:00	52:03:00	IIB – IVA
Haie	1998	228	213	53:06:00	52:07:00	I – III
Huang	2021	17	17	57	55	IB – IVA
Kim	2016	58	58	54	54	IB1 – IVA
Rotman	1995	167	168	53	48	IB – IIB

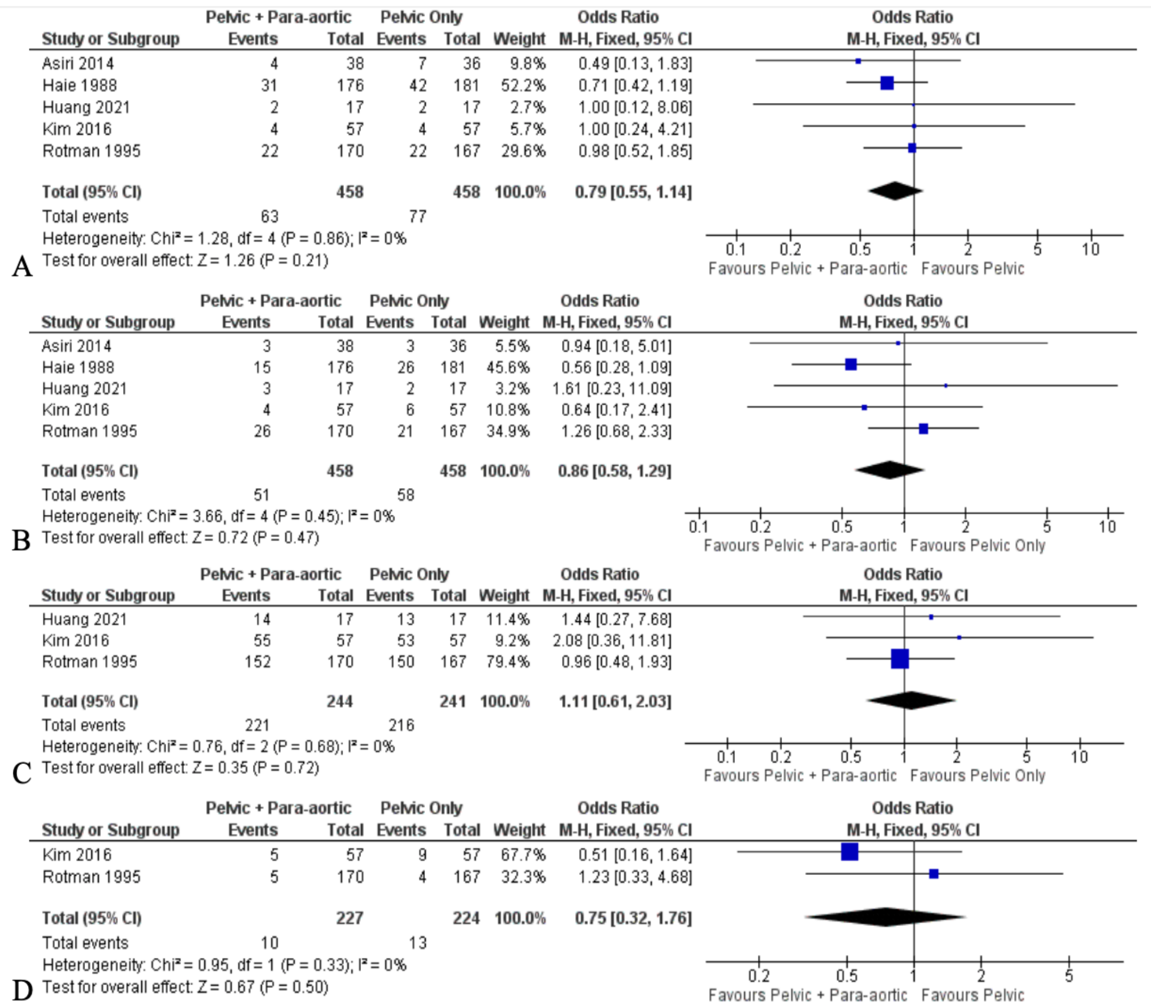

Figure 5. Forest Plot of Odd Ratio of Secondary Outcomes. (A), Distant Metastasis; (B), Pelvic Recurrence; (C), Complete Remission; (D), Death due to Cervical Cancer

Table 4. Treatment and Follow-up Protocols of Included Studies

First Author	Year	Treatment Protocol		Follow-up Protocol
		Control Arm	Intervention Arm	
Asiri	2014	WP-CCRT covering area at the junction of L3/L4 cranially, 3 cm below the most inferior vaginal involvement caudally, and 2 cm lateral to pelvic brim Radiation dose 45-50 Gy Preceded by weekly cisplatin 40 mg/m^2 for 6 doses Followed by HDR brachytherapy	EF-CCRT with additional area to superior field border at the junction of T12/L1 Radiation dose 45 Gy Preceded by weekly cisplatin 40 mg/m^2 for 6 doses Followed by HDR brachytherapy	every 3 months for the first 2 years every 6 months until 5 years (60 months, range 18-66 months)
Haie	1998	Pelvic irradiation with upper limit of the field was lower border of L4 Radiation dose 45-50 Gy (1.5-1.7 Gy/fraction, 5 fractions weekly)	Pelvic and para-aortic irradiation with extended field to upper border of L1 Radiation dose 45-50 Gy (1.5-1.7 Gy/fraction, 5 fractions weekly)	every 2 months for the first year every 4 months for next 2 years every 6 months until 4 years
Huang	2021	IMRT within region based on guidelines recommended for radical radiotherapy of cervical cancer Radiation dose 45.0-50.4 Gy (1.8-2.0 Gy/fraction, 5 times/week, 25-28 fractions) Accompanied with platinum-based chemotherapy weekly until end of radiotherapy Followed by Ir192 intracavitary brachytherapy 3 weeks after intervention	EF-IMRT within 5 mm in front of the inferior vena cava and abdominal aorta (the anterior bound), the vertebral anterior border (the posterior bound), and the medial of the psoas muscle (the bilateral bound) Radiation dose 40.0-45.0 Gy (1.8-2.0 Gy/fraction, 5 times/week, 25-28 fractions) Accompanied with platinum-based chemotherapy weekly until end of radiotherapy Followed by Ir192 intracavitary brachytherapy 3 weeks after intervention	every 3 months for the first 2 years every 6 months for years 2 to 5 years
Kim	2016	CT-based EBRT with L4-L5 inter space as superior border Radiation dose 45.0-50.4 Gy Accompanied with high dose–rate brachytherapy 39.6–45 Gy, with 6 fractional 5-Gy doses given twice a week Accompanied with weekly cisplatin 40 mg/m^2 for maximum 7 doses	CT-based EFI-EBRT with T12-L1inter space as superior border Radiation dose 45 Gy in 25 fractions Accompanied with high dose–rate brachytherapy 39.6–45 Gy, with 6 fractional 5-Gy doses given twice a week Accompanied with weekly cisplatin 40 mg/m^2 for maximum 7 doses	3 month after completion of radiotherapy 60 months (range 6.8-102.1 months)
Rotman	1995	Pelvic only irradiation Radiation dose 40-50 Gy for 4.5-6.5 weeks (1.6-1.8 Gy/day for 5 days/week) Followed by brachytherapy 3 weeks after intervention	Pelvic and para-aortic irradiation Radiation dose 44-45 Gy for 4.5-5 weeks (1.6-1.8 Gy/day for 5 days/week) Followed by brachytherapy 3 weeks after intervention	every 3 months for the first 3 years every 6 months for next 2 years every 12 months until 10 years

cervical cancer (OR = 0.75, 95% CI [0.32;1.76], p-value >0.05, 2 studies). All forest plots of secondary outcomes are presented in Figure 5.

Side Effects of Prophylactic Para-Aortic Lymph Node Irradiation

Adverse events were classified on a scale of 0 (no adverse events) to 5 (fatal), based on the RTOG toxicity criteria. Major toxicities were categorized as grades 3 (severe), 4 (requiring surgery), and 5 (fatal). Gastrointestinal complications are significantly more common in the EF-RT group (OR = 1.69, 95% CI [1.18;2.43], p-value<0.05, 5 studies), while urological and gynecological side effects are not significantly associated with EF-RT (OR = 1.33, 95% CI [0.82;2.15], p>0.05, 5 studies, and OR = 1.14, 95% CI [0.66;1.94], p-value<0.05, 2 studies, respectively). All side effect forest plots was shown in Figure 6.

Discussion

Results of this analysis were derived from six RCTs, each comparing prophylactic para-aortic lymph node irradiation combined with standard pelvic radiotherapy against standard pelvic-only radiotherapy [3,5,6,10,11]. Although detailed radiation fields, dose fractionation, and chemotherapy regimens were comprehensively described in the Materials and Methods section, it is important to acknowledge here that these treatment parameters were generally consistent across included trials, supporting comparability of the intervention effects.

One study specified the superior border of pelvic radiotherapy as the L3/L4 junction [6], with others using the L4/L5 level [5, 8], and doses ranged between approximately 39.6 to 50.4 Gy [3, 8–12] delivered in delivered in 5 fractions weekly [3, 8–12] or 6 fractions twice a week [5], with some dose delivery variations, such as 1.5-1.7 Gy/fraction [8], 1.8-2.0 Gy/fraction [3], and 1.6-1.8 Gy/fraction [10,11]. Prophylactic PALN irradiation was delivered via extended-field techniques, with fields covering para-aortic nodes up to the T12-L1 vertebral level [3,5,6]. Platinum-based chemotherapy, mainly cisplatin 40 mg/m² for six doses doses, was given concurrently or sequentially in most trials, and brachytherapy was routinely administered post-EBRT [5, 6]. Some studies also included brachytherapy as subsequent treatment

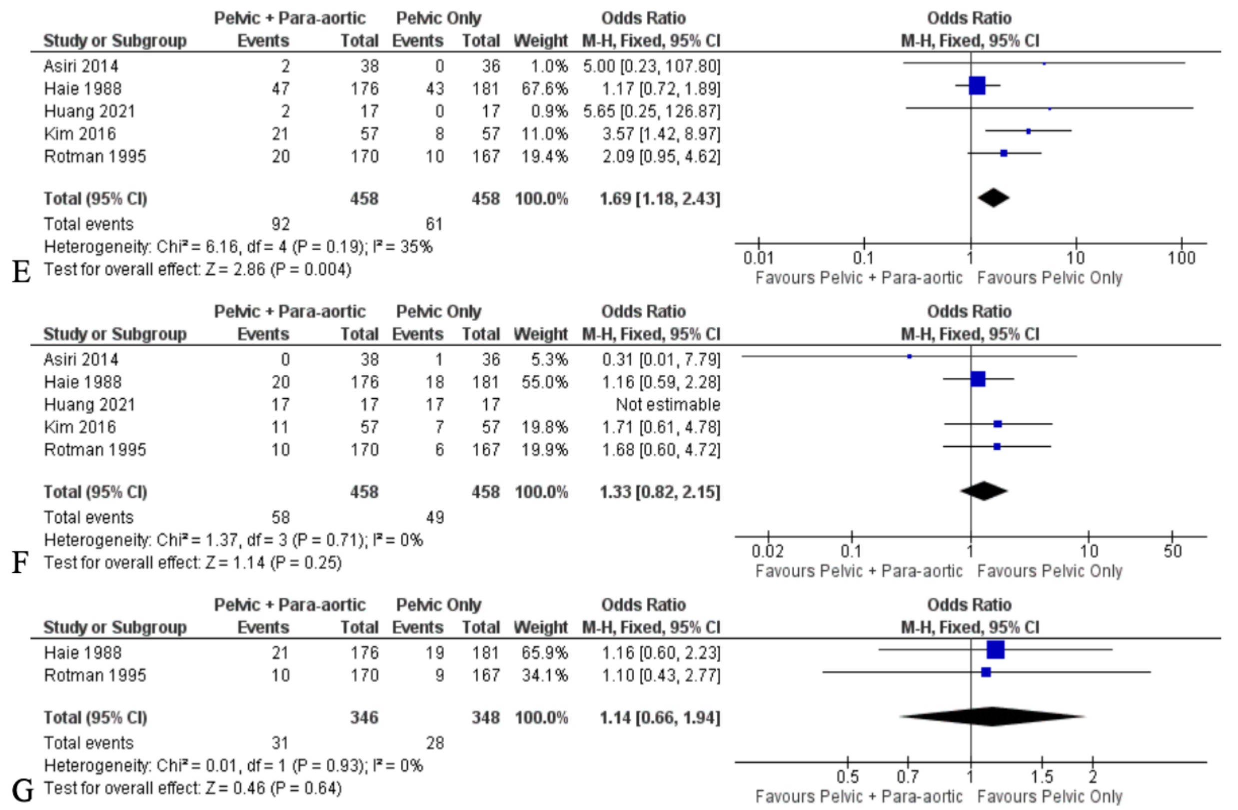

Figure 6. Forest Plot of Odd Ratio of Toxicity Side Effects. (E), Gastrointestinal Complications; (F), Urological Complications; (G), Gynecological Complications

in both arms, with three studies indicating that it was administered three weeks after radiotherapy [3, 10, 11].

Compared to standard pelvic radiotherapy, EF-RT, with its tolerable toxicities, should be strongly considered as an option for preventing para-aortic lymph node (PALN) metastasis, even though it does not significantly alter overall survival, distant metastasis, or complete remission of cervical cancer. Based on four included studies, the incidence of PALN metastasis in the follow-up period after prophylactic PALN irradiation is 11 events from 288 subjects compared to 46 events from 291 subjects in the control arm [3, 5, 6, 8]. Despite the established role of PALN metastasis as a prognostic factor in cervical cancer, current imaging techniques, including CT, MRI, and PET, are not sufficiently sensitive to detect small-bulk metastases in lymphatic systems of normal size or occult metastases [3, 5, 6, 12]. Due to this limitation, prophylactic PALN irradiation was expected to prevent PALN metastases in individuals with negative or occult PALN metastases and improve overall survival [3,5,6,12]. However, even though our study demonstrated that prophylactic PALN irradiation significantly reduced the incidence of PALN metastases (OR = 0.23, 95% CI [0.12;0.44], p-value<0.00001), it did not markedly enhance overall survival in comparison to standard pelvic radiotherapy (HR = 0.97, 95% CI [0.82;1.16], p-value>0.05).

Our study additionally revealed that EF-RT elevated the risk of late-onset severe gastrointestinal toxicities, including severe enteritis, obstruction, or bleeding (grade 3), bowel necrosis, perforations, or fistulas requiring surgery (grade 4), or those bowel toxicities resulting in fatality (OR = 1.69, 95% CI [1.18;2.43], p-value< 0.05). Late toxicities were defined as complications occurring after 90 days or when acute toxicity that manifested <90 days after treatment initiation persisted beyond day 90 [5, 10]. This finding corresponds with the EORTC trial in one of our included studies, which revealed a 2.3-fold increase in the prevalence of severe digestive problems (grades 3 and 4) in the para-aortic group (p-value=0.05) [8]. Moreover, our study revealed no significant increase in toxicity in the urological and gynecological regions.

This corresponds with the results of one of our included studies, which indicated similar severe radiation reactions in the ureter and vagina in both arms, although problems involving the small and large intestine were more frequent in the EF-RT arm [10]. Recently developed sophisticated procedures, like as IMRT, permit the precise administration of elevated radiation doses to the para-aortic lymph nodes while reducing exposure to adjacent organs, including the colon, bladder, and bone marrow. Our analysis included just one trial employing IMRT as standard therapy, which revealed no significant difference in the incidence of grade III and grade IV radiation enteritis and radiation cystitis between the treatment groups (p-value=0.48 and p-value=1, respectively) [3]. This can serve as a recommendation for future research and trials to maximize the safety of prophylactic lymph node irradiation.

Although employing a comprehensive approach that included a cited reference search, this study is not without limitations. Certain potentially relevant studies could not be located, and acquiring some studies proved challenging due to restricted access and difficulties contacting authors. Moreover, absence of data on disease-free survival (DFS) constrains this study's capacity to evaluate the intervention's efficacy appropriately. DFS is known to be a more sensitive and reliable measure of treatment efficacy, as some treatments can improve DFS without improving OS by controlling the cancer without curing it.

Despite the insufficient data regarding DFS, one included study indicated that the difference in DFS prevalence between the control and intervention groups was not significant [8]. Another study reported that the improvement in DFS was not significant due to the development of distant metastases outside the para-aortic field, predominantly affecting the subsequent level lymph node to the PAN, which may be influenced by various baseline factors [5].

In conclusion, prophylactic para-aortic irradiation conducted by EF-RT for cervical cancer patients with negative PALN metastasis significantly decreases para-aortic lymph node metastatic occurrences; however, it is improbable to offer any advantages regarding overall survival, pelvic disease control, or distant metastatic sites. Moreover, its side effects on gastrointestinal complications were found to be higher than those of standard pelvic radiotherapy, which warrants further consideration.

Author Contribution Statement

CTS conceptualized the study and was primarily responsible for writing the manuscript. MFBG, CTS, PED and BGDL contributed to the data analysis and interpretation. MFBG, PED, and BGDL were also involved in writing portions of the manuscript. INGB provided valuable consultation throughout the study. All authors reviewed and approved the final manuscript.

Acknowledgements

General

We would like to express our sincere gratitude to all the researchers and institutions whose work contributed to this meta-analysis. We also extend our appreciation to the authors of the randomized controlled trials included in this study for their invaluable contributions to advancing knowledge in the field of cervical cancer treatment.

Availability of data

All dataset in this study were extracted from previously publisherd paper through the online databases (e.g. PubMed, Cochrane CENTRAL, and ScienceDirect).

Study Registration

This study was registered in PROSPERO (International prospective register of systematic reviews) with ID : CRD42024496429

Conflict of Interest

The authors declare no conflict of interest.

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