Section: Radiation Oncology

Systematic Review

A SYSTEMATIC REVIEW OF ADJUVANT RADIATION THERAPY EFFECTS IN CERVICAL CANCER (CERVIX UTERI)

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Abstract

Background: Adjuvant radiation therapy, often administered following primary treatment such as surgery or chemotherapy, is a critical aspect of cervical cancer management. The effectiveness of adjuvant radiation therapy in enhancing patient outcomes, including overall survival, disease-free survival, and recurrence rates, continues to be a topic of significant research. This systematic review aimed to assess the effect of adjuvant radiation therapy on the outcomes of patients with cervical cancer. By analysing the existing literature, this study aimed to address research gaps in the effects of this therapy, providing insights to improve cervical cancer management. **Materials and Methods:** A systematic search of PubMed and Google Scholar databases from January 2016 to April 2024 was conducted. The inclusion criteria for this systematic review were studies that examined the effectiveness of adjuvant radiation therapy in managing cervical cancer (Cervix Uteri). Data synthesis involved a comprehensive analysis of the study methodologies, characteristics, and main findings, with particular emphasis on elucidating the distinct contributions of each study to the understanding of adjuvant radiation therapy effects in cervical cancer treatment. **Result:** This systematic review identified seven studies that met the inclusion criteria. Various outcomes including recurrence-free survival, overall survival, and treatment-related complications were evaluated in these studies. Key findings highlight the efficacy of adjuvant radiation therapy, particularly in reducing extra-pelvic recurrence and improving recurrence-free survival. **Conclusion:** The analysis highlights the effectiveness of adjuvant radiation therapy in diminishing extrapelvic recurrence and enhancing recurrence-free survival among individuals with cervical cancer. Concurrent chemoradiotherapy has potential benefits, especially in high-risk patients.

INTRODUCTION

Cervical cancer is the second most prevalent cancer in women globally. Managing locally advanced cervical cancer (LACC, stage IIB-IVA) poses a significant treatment challenge. Approximately 85% of these cases originate in regions with lower development status. Statistics suggest that 87% of cervical cancer-related fatalities occur in countries categorized as low- and middle-income group countries (LMICs).[1] The pathological factors associated with the recurrence of early stage cervical cancer following radical hysterectomy were initially documented in the 1980s. Parameters such as parametrial invasion, positive resection margin, and pelvic lymph node metastasis were classified as high-risk factors. Additionally, lymphovascular space invasion (LVSI), deep stromal invasion (DSI), and large tumour size are considered intermediate risk factors for recurrence.[2]

From a histological perspective, squamous cell carcinoma is the predominant malignant tumour of the cervix uteri, accounting for approximately 85% of cases. The remaining 15% consisted of adenocarcinoma and smaller groups exhibiting mixed compositions with both benign and malignant squamous and adenoma cell components.[3] For certain age groups, the mortality rate decreased by 60%. However, the overall treatment results for all patients diagnosed with invasive cervical cancer remain relatively stable. This could be attributed to

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the fact that despite advancements in treatment modalities, screening initiatives may be more successful in identifying slow-growing and less aggressive invasive cervical tumours.[4] Although postoperative pelvic radiotherapy combined with concurrent platinum-based chemotherapy is advised for post-surgical patients with high-risk factors, the appropriate treatment approach for patients with intermediate-risk factors remains unclear.[5]

The most reliable treatment option for managing early stage cervical cancer includes radical hysterectomy with pelvic lymph node dissection (PLND) or definitive radiotherapy (RT).[6] However, recent studies have indicated that adjuvant radiotherapy (RT) is more likely to yield only partial effects, which may not be beneficial in preventing extrapelvic recurrence. Physicians often exercise caution when considering supplementary treatment, particularly in cases where patients exhibit intermediate risk factors, leading to hesitation in employing a concurrent chemoradiotherapy (CRT) strategy. This suggests that patients with intermediate-risk factors may require chemotherapy alongside radiotherapy. The integration of chemotherapy and radiotherapy, commonly referred to as chemoradiotherapy (CRT), has been widely adopted for the treatment of various malignant tumours.[7]

In this systematic review, we aimed to examine the existing body of literature and assess the impact of adjuvant radiation therapy on outcomes in patients diagnosed with cervical cancer (cervix uteri).

MATERIALS AND METHODS

The overall quality of evidence for each outcome was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology. In this systematic review, we conducted a comprehensive search across several reputable databases, including PubMed and Google Scholar, to compile all relevant randomised clinical trials and meta-analyses examining the effects of adjuvant radiation therapy in managing cervical cancer (cervix uteri). This report conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Literature Search Strategy: A thorough and systematic examination was carried out across prominent academic databases, such as PubMed and Google Scholar, to identify pertinent research investigating the impact of adjuvant radiation therapy in cervical cancer (Cervix Uteri). The search was conducted between January 2016 and April 2024, covering studies published during this period. Keywords employed in the search strategy included different forms of "cervical cancer," "Cervix Uteri," and "adjuvant radiation therapy," alongside terms such as "treatment effectiveness," "outcome assessment," and "radiation side effects." Boolean operators (AND, OR) were used to enhance the search and guarantee the identification of relevant literature.

Inclusion and Exclusion Criteria:

Studies were included if they met the following criteria.

- Individuals diagnosed with cervical cancer (Cervix Uteri)
- Studies examining the effects of adjuvant radiation therapy
- Randomised controlled trials (RCTs), observational studies, and systematic reviews.
- Publications from January 2016 to April 2024
- Articles published in peer-reviewed journals
- Involvement of human subjects
- Availability of studies in English.

Studies were excluded if they met the following criteria:

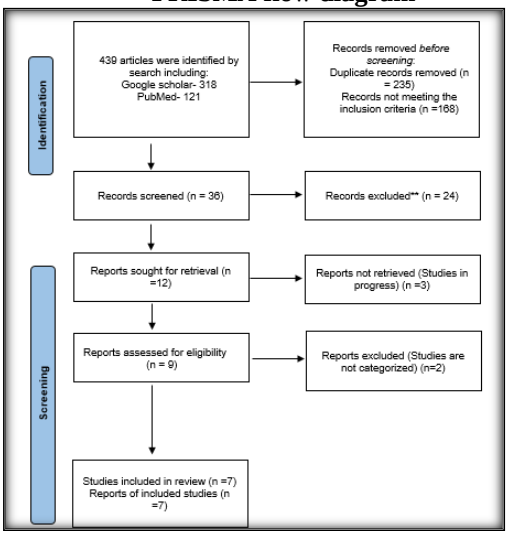
- Studies published before January 2016
- Studies not focusing on the effects of adjuvant radiation therapy in cervical cancer (Cervix Uteri)
- Studies lacking adequate data or having unclear methodology and
- Studies published in languages other than English.

Synthesis of Findings: Data synthesis involved a comprehensive narrative review of the key study characteristics, methodologies employed, and notable findings regarding the impact of adjuvant radiation therapy in cervical cancer (Cervix Uteri). Given the anticipated variation in study designs, a qualitative approach was adopted to emphasise the unique insights provided by each study to understand the comparative effectiveness of adjuvant radiation therapy in the management of cervical cancer.

Ethical Considerations: As this review was based on an analysis of previously published studies, ethical approval was not required. All the included studies adhered to ethical standards, as outlined in their respective publications.

RESULTS

PRISMA flow diagram



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We incorporated Cochrane systematic reviews of randomised controlled trials (RCTs) to investigate the efficacy of adjuvant radiation therapy in cervical cancer (Cervix Uteri). Additionally, non-Cochrane systematic reviews of RCTs and meta-analyses examining various aspects of adjuvant radiation therapy effects in cervical cancer were included, provided that they demonstrated a systematic approach, including a comprehensive search strategy, inclusion of only RCTs, clear criteria for study selection, evaluation of methodological aspects of the included studies, and synthesis of evidence. Mixed treatment comparison meta-analyses were eligible for inclusion if they were conducted as part of a systematic review of RCTs.

A thorough search of Google Scholar and PubMed identified 439 articles related to the selected topics. After the removal of 235 duplicate records, 168 articles were excluded because they did not meet the inclusion criteria. Subsequently, 36 records were screened and 24 studies were excluded. Further evaluation categorised three studies as in progress and two as pending. Ultimately, seven studies were found to be eligible and included in the review, aligned with the specified inclusion criteria.

Table 1: Types of cervical cancer with treatment options

Type of Cervical Cancer	Description	Treatment Options
Squamous Cell Carcinoma	Arises from flat, thin cervical cells	Surgery, Radiation, Chemotherapy.[8]
Adenocarcinoma	Develops from cervical glandular cells	Surgery, Radiation, Chemotherapy.[8]
Adenosquamous Carcinoma	Contains both squamous and glandular cells	Surgery, Radiation, Chemotherapy,[8]
Small Cell Carcinoma	Rare aggressive type with small, round cells	Chemotherapy, Radiation.[8]
Neuroendocrine Tumours	Rare neuroendocrine malignancies	Surgery, Chemotherapy, Radiation.[8]
Clear Cell Carcinoma	Rare type with clear cytoplasm	Surgery, Chemotherapy, Radiation.[8]

Table 2: Characteristics of Included Studies

Study Authors	Study Year	Study Type	Participants (n)	Discussion
Matsuo et al,[9]	2017	Retrospective cohort study	555 participants	The study found that women with stage IB cervical cancer in the intermediate-risk group who received systemic chemotherapy had similar disease-free survival rates compared to those who received concurrent chemoradiotherapy (CCRT) or radiotherapy alone. The 5-year disease-free survival rates in the chemotherapy and CCRT groups were 88.1% and 90.2%, respectively. The adjusted hazard ratio for disease-free survival between the chemotherapy and CCRT groups was 0.98 (95% confidence interval 0.52–1.83, P = 0.94).
Datta et al,[10]	2018	Systematic review, meta-analysis and randomized controlled trials	59 randomized controlled trials involving 9894 patients	The results showed that different interventions had varying effects on long-term locoregional control (LRC), overall survival (OS), acute morbidity (AM), and late morbidity (LM). Hyperthermia with radiation therapy versus concurrent chemoradiation therapy with adjuvant chemotherapy showed a favourable OR of 1.23 for LRC. Chemoradiotherapy with 3-weekly cisplatin versus hyperthermia combined with chemoradiotherapy had an OR of 1.14 for OS.
Li et al,[11]	2019	Systematic review and meta-analysis	The study included a total of 870 patients in the chemoradiotherapy group and 932 patients in the radiotherapy group, making a combined total of 1802 participants.	The study assessed various endpoints including recurrence-free survival (RFS), overall survival (OS), grade III/IV haematologic toxicity, and grade III/IV non-haematologic toxicity in patients with intermediate-risk factors. The results indicated that there was no significant publication bias affecting the results of the meta-analysis. This study found that pelvic radiotherapy is recommended as a category I treatment for cervical cancer, and adjuvant therapy after radical surgery should aim to reduce extrapelvic recurrence.
Nasioudis et al,[12]	2021	Retrospective cohort study	765 participants	The study included 765 patients, predominantly white (78.2%), with a median age of 43 years, and 86.9% were devoid of comorbidities. Squamous cell carcinoma was the histological subtype (68.5%), with 65.6% showing lymphovascular invasion. Approximately half of the patients (49.4%) received adjuvant external beam radiation therapy with a median interval of 54 days between surgery and radiation therapy initiation. Among the radiation therapy recipients, 27% underwent vaginal brachytherapy and 57.9% received chemotherapy. Nonetheless, among patients with lymphovascular invasion, those receiving adjuvant radiation therapy exhibited a trend toward improved overall survival (p = 0.053).
Horeweg et al,[13]	2021	Systematic review and meta-analysis	622 participants	The study found that the addition of an adjuvant platinum–pyrimidine antagonist after chemoradiation did not result in a statistically significant overall survival benefit (HR 0.76, 95%CI: 0.43–1.34, p = 0.22). Similarly, adjuvant platinum–taxane did not show a significant benefit in overall survival (HR 0.47, 99%CI: 0.12–1.86, p = 0.16).

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Scharl et al,[14]	2021	Observational cohort study	442 participants	The results showed no significant OS difference in low-risk patients with or without adjuvant therapy, but those receiving RT had worse RFS than those receiving surgery alone. In contrast, adjuvant RT significantly improved RFS in intermediate-risk patients with no significant effect on OS. Although high-risk patients showed trends toward improved OS and RFS with adjuvant therapy, these trends were not statistically significant.
Guo et al,[15]	2022	Systematic review and meta-analysis	3785 participants	The study included 3785 women diagnosed with early stage cervical cancer who underwent radical hysterectomy. Among them, 1796 individuals underwent adjuvant radiotherapy and 1805 received adjuvant chemoradiotherapy. Participants were monitored for a maximum duration of 16.8 years, with a minimum follow-up period of 16 months. Analysis of the data revealed no statistically significant difference in overall survival rates between those who underwent adjuvant radiotherapy and those who received adjuvant chemoradiotherapy.

DISCUSSION

Cervical cancer poses a considerable global public health challenge and is one of the most prevalent cancers diagnosed in women. While it can impact women across all age groups, it tends to be most frequently identified in women aged 35 to 44, with a distinct peak incidence observed among those aged 45 to 49.[16] The primary risk factor for cervical cancer is persistent infection with high-risk strains of human papillomavirus (HPV), underscoring the critical importance of HPV vaccination and routine cervical screening. Implementing effective prevention measures such as HPV vaccination programs and structured cervical screening efforts holds substantial promise in reducing both the occurrence and fatalities associated with cervical cancer.[17]

Therapeutic approaches for early stage cervical cancer, such as radical surgery, radiotherapy, and chemotherapy, are primarily determined by the FIGO stage, patient's overall physical condition, treatment preferences, surgeon's expertise, and clinical assessment. The prognostic factors influencing the outcome of cervical cancer include pathological staging, tumour differentiation, lymph node involvement, and surgical margins. Postoperative management options for patients with early-stage cervical cancer and intermediate-risk factors for recurrence remain unclear.[18]

The National Comprehensive Cancer Network (NCCN) guidelines endorse pelvic radiotherapy as the primary therapeutic approach for cervical cancer, categorised as class I. Given its effectiveness, radiotherapy has become the leading adjuvant treatment choice for individuals with intermediate-risk factors after radical surgical resection. However, the primary aim of adjuvant therapy post-radical surgery should prioritize the reduction of extra pelvic recurrence over local recurrence.[19]

Recently, chemoradiotherapy (CRT) has emerged as a definitive approach for reducing the occurrence of extrapelvic recurrence in cervical cancer. Combination chemotherapy with radiotherapy (RT) has been shown to effectively combats recurrence and improves recurrence-free survival (RFS). Qin et al,[20] analysed eleven studies that compared the effectiveness of adjuvant CRT with adjuvant RT following radical surgery in cervical cancer patients with high-risk and intermediate-risk factors. The review revealed that patients with high-risk factors significantly benefited from CRT in terms of overall survival (OS) (hazard ratio [HR] 0.44, 95% confidence interval [CI] 0.28-0.67) and RFS (HR 0.48, 95% CI 0.33-0.70), whereas those with intermediate-risk factors did not derive any advantage from CRT.

Cibula et al,[21] conducted a comparative analysis of oncologic outcomes in patients with lymph-node-negative intermediate-risk cervical cancer. In their study, 127 patients who underwent surgery alone and 104 patients who received chemoradiation were evaluated for a range of oncologic measures, including overall survival, recurrence-free survival, and disease-free survival, to ascertain the efficacy of these treatment approaches.

Mabuchi et al,[22] studied that concurrent administration of cisplatin and pelvic radiotherapy was the established treatment for cervical cancer. However, in their study, a challenge encountered during the treatment of stage IIIB/IVA disease with cisplatin-based concurrent chemoradiotherapy (CCRT) was the development of hydronephrosis due to ureteral obstruction. Although the precise incidence of ureteral obstruction is not well defined, it has been reported to occur in 7% of all cases of invasive cervical cancer and 55.8% of patients with stage III-IV disease in their study.

CONCLUSION

In conclusion, this systematic review thoroughly examined the effects of adjuvant radiation therapy on the outcomes of patients with cervical cancer. This emphasises the significant role of adjuvant radiation therapy in managing cervical cancer, particularly in reducing extrapelvic recurrence and improving recurrence-free survival. This review highlighted the efficacy of concurrent chemoradiotherapy (CRT) in specific patient groups, notably those with high-risk factors, while also stressing the necessity for further research to determine the best treatment approach for patients with intermediate-risk factors.

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Furthermore, the review identified treatment challenges such as the occurrence of hydronephrosis due to ureteral obstruction in patients undergoing cisplatin-based concurrent chemoradiotherapy for stage IIIB/IVA disease. This review provides valuable insights for improving strategies for managing cervical cancer and highlights the significance of customising treatments according to the unique characteristics and risk profiles of individual patients.

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