PATTERNS OF FAILURE AND FIVE-YEAR OVERALL SURVIVAL IN PATIENTS WITH EARLY AND LOCALLY ADVANCED CERVICAL CANCER: A NARRATIVE REVIEW COMPARING CONCURRENT CHEMORADIOTHERAPY AND RADIOTHERAPY

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ABSTRACT

BACKGROUND: This systematic review aims to compare chemoradiotherapy (CRT) and radiotherapy (RT) failure patterns, particularly the incidence of distant metastases and overall survival outcomes, in patients with early-stage and locally advanced cervical cancer.

METHODS: Following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, a comprehensive literature search was conducted for articles published between January 1, 2020, and January 1, 2025. The search included the terms: "cervical cancer," "chemoradiotherapy," "radiotherapy," and "chemotherapy." Studies were selected based on their evaluation of CRT versus RT in patients with early-stage and locally advanced cervical cancer, with specific attention to distant metastasis rates and overall survival.

RESULTS: Across multiple studies, CRT was associated with a lower incidence of distant metastases compared to RT. Olthof et al. reported 54% metastasis in the CRT group versus 80% in the RT group. Van den Akker et al. observed 37.2% in CRT versus 62.7% in RT. Kushwaha et al. found the lowest rates, with 10.5% in CRT compared to 19.8% in RT. However, results regarding overall survival were inconsistent. Van den Akker et al. reported higher 5-year survival in the RT group (66.8%) compared to CRT (50.1%). Olthof et al. found no significant difference, while Kushwaha et al. observed longer median survival in CRT (66 vs. 44 months), though not statistically significant ($p = 0.087$).

CONCLUSION: Chemoradiotherapy may help lower the risk of distant metastases in high-risk early-stage cervical cancer, likely due to the systemic effects of chemotherapy. However, its impact on overall survival remains uncertain, with inconsistent evidence across studies. Further well-designed prospective trials are needed to evaluate long-term survival benefits, considering chemotherapy-related toxicity.

KEYWORDS: Cervical cancer, chemoradiotherapy, radiotherapy, distant metastasis, overall survival

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INTRODUCTION

Cervical cancer is the fourth most common cancer affecting women worldwide, following breast, colorectal, and lung cancers, and also represents the fourth leading cause of cancer-related morbidity and mortality among women globally, as reported by GLOBOCAN 2018[1,2]. In 2022, cervical cancer accounted for an estimated 662,044 new cases (age-standardized incidence rate: 14.12 per 100,000) and 348,709 deaths (age-standardized mortality rate: 7.08 per 100,000) worldwide, making it the fourth leading cause of cancer-related morbidity and mortality among women globally [3]. The burden is significantly heavier in low- and lower-middle-income countries, where the majority of cases, over two-thirds, are diagnosed at a locally advanced stage[1].

Each year, approximately 600,000 new cases are reported worldwide, with nearly 90% occurring in low- and middle-income countries (LMICs). Despite being potentially curable when detected early, a substantial proportion of cases—ranging from 40% to 50%—are diagnosed at a locally advanced stage, as classified by the International Federation of Gynecology and Obstetrics (FIGO) stages IB2–IVA or IB3–IVA (4). The crude annual incidence rate is estimated at 13.6 per 100,000 women, with up to 30% of cases identified at locally advanced stages (IIA–IVA). Approximately 85% of new cases and 87% of cervical cancer deaths occur in these regions, reflecting disparities in early detection and the availability of radiotherapy services [5].

For patients with locally advanced cervical cancer (FIGO 2018 stages IB3–IVA), platinum-based concurrent chemoradiotherapy (CCRT) followed by intrauterine brachytherapy is the current standard of care [2,6]. This approach, supported by multiple randomized trials and meta-analyses, reduces mortality by 30–35% compared to radiotherapy alone [6]. While earlier studies used the FIGO 2009 staging, current guidelines recommend adopting the updated 2018 classification. Surgery remains the primary treatment for early-stage disease (FIGO stages IA–IB2) [2,6].

Radiotherapy has historically been essential in treating advanced cervical cancer[7]. Ionizing radiation destroys cellular components, including nucleic acids, proteins, and lipids, thus inhibiting cell division, inducing cell-cycle arrest, and triggering programmed cell death mechanisms[7]. The primary mechanism involves DNA damage, which occurs either by directly ionizing DNA molecules (approximately 40% of the effect) or indirectly through the generation of free radicals—especially hydroxyl radicals—from water radiolysis, which subsequently attack DNA, leading to strand breaks or mutations (the majority, about 60%)[7].

This systematic review investigates differences in the patterns of failure and five-year overall survival in patients with cervical cancer treated with chemoradiotherapy compared to radiotherapy.

Materials and Methods

Search Strategy

This systematic review followed the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for the process of article selection and reporting (Fig. 1). The search was conducted for studies between January 2020 and January 2025.

Study Selection

We searched for studies from several databases, including Medline (PubMed), the Cochrane Library, and Scopus. A systematic search for studies was conducted in these scientific databases covering publications from January 1, 2020, to January 1, 2025. The search was performed using the keywords: "Cervical cancer" AND "Chemoradiotherapy" AND "Radiotherapy" AND "Chemotherapy."

The inclusion criteria for the study were as follows:
(1) patients must have received definitive radiation therapy;
(2) a confirmed diagnosis of cervical cancer with a clinical tumor stage between cT IA2 – IIIB; and
(3) treatment involving radical hysterectomy with pelvic lymphadenectomy, with or without para-aortic lymph node dissection, followed by adjuvant radiotherapy or chemoradiotherapy. Patients who

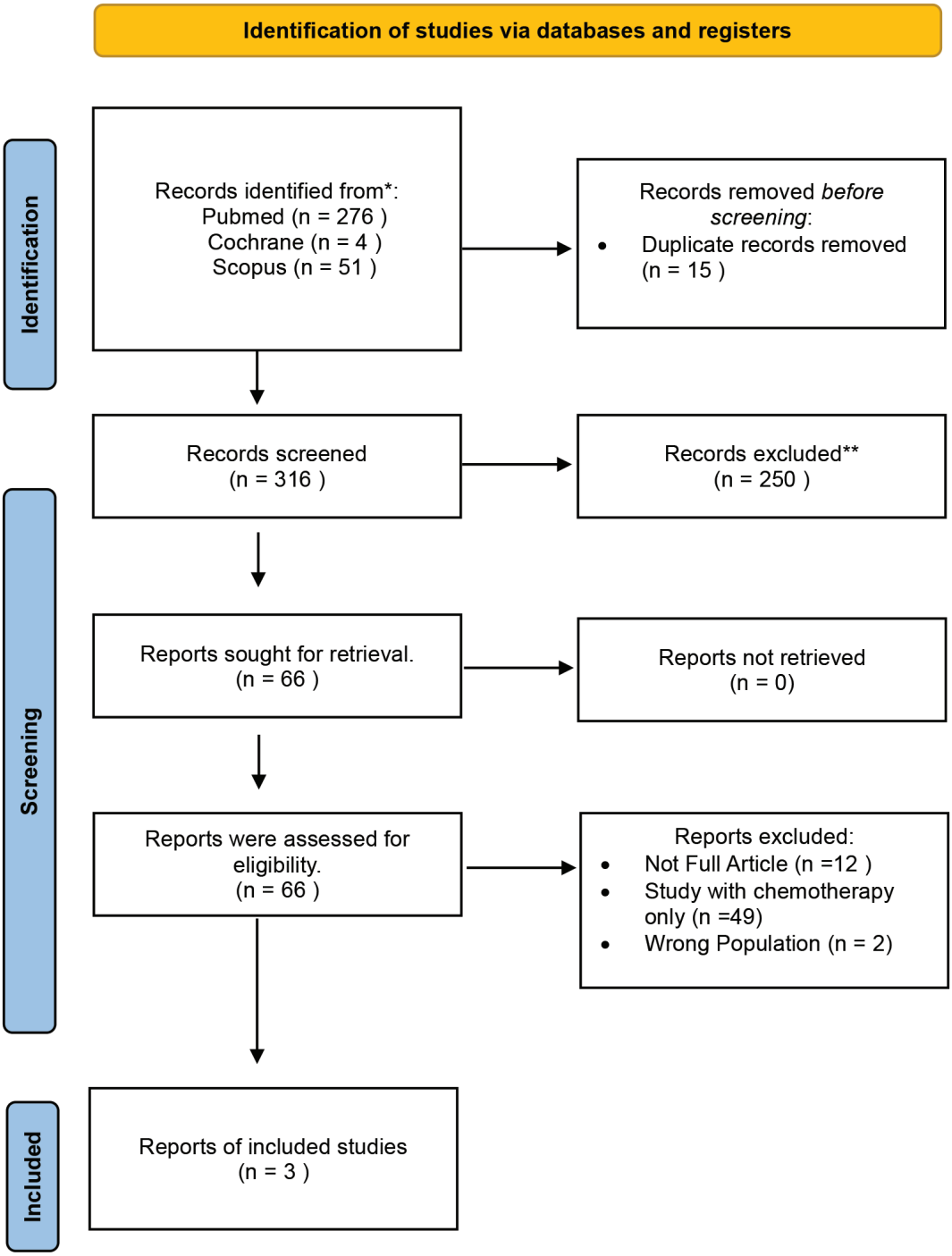

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram for the process of selecting the included papers.

underwent neoadjuvant chemotherapy as the sole treatment modality were excluded from the study. Radiotherapy-only treatment, consisting of pelvic external beam radiotherapy, was defined as radiation administered either alone or in combination with chemotherapy (i.e., chemoradiotherapy).

Data Extraction

The extracted data included the author, country, and year of the study; study population size; study design; database analyzed; cancer type and stage; radiation therapy modality or technique and dosage; and patient characteristics.

Quality of Studies

This review aimed to collect and extract data on resource parameters from scientific literature for use in mathematical modeling rather than to conduct a meta-analysis of the identified parameters. As a result, the three studies included were not evaluated for risk of bias at the individual or collective level, and no formal quality assessment was carried out before data extraction.

Results

On July 27, 2025, a systematic literature search was conducted in the PubMed, Cochrane Central Register of Controlled Trials, and Scopus databases, identifying 331 citations. After screening all abstracts, 15 duplicate publications were found among the 331 citations. After removal, 316 citations remained. These were screened using inclusion and exclusion criteria, resulting in 66 citations. Among these, 12 articles were inaccessible, 48 discussed chemotherapy only, and 2 involved an irrelevant population. Finally, we included three studies in the final analysis.

In a study by Ester P. Olthof et al., 122 Patients with squamous cell carcinoma and one high-risk factor after radical hysterectomy and pelvic lhymphadenectomy, 62% received adjuvant chemoradiotherapy, while 38% underwent adjuvant radiotherapy alone. Median follow-up durations for recurrence-free survival (9 vs. 5 years; $p < 0.001$) and overall survival (8 vs. 6 years; $p < 0.001$) were longer in the chemoradiotherapy group[8]. Recurrence occurred in 17% of patients treated with chemoradiotherapy and 11% in the radiotherapy group ($p = 0.44$), predominantly due to distant metastases (54–80%). Mortality rates did not differ significantly between the groups (20% vs. 11%; $p = 0.31$)[8]. Adjusted analysis based on recurrence site indicated a substantially lower risk of locoregional recurrence with adjuvant radiotherapy (HR 0.09; 95% CI: 0.01–0.79; $p = 0.03$), while the risk of distant recurrence remained comparable between the two modalities (HR 0.85; 95% CI: 0.21–3.37; $p = 0.81$)[8].

A total of 154 patients stage IB1-IIB after radical hysterectomy were evaluated in Mick J E van den Akker et al.'s study, with a median follow-up duration of 9.6 years (IQR: 6.1–12.8)[9]. The five-year pelvic recurrence-free survival rate was 75.3%, with 74.7% in high-risk patients treated with radiotherapy and 77.3% in those receiving chemoradiation ($p = 0.43$). Five-year distant metastasis-free survival was 63.4%, including 63.6% in the radiotherapy group and 57.1% in the chemoradiation group among high-risk patients ($p = 0.36$)(9). Overall five-year survival was 63.9%, with survival rates of 66.8% after radiotherapy and 51.6% after chemoradiation in patients with high-risk factors ($p = 0.37$). Larger tumour size was associated with an increased risk of vaginal and pelvic recurrence, while having two or more positive lymph nodes significantly increased the risk of para-aortic recurrence and mortality[9].

In a prospective randomized study by Vandana Singh Kushwaha et al. A total of 191 Patients in a comparative analysis between CRT (control arm, $n = 95$) and ART (study arm, $n = 96$), 43.2% of patients in the CRT locally advanced cervical cancer (FIGO stage IIB – IIIB) group remained recurrence-free[10]. In contrast, 14.7% never achieved disease-free status, 30.5% experienced recurrence, and 11.6% were lost to follow-up. In the ART group, 31.3% were recurrence-free, 19.8% were never disease-free, 38.5% experienced recurrence, and 10.4% were lost to follow-up[10].

Over five years, overall survival was similar between groups. In the CRT arm, 48.8% of patients died due to disease, and 51.2% were alive, with a median overall survival of 66 months[10]. In the ART arm, 62.8% died and 37.2% were alive, with a median survival of 44 months[10]. Although the log-rank test did not show a significant difference in overall survival between the groups ($\chi^2 = 2.93$, $p = 0.087$), the monthly death rate was 1.43 times higher in the ART group (HR = 0.70; 95% CI: 0.46–1.05). Similarly, for five-year disease-free survival, 42.9% of patients in the CRT arm died and 57.1% were alive (median survival: 86 months), while in the ART arm, 53.7% died and 46.3% were alive (median survival: 67 months). No significant difference was found in disease-free survival between the groups ($\chi^2 = 1.49$, $p = 0.223$), although the monthly death rate was also higher in the ART group (HR = 0.74; 95% CI: 0.45–1.20)[10].

This systematic review analyzed three comparative studies evaluating the impact of adjuvant chemoradiotherapy (CRT) versus radiotherapy (RT) alone in patients with high-risk cervical cancer, with a focus on distant metastasis and overall survival outcomes. The included studies demonstrated notable variations in their inclusion criteria, which may contribute to differences in outcomes. Olthof et al. selected patients with early-stage cervical cancer (FIGO stages IA2–IIA2), limiting their cohort to individuals diagnosed with squamous cell carcinoma and presenting with only one high-risk factor. In contrast, the study by Mick J. E. van den Akker et al. included patients with more advanced disease (stages IB1–IIB), primarily involving non-squamous cell carcinoma histology and multiple high-risk features. Vandana Singh Kushwaha et al. focused on a more narrowly defined group: women aged ≤70 years with locally advanced cervical cancer (stages IIB–IIIB), diagnosed with invasive squamous cell carcinoma of the cervix.

Table 1. Total Studies included for systematic review

Author	Study Year	Metode	Primary Objective	Result			
				Distant Metastasis		Overall Survival	
				CRT	ART	CRT	ART
Ester P. Olthof et.al	2025	Retrospective study	To compare clinical Recurrence-free survival and overall survival of adjuvant CRT versus RT only.	7 (54%)	4 (80%)	8 (3.6)	6 (3.7)
Mick J E van den Akker et. al	2020	Retrospective cohort study	To assess the impact of adding chemotherapy to postoperative radiotherapy on oncologic outcomes and toxicity in early-stage cervical cancer.	16 (37.2%)	27 (62.7%)	50.1 (SE 8.7)	66.8 (SE5.6)
Vandana Singh Kushwaha et. al	2024	Prospective randomized	study To compare survival rates and toxicity between adjuvant radiotherapy (ART) and chemoradiotherapy (CRT)	10 (10.5%)	19 (19.8%)	41 (48,8%) patients died	54 (62,8%) patients died
						43 (51,2%) patients alive	32 (37,2%) patients alive

DISCUSSION

Cervical cancer is the fourth most common cancer and a leading cause of cancer-related death among women worldwide[11]. In 2022, cervical cancer accounted for an estimated 662,044 new cases (age-standardized incidence rate: 14.12 per 100,000) and 348,709 deaths (age-standardized mortality rate: 7.08 per 100,000) worldwide, making it the fourth leading cause of cancer-related morbidity and mortality among women globally[3]. The burden is highest in low- and middle-income countries, where it often ranks as the most diagnosed cancer in women[7]. Despite this, cervical cancer is largely preventable through routine screening and early detection[7,11].

Several risk factors contribute to the development of cervical cancer, including infection with human papillomavirus (HPV), other sexually transmitted infections, immunodeficiency, early sexual activity, multiple sexual partners, early childbirth, long-term use of oral contraceptives, and smoking[2,12]. In high-income countries, widespread HPV vaccination and regular screening programs have significantly reduced incidence and enabled earlier detection[2,12]. However, in many low-resource settings, a large proportion of patients are still diagnosed at advanced stages[12].

The 2018 FIGO revision introduced key updates to cervical cancer staging, including the removal of lateral extent in stage IA and the subdivision of stage IB into IB1 (<2 cm), IB2 (2–4 cm), and IB3 (≥4 cm) (13). Imaging and pathology are now incorporated into staging, allowing assessment of tumor size, local spread, and nodal involvement. Stage IIIC was added to denote pelvic (IIIC1) and para-aortic (IIIC2) lymph node metastases[13].

Radiotherapy and concurrent chemoradiotherapy (CCRT) are essential in cervical cancer treatment[14]. Adjuvant radiotherapy/CCRT is recommended for early-stage patients with risk factors, while definitive CCRT is the standard for locally advanced disease[14]. Palliative or salvage radiotherapy is used in stage IVB or recurrent cases. Although concurrent chemoradiotherapy followed by brachytherapy remains the standard treatment for LACC, long-term outcomes remain suboptimal[15].

This systematic review analyzed three studies reporting the risk of distant metastasis. In the study by Olthof et al., patients treated with chemoradiotherapy (CRT) showed a slightly lower incidence of distant metastasis compared to those treated with radiotherapy (RT) alone. Among 13 patients receiving CRT, 7 (54%) developed distant metastases, whereas in the RT group, 4 out of 5 patients (80%) experienced distant spread[8]. However, the opposite trend was observed for locoregional recurrence, where RT was associated with a lower risk of locoregional relapse (HR = 0.09; 95% CI: 0.01–0.79; p = 0.03)[8].

In the study by Van den Akker et al., among 43 high-risk patients, 16 (37.2%) developed distant metastasis after CRT compared to 27 (62.7%) after RT[9]. Similarly, in the study by Kushwaha et al., distant metastasis occurred in 10 of 95 patients (10.5%) treated with CRT and in 19 of 96 patients (19.8%) treated with RT[10].

Overall, across the three reviewed studies, the incidence of distant metastasis was consistently lower in patients treated with CRT compared to RT alone. This finding aligns with the theoretical understanding that adding systemic chemotherapy to radiotherapy enhances local tumor control and targets micrometastatic disease, thereby reducing the likelihood of distant spread.

Pathological risk factors for recurrence in early-stage cervical cancer following radical hysterectomy were first identified in the 1980s[16]. High-risk factors include parametrial invasion, positive surgical margins, and pelvic lymph node metastasis. In contrast, intermediate-risk factors comprise lymphovascular space invasion (LVSI), deep stromal invasion (DSI), and large tumor size[16]. Postoperative pelvic radiotherapy combined with platinum-based chemotherapy is recommended for patients with high-risk features; however, optimal management for intermediate-risk patients remains unclear. Phase III data (GOG 92) demonstrated

that adjuvant radiotherapy reduces recurrence risk and improves recurrence-free survival in stage IB disease[16]. Nonetheless, recent evidence suggests limited efficacy of radiotherapy alone, particularly in preventing extra-pelvic recurrence, indicating a potential role for chemoradiotherapy (CRT) in intermediate-risk patients[16]. CRT has been broadly utilized across various malignancies[16].

Three studies comparing adjuvant chemoradiotherapy (CRT) with adjuvant radiotherapy (ART) in early-stage cervical cancer were included in this review. Olthof et al. reported longer median follow-up times in the CRT group for both recurrence-free survival (RFS) (9 vs. 5 years; $p < 0.001$) and overall survival (OS) (8 vs. 6 years; $p < 0.001$). Nevertheless, five-year RFS and OS rates were statistically comparable between CRT and ART groups. For RFS, unadjusted rates were 85% vs. 87% ($p = 0.58$), and adjusted rates were 84% vs. 91% ($p = 0.29$). Similarly, OS rates were 84% vs. 87% ($p = 0.61$) unadjusted and 84% vs. 91% ($p = 0.30$) adjusted[8]. Multivariable analysis using inverse probability treatment weighting showed no significant association between treatment modality and either RFS (HR = 0.54; 95% CI: 0.17–1.71; $p = 0.29$) or OS (HR = 0.56; 95% CI: 0.19–1.67; $p = 0.30$)[8].

Van den Akker et al. found a five-year OS of 50.1% (SE: 8.7) in the CRT group and 66.8% (SE: 5.6) in the ART group (9). In the study by Kushwaha et al., the median OS was 66 months for CRT and 44 months for ART. Although numerically better outcomes were observed in the CRT group, the log-rank test indicated no statistically significant difference ($\chi^2 = 2.93$; $p = 0.087$). The estimated hazard ratio for mortality in the ART group was 0.70 (95% CI: 0.46–1.05), suggesting a non-significant trend favoring CRT[10].

Compared to early-stage disease, locally advanced cervical cancer (LACC) is associated with significantly lower cure rates[12]. Although concurrent chemoradiotherapy (CCRT) achieves five-year disease-free and overall survival rates of approximately 68% and 74%, recurrence or distant metastasis still occurs in 23.3% to 34.4% of patients[12,17]. Prognostic factors such as advanced stage and lymph node involvement are linked to poorer outcomes, with five-year mortality rates for LACC remaining high at 30–40%[17]. These figures reflect the limitations of current treatment strategies and highlight the need for improved therapeutic approaches[12,17]. Emerging modalities, including neoadjuvant chemotherapy, targeted therapy, and immunotherapy, are under investigation for their potential to enhance survival and reduce relapse[12,17]. Continued research is essential to optimize treatment combinations and sequences tailored to this heterogeneous patient population[17].

One limitation of the study by Olthof et al. is that the study population was restricted to patients with early-stage cervical cancer (FIGO stages IA2–IIA2), specifically those diagnosed with squamous cell carcinoma and presenting with only one high-risk factor. Additionally, population heterogeneity in terms of tumor size, tumor grade, parametrial invasion, and lymph node metastases may have influenced the outcomes. These factors limit the generalizability of the findings and reduce comparability with studies involving broader populations receiving adjuvant therapy.

In the study by Van den Akker et al., patients had more advanced disease (FIGO stages IB1–IIB), with a predominance of non-squamous cell carcinoma histology and multiple high-risk features. The cohort included patients who underwent postoperative radiotherapy or chemoradiotherapy between November 1999 and May 2015. Differences in treatment eras (1999–2007 vs. 2008–2016) may have contributed to the unexpected finding that early-stage patients did not have better outcomes than those with more advanced localized disease. This suggests that evolving treatment practices over time may have impacted the significance of the results.

In the study by Kushwaha et al., the focus was on a narrowly defined cohort: women aged ≤70 years with locally advanced cervical cancer (FIGO stages IIB–IIIB), all diagnosed with invasive squamous

cell carcinoma. The inclusion of patients with significant comorbidities, elderly individuals, and those with advanced-stage disease where the efficacy of concurrent chemotherapy may be diminished could have influenced the overall outcomes. The benefit of concurrent chemotherapy appears to decrease with advancing disease stage. Furthermore, the addition of chemotherapy is associated with increased toxicity, suggesting that age and comorbid conditions may act as confounding factors in this study.

The chemotherapeutic agents, primarily acting as radiosensitizers, enhance the efficacy of radiation treatment[10]. However, the integration of chemotherapy is also associated with increased treatment-related toxicities, particularly acute hematologic and gastrointestinal adverse effects, which are more prevalent in patients receiving CRT than in those treated with RT alone[10]. Notably, the incidence and severity of these toxicities vary widely across studies, indicating that treatment-related toxicity may serve as a critical determinant of clinical outcomes and survival in patients undergoing CRT[10].

Five-year RFS and OS were broadly equivalent, regardless of whether chemotherapy was added to radiotherapy. Interestingly, the ART group reported a lower locoregional recurrence rate. However, as both groups received radiotherapy, this finding may reflect differences in surgical approach, particularly the extent of radical hysterectomy, rather than the effect of chemotherapy. These findings underscore the importance of individualized treatment planning, considering both tumor characteristics and surgical factors when selecting adjuvant therapies.

Conclusions

Adjuvant chemoradiotherapy may reduce the risk of distant metastases in patients with high-risk early-stage cervical cancer, supporting the pharmacological rationale for systemic chemotherapy in targeting micrometastatic disease. However, its effect on overall survival remains inconclusive, with no consistent or statistically significant benefit observed across studies. These findings emphasize the need for further high-quality prospective trials to clarify the long-term survival benefits of primary CRT, taking into account both the direct and indirect toxicities of chemotherapy that may influence patient outcomes.

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