REVIEW

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Efficacy and Safety of Neoadjuvant Chemotherapy Plus Concurrent Chemoradiotherapy Compared to Concurrent Chemoradiotherapy Alone in Locally Advanced Cervical Cancer: A Systematic Review and Meta-Analysis

Candra Novi Ricardo Sibarani[1]*, Siti Salima[1], Dodi Suardi[1], Nicholas Adrianto[2], Ghea Mangkuliguna[3]

Abstract

Introduction: This systematic review and meta-analysis assessed the efficacy and safety of neoadjuvant chemotherapy (NACT) followed by concurrent chemoradiotherapy (CCRT) compared to CCRT alone in locally advanced cervical cancer (LACC). **Methods:** We systematically searched PubMed, ScienceDirect, Cochrane Library, EBSCOHost, ProQuest, and grey literature (Google Scholar, OpenGrey, WorldCat) up to April 26, 2024 (PROSPERO: [CRD42024540599]). Seven studies were included (stages IB2–IVA, FIGO 2018), involving 446 participants. Outcomes included complete response (CR), progression-free survival (PFS), overall survival (OS), and adverse effects. **Results:** Seven studies were included (n = 1,638), with 825 patients receiving NACT+CCRT and 813 receiving CCRT alone. The NACT+CCRT group showed higher CR rates (77% vs. 70.9%), but the difference was not statistically significant (OR 1.23, 95% CI 0.40–3.83). No significant differences were found in PFS (HR 0.94, 95% CI 0.53–1.69) or OS (HR 1.07, 95% CI 0.56–2.03). Adverse effects, including anemia, neutropenia, thrombocytopenia, nausea, vomiting, fatigue, and creatinine elevation, showed no significant differences between the groups. **Conclusion:** In patients with locally advanced cervical cancer, NACT followed by CCRT is associated with comparable survival outcomes and a similar safety profile to standard CCRT, with a non-significant trend toward improved CR.

Keywords: Cervical cancer- neoadjuvant therapy- chemoradiotherapy- treatment outcome- meta-analysis

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Introduction

Cervical cancer ranks as the fourth most prevalent cancer globally and stands as the fourth leading cause of cancer-related deaths among women [1]. However, within developing nations, it ranks as the second most common cause of both cancer incidence and mortality [2]. Locally advanced cervical cancer (LACC), classified as stages IB3–IVA under the FIGO 2018 system [3]. Presently, the standard treatment for LACC involves definitive chemoradiation therapy (CCRT), combining pelvic radiotherapy with concurrent cisplatin-based chemotherapy [4, 5]. Brachytherapy is a fundamental part of this standard treatment for women with LACC [6]. Limited research has been carried out on the use of neoadjuvant chemotherapy (NAC) prior to CCRT. Compared to adjuvant chemotherapy, employing NAC before CRT may result in improved tolerance and adherence to chemotherapy. This is especially essential in regions with high cervical cancer rates and limited access to radiotherapy facilities, where treatment delays can worsen prognosis [7, 8]. Numerous low-resource countries lack the healthcare infrastructure and facilities required to deliver recommended therapies, necessitating the adaptation of treatment guidelines [9]. Theoretically, NAC might reduce tumor hypoxia and size, potentially improving surgical outcomes and radiotherapy sensitivity [10]. Validating the effectiveness of NAC could help reduce delays and enhance outcomes in communities with limited resources. This study aims to assess the efficacy and safety of neoadjuvant chemotherapy followed by CCRT in comparison to CCRT alone through a systematic review and meta-analysis.

*[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Universitas Padjadjaran, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. [2]Department of Obstetrics and Gynecology, Universitas Padjadjaran, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia. [3]School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Penjaringan, North Jakarta, Daerah Khusus Ibukota Jakarta, Indonesia. *For Correspondence: richardsibarani32@gmail.com*

Materials and Methods

Search Strategy and Selection Criteria

This systematic review and meta-analysis were conducted according to the Cochrane Collaboration guidelines and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The study protocol was registered with PROSPERO (registration number: CRD42024540599). We systematically searched multiple electronic databases, including PubMed, ScienceDirect, Cochrane Library, EBSCOHost, ProQuest, and additional grey literature sources (Google Scholar, OpenGrey, WorldCat), from inception up to April 26, 2024. The search strategy incorporated Medical Subject Headings (MeSH) and relevant keywords: "locally advanced cervical cancer," "neoadjuvant chemotherapy," "concurrent chemoradiotherapy," "efficacy," and "safety." We also manually examined the reference lists of identified articles and existing systematic reviews to ensure comprehensive coverage of eligible studies.

Eligible studies were required to meet the following criteria: (1) randomized controlled trials (RCTs) or controlled observational studies comparing NACT+CCRT versus CCRT alone, (2) inclusion of patients diagnosed with locally advanced cervical cancer according to FIGO staging (2008 or 2018), primarily encompassing stages IB2–IVA, with selected cases such as IB1 included if lymph node involvement was explicitly documented; (3) studies clearly reporting at least one of the predefined outcomes of interest: complete response (CR), progression-free survival (PFS), overall survival (OS), or detailed adverse events. The primary outcomes were CR, PFS, and OS, as these reflect the therapeutic efficacy of the intervention. Secondary outcomes included detailed adverse events, representing the safety profile of the treatments. Studies were excluded if they (1) involved previously treated patient cohorts without clear baseline data; (2) were non-comparative, observational case-series, or case reports; or (3) lacked relevant or complete outcome data. No language restrictions were applied during the literature search and selection process.

Data Extraction and Quality Assessment

Four authors (CNRS, NA, GM, SS) authors performed data extraction using predefined forms. Extracted data included study characteristics, patient demographics, tumor stage, chemotherapy regimens, radiotherapy protocols, and treatment outcomes (CR, PFS, OS, adverse events). Disagreements were resolved through discussion and consensus involving a third reviewer (DS). The quality and risk of bias of included studies were assessed using the Cochrane Risk of Bias tool (ROB-2) for RCTs and the Risk of Bias in Non-randomized Studies–of Interventions (ROBINS-I) for observational studies [11, 12]. Each included study was assessed for risk of bias across several domains, including selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each domain was graded as low, high, or unclear risk. Publication bias was visually assessed using funnel plots of standard error against log odds or hazard ratios.

Statistical Analysis

The treatment effects for binary outcomes were presented using pooled odds ratios (ORs) or hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Specifically, HRs were used for analyzing time-to-event data, such as PFS and OS, to preserve the temporal aspect of survival data. A fixed-effects model was employed for analysis if heterogeneity was low ($I^2 < 25\%$). If heterogeneity was moderate or high ($I^2 \geq 25\%$), a DerSimonian and Laird random-effects model was applied. Heterogeneity was quantified using the Cochran Q test and I^2 statistic, with a significance threshold set at $p < 0.10$ and $I^2 > 25\%$. Subgroup analyses were planned to evaluate potential sources of heterogeneity, including tumor staging, chemotherapy dosing intensity, and variations in treatment protocols. Statistical analyses were conducted using Review Manager software version 5.4 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) [13].

Results

The initial electronic database search identified 2051 studies, which were screened based on titles and abstracts to determine their eligibility for inclusion. Following detailed assessment, four RCTs and three cohort studies met the inclusion criteria for this systematic review and meta-analysis [5, 14–19]. Reasons for exclusion primarily included interventions not meeting predefined criteria or different study designs. The detailed literature screening and selection process are illustrated in the PRISMA flow diagram (Figure 1). These seven included studies enrolled a total of 1638 participants, with 825 patients receiving NACT+CCRT and 813 patients receiving CCRT alone. The studies were conducted across multiple international settings, including Brazil, China, and India. Participants predominantly presented with squamous cell carcinoma (SCC), with reported age ranges between 20 and 70 years. Three of the included studies had a low risk of bias. The remaining studies showed some bias concerns, mostly in selecting the reported result, as the studies did not report any trial protocols as a comparison of the present study and the planned procedure. Three studies had moderate-to-serious concerns about bias as the potential confounders were not appropriately controlled in the analysis. The risk of bias assessment is summarized in Figure 2.

Efficacy

Progression-free survival

Four studies reported PFS data [5, 14, 16, 20]. The pooled analysis showed no significant difference between treatment groups (HR 0.94; 95% CI 0.53–1.69; $p = 0.84$; $I^2 = 81\%$; Figure 2A), indicating substantial heterogeneity among studies. A random-effects model was applied due to this variability.

Overall survival

Six studies reported OS data [5,14,16,18,19]. The pooled hazard ratio showed no significant difference between NACT+CCRT and CCRT groups (HR 1.07; 95% CI 0.56–2.03; $p = 0.84$; $I^2 = 73\%$; Figure 2B).

Table 1. Characteristic of Study

No	Author	Country	Design	Number of Sample	Protocols	LACC Stage	Histopathology				Age (Median, years)
							SCC (%)	AC (%)	ASC (%)	UC (%)	
1	Da Costa et al, [5]	Brazil	RCT	NACT + CCRT (n=55)	Cisplatin 50 mg/m2 on day 1 and gemcitabine at a dose of 1,000 mg/m2 on day 1 and day 8, repeated every 3 weeks for three cycles. NACT followed by standard CRT started 3 to 4 weeks after the last cycle of NACT.	IIB - IVA	48 (87.2)	7 (12.7)	-	-	48 (22-69)
				CCRT (n=52)	Standard CCRT : Cisplatin at a dose of 40 mg/m2 for 6 weeks concurrent with pelvic radiotherapy. The external beam radiation therapy was delivered at a dose of 45 to 50.4 Gy in 25 to 28 fractions. Intracavitary brachytherapy was delivered in four weekly fractions of 7 or 7.5 Gy, with a total dose of 28 or 30 Gy.		46 (88.4)	5 (9.6)	-	1 (1.9)	45 (20-67)
1	Da Costa et al, [5]	Brazil	RCT	NACT + CCRT (n=55)	Cisplatin 50 mg/m2 on day 1 and gemcitabine at a dose of 1,000 mg/m2 on day 1 and day 8, repeated every 3 weeks for three cycles. NACT followed by standard CRT started 3 to 4 weeks after the last cycle of NACT.	IIB - IVA	48 (87.2)	7 (12.7)	-	-	48 (22-69)
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2	Li et al, [14]	China	RCT	NACT + CCRT (n=73)	Paclitaxel was intravenously infused at 135–175 mg/m2 for 3 hours, and cisplatin was intravenously infused at 60–80 mg/m2 , with a course of 21 days per cycle for 2 consecutive cycles. Two weeks after NACT, external beam radiation therapy (EBRT) and intensity modulated radiotherapy was administered in CCRT.	IB2 to IVA, and the cervical tumor diameter is greater than 4 cm	65 (89)	6 (8.2)	2 (2.8)	-	51 (35 -69)
				CCRT (n=73)	Received concurrent chemoradiotherapy with the same regimen as the NACT + CCRT group.		64 (87.7)	6 (8.2)	3 (4.1)	-	53 (30-63)
3	Tripathi et al, [15]	India	RCT	NACT + CCRT (n=40)	Two cycles of neoadjuvant chemotherapy with each cycle three weeks apart, paclitaxel in a dose of 175 mg/m2 and cisplatin 75 mg/m2 followed by definitive chemoradiotherapy.	IIA-IIIB	-	-	-	-	46.85 ± 8.44
				CCRT (n=40)	Defnitive CT/RT 50 Gy/25# 2 Gy per fraction, 5 days a week with concurrent cisplatin. Followed by ICRT 3, fraction of weekly ICRT was given at the dose of 700 cGy × 3 # at point A by using HDR brachytherapy		-	-	-	-	47.13 ± 10.28
4	Hong-bo et al, [17]	China	Retrospective study	NACT + CCRT (n=62)	Cisplatin 20 mg IV (d1-5), 5-Fu 750 mg IV (for 5 consecutive days) for 2 cycles every 28 days followed by CCRT. After radiotherapy, 4 cycles of Cisplatin and 5-Fu	II-IIB	-	-	-	-	"45.5 (27-60)
				CCRT (n=64)	CCRT : Cisplatin 20 mg IV (d1-5), 5-Fu 750 mg IV (for 5 consecutive days)		-	-	-	-	
5	Hui-hui et al, [16]	China	Retrospective study	NACT+	Paclitaxel 135-175 mg/m2 IV (1st day)	IIA-IIIB	-	-	-	-	"52 (36-70)
				CCRT (n=27)	Carboplatin 300-350 mg/m2 IV (2nd day)		-	-	-	-	
6	Narayan et al, [18]	India	Retrospective study	NACT + CCRT (n=318)	Cisplatin 40 mg/m2 (d1, 2), paclitaxel 175 mg/m2 (d1), and 5-fluorouracil in 750 mg/m2 (d1, 2, 3) in TPF arm while in PF arm injection cisplatin 40 mg/m2 (d1, 2) and 5-fluorouracil in 750 mg/m2 (d1, 2, 3). Two cycles of NACT were given"	Bulky stage I (IB2) and locally advanced (stages II–IVA)	612	-	-	-	41-50
				CCRT (n=294)	CCRT treatment was same in both arm NACT and CCRT-alone arm. External beam radiation therapy was administered using cobalt 60 teletherapy machine. A dose of 50 Gy in 25 fractions in 5 weeks was given at a dose of 200 centi gray per fraction daily, for 5 days in a week.			-	-	-	
7	McCormack et al, [20]	United Kingdom	RCT phase III	NACT + CCRT (n=250)	6 weeks carboplatin AUC2 and paclitaxel 80mg/m2) followed by the same CRT in week 7. Mandated minimum total EQD2 dose 78Gy to Point A with 3D brachytherapy recommended.	FIGO (2008) stage IB1 node involvement,IB2,II,IIIB, IVA	-	-	-	-	46 (24-78)
				CCRT (n=250)	CRT alone (5 cycles weekly cisplatin)		-	-	-	-	

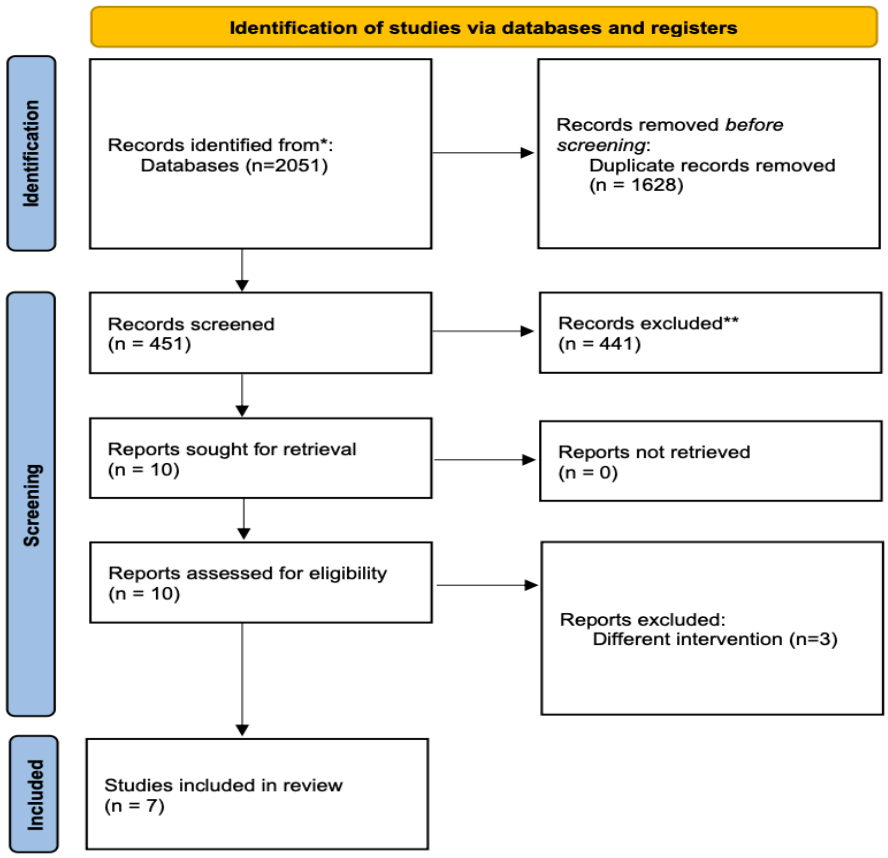

Figure 1. PRISMA Flow Diagram

Complete Response

NACT+CCRT yielded a higher CR rate (77.0%) compared to CCRT alone (70.9%), but this difference did not reach statistical significance (OR 1.23; 95% CI 0.40–3.83; p = 0.71; I^2 = 81%; Fig. 2C), again indicating considerable heterogeneity (Figure 3) [5, 14–16].

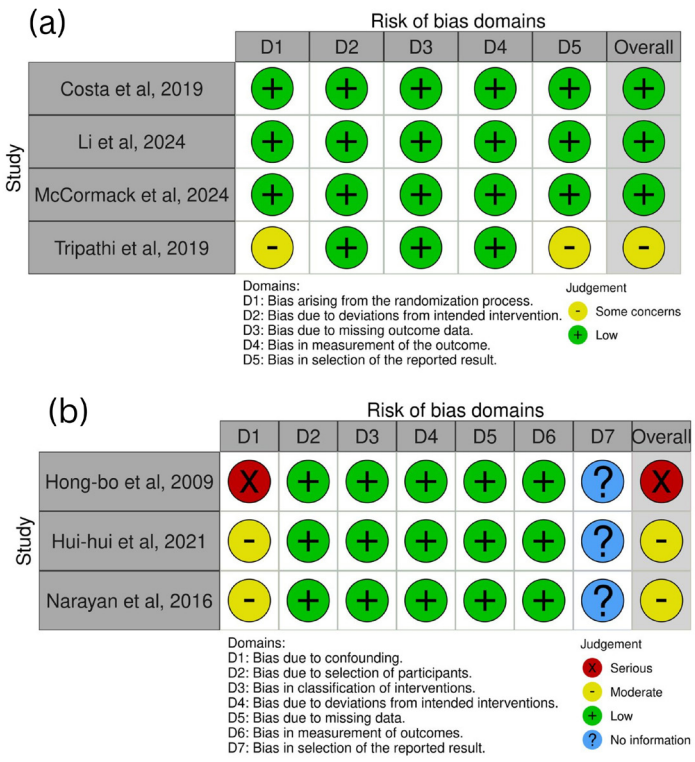

Figure 2. Risk of Bias Assessment using Cochrane ROB-2 (a) and ROBINS-I (b) Tool

Table 2. Efficacy

No	Author	Group	PFS	HR	OS	HR	CR (%)	PR (%)	SD (%)	DP (%)	Death (%)
1	Da Costa et al, [5]	NACT + CCRT (n=55)	3 years: 40.9% (95% CI, 27.2%-54.1%)	1.84 (95% CI, 1.04- 3.26) p=0.033	3 years: 60.7% (45.6%-72.8%)	2.79 (1.29-6.01) p=0.006	1 year : 31/55 (56.3%)	-	-	-	50/107 (46.7)
		CCRT (n=52)	3 years: 60.4% (95% CI, 44.1% to 73.3%)		3 years: 86.8% (72.7%-93.9%)		1 year : 42/52(80.3%)	-	-	-	
2	Li et al, [14]	NACT + CCRT (n=73)	1 year PFS 90% 2 year PFS 81%	1.38 (95% CI, 0.59-3.20) p=0.340	1 year 96%; 2 year OS 89%	1.459 (95% CI, 1.084 to 9.513); p=0.017	12 weeks : 58/73 (79.5) 1 year : 64/73 (87.7%)	12 weeks : 15/73 (20.5) 1 year : 9/73 (12.3%)			
		CCRT (n=68)	1 year PFS 85% 2 year PFS 78%		1 year 89%; 2 year 79%		12 weeks : 38/73 (55.9) 1 year : 46/68 (67.6%)	12 weeks : 30/73 (44.1) 1 year : 12/68 (30.9%)			
3	Tripathi et al, [15]	NACT + CCRT (n=40)					34/40 (85.0)	5/40 (12.5)	1/40 (2.5)		
		CCRT (n=40)					33/40 (82.5)	5/40 (12.5)	2/40 (5)		
4	Hong-bo et al, [17]	NACT + CCRT (n=62)			3 year OS : 42/62 (67.7) 5 year OS : 29/62 (46.8)	1.54 (95%CI; 0.913-2.627) p=0.109					
		CCRT (n=64)			3 year OS : 52/64 (82.8) 5 year OS : 42/64 (65.6)						
5	Hui-hui et al, [16]	NACT + CCRT (n=27)	3 year PFS 19/27 (70.4)	0.54 (95%CI; 0.260 - 1.117) p=0.127	3 year OS: 21/27 (77.8)	0.63 (95% CI; 0.260-1.552) p=0.347	21/27 (77.8)	3/27 (11.1)	2/27 (7.4)	1/27 (3.7)	
		CCRT (n=40)	3 year PFS 18/40 (45)		3 year OS : 26/40 (65)		23/40 (57.0)	4/40 (10.0)	8/40 (20.0)	5/40 (12.5)	
6	Narayan et al, [18]	NACT + CCRT (n=318)			52 months	1.67 (95% CI 1.26–2.22)					
		CCRT (n=294)			48 months						
7	McCormack et al, [20]	NACT + CCRT (n=250)	5 year PFS: 73%	0.65 (95% CI; 0.46-0.91)	5 year OS: 80%	0.60 (95% CI; 0.40-0.91)					
		CCRT (n=250)	5 year PFS: 64%		5 year OS: 72%						

NACT, Neoadjuvant + concurrent chemoradiotherapy; CCRT, Concurrent chemoradiotherapy; PFS, Progression-free survival; HR , Hazard ratio; OS, Overall-survival; CRR, Complete response; PR, Partial response; DOR,Duration of response.

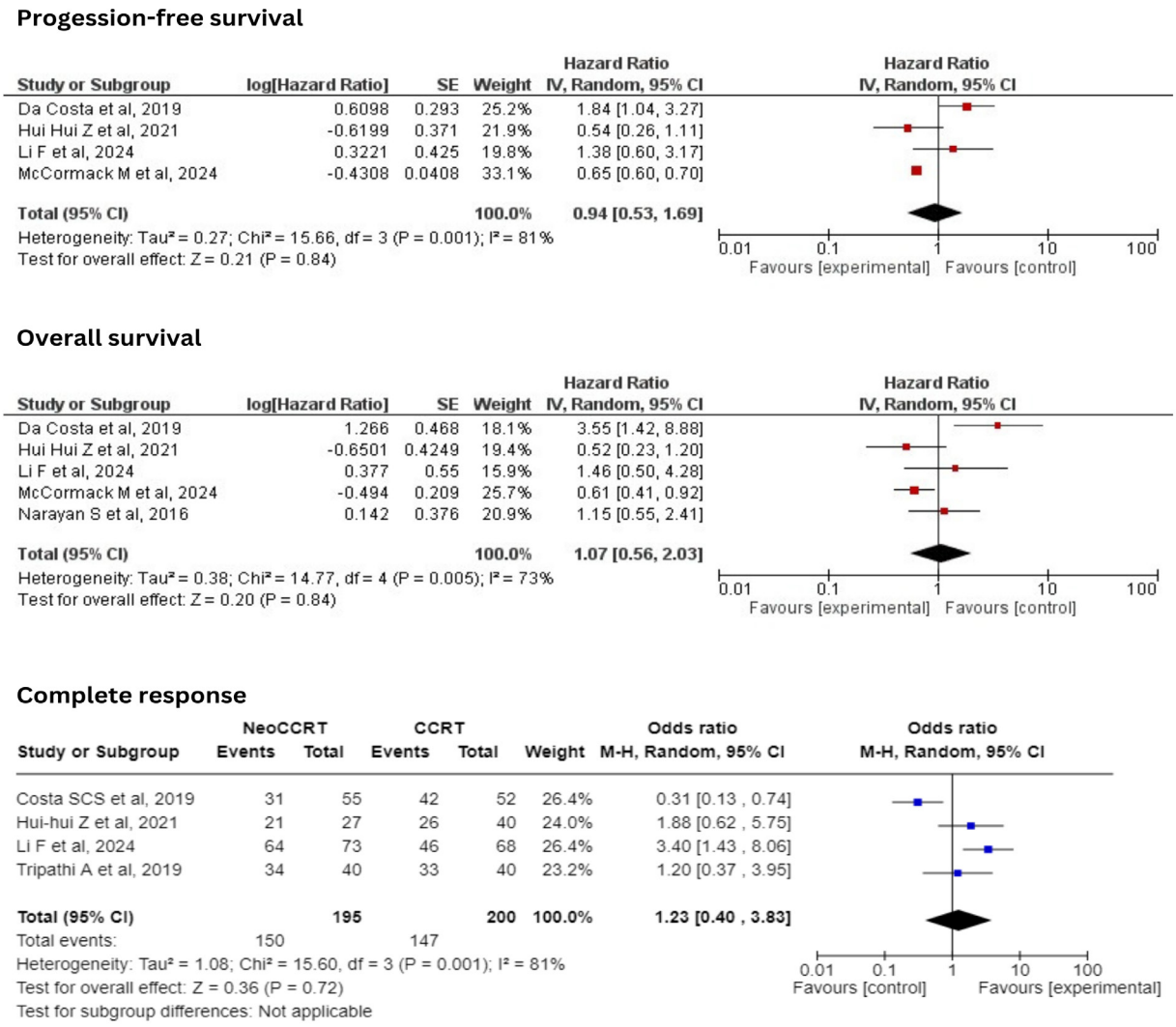

Figure 3. Forest Plot of PFS, OS, and CR.

Safety

Adverse event profiles were reported in four studies [5, 14, 15, 19]. No statistically significant differences were observed between the NACT+CCRT and CCRT groups in the incidence of anemia, leukopenia, neutropenia, thrombocytopenia, nausea, vomiting, abdominal pain, and creatinine elevation (all $p > 0.05$; Figure 4). Subgroup analyses did not reveal meaningful variation in toxicity profiles across treatment arms. However, a significantly higher risk of Grade 3-4 fatigue was observed in the NACT+CCRT group compared to CCRT alone (RR 1.83; 95% CI, 1.02–3.32; $p = 0.05$), indicating a potential increase in treatment-related fatigue severity (Supplementary Table 1).

Confidence in Cumulative Evidence

The studies included in this meta-analysis were mostly RCTs which indicated initial high-quality evidence in the GRADE system. Most of the included studies had some concerns of bias and one study had high risk of bias. However, sensitivity analysis by excluding studies with bias concerns did not reveal meaningful differences, hence we concluded that the results were unlikely to be affected by bias from each study. No serious indirectness and imprecision were found in this study that could affect the whole results. We observed moderate-to-high inconsistencies in some of the analyses, probably due to the heterogeneous nature of the studies which originated from the true differences in the population and various chemotherapy regimens. Publication bias could not be assessed as the included studies were less than 10. Overall, the included studies were judged to have low-to-moderate quality of evidence. GRADE evidence profile was generated in Supplementary Table 2.

Discussion

Patients with locally advanced cervical carcinoma, ranging from stage IB3 to IVA, exhibit an elevated recurrence rate and diminished survival compared to individuals diagnosed with early-stage malignancies, spanning from stage IA to IB2 [21]. Concurrent administration of cisplatin-based chemotherapy alongside radiotherapy followed by brachytherapy constitutes the established therapeutic regimen for locally advanced cervical cancer [22]. However, in developing nations, prolonged waiting times for access to radiotherapy machines frequently necessitate the administration of

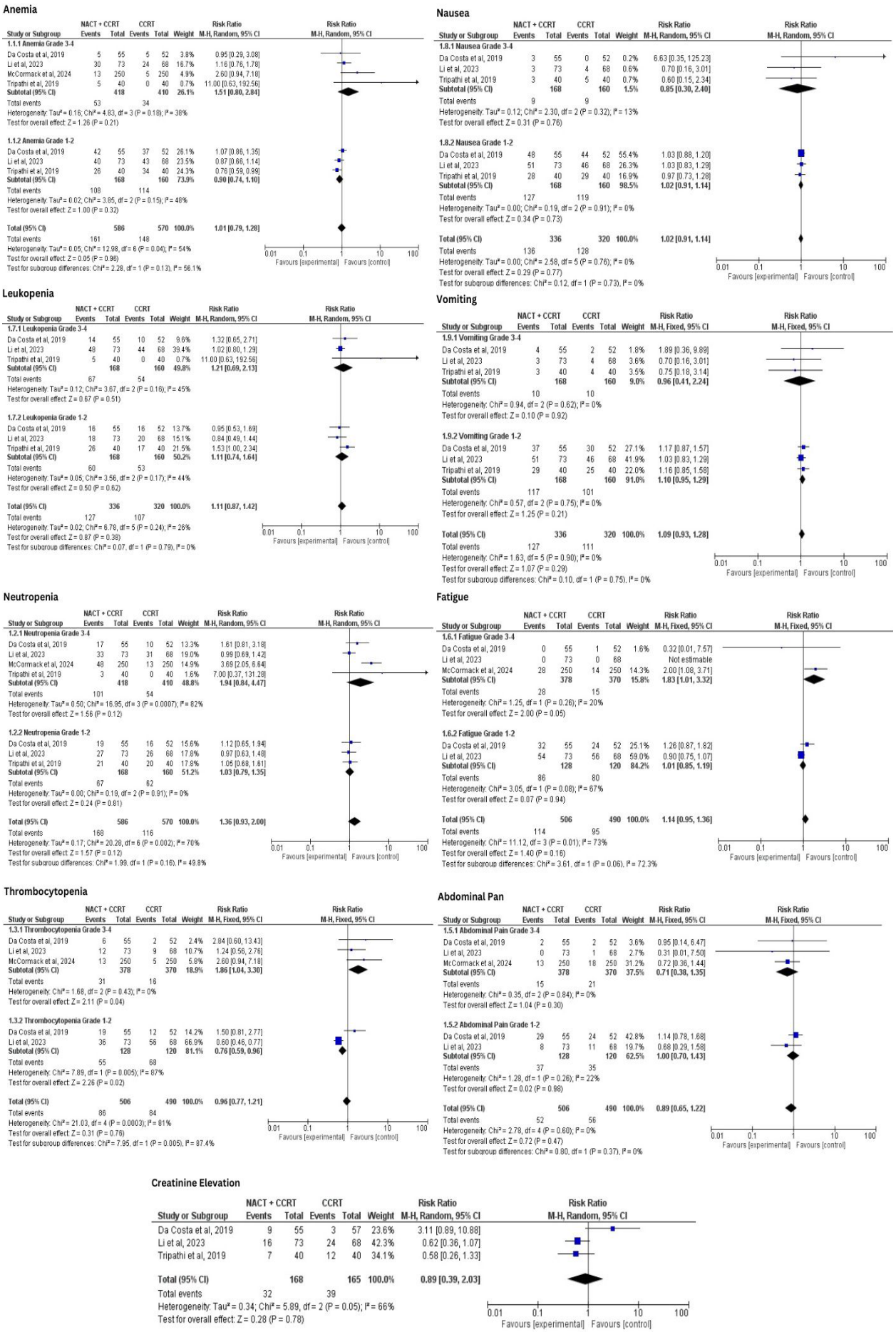

Figure 4. Forest Plot of Safety Analysis

NACT as the sole viable recourse. In many low- and middle-income countries, radiotherapy infrastructure remains critically underdeveloped. A systematic review by Grover et al. demonstrated that several LMICs have insufficient numbers of RT centers and equipment. High patient volumes and lack of trained personnel often lead to long waiting lines and continued disease progression long after diagnosis [18, 23]. Neoadjuvant chemotherapy serves as a promising adjunct to CCRT, laying a solid groundwork by augmenting treatment sensitivity, bolstering efficacy, diminishing tumor burden, and mitigating the risk of micrometastasis [14]. In this meta-analysis, we observed a trend toward improved CR rates in the NACT + CCRT group compared to CCRT alone, although this difference was not statistically significant. PFS and OS were also comparable between groups. While definitive conclusions cannot be drawn, these findings suggest that NACT + CCRT may offer potential therapeutic benefits for selected patients.

While our study demonstrates comparable OS and PFS between the groups underscore the effectiveness of both therapeutic regimens. Emerging research from other meta-analyses hinted at potential benefits from more intense dosing regimens, recent meta-analyses, including Nguyen et al., provide stronger evidence supporting the intensification of NACT [24, 25]. This raises important considerations for treatment protocols, particularly in settings where maximizing the efficacy of NACT could significantly impact patient outcomes, aligning treatment intensity with the severity and stage of the disease. Specifically, three studies within our meta-analysis reported superior OS and PFS in the NACT arm, underscoring the potential of adopting NACT as a standard therapeutic approach [14, 16, 19]. A critical factor influencing these outcomes is the overall treatment time (OTT). Extended OTT can significantly reduce local control by allowing accelerated repopulation of clonogenic cells. This potential risk of delayed definitive radiotherapy following NACT must be carefully considered, particularly in resource-constrained settings where timely initiation of CCRT remains challenging [8, 26].

This observation is particularly crucial in developing countries, where prolonged waiting times for radiotherapy necessitate alternative initial treatments [8]. Our findings suggest that NACT not only serves as a viable stopgap but might also enhance the overall treatment efficacy by reducing tumor volume and potentially lowering the risk of micrometastasis, which are significant concerns in advanced cancer stages. Heterogeneity observed warrants deeper exploration into the factors influencing treatment outcomes, encompassing patient attributes, tumor staging, and treatment protocols [5]. In addition, patients with advanced cervical cancer stages typically face a poorer prognosis and may be more susceptible to disease progression and mortality, the predominance of advanced-stage patients in the study cohort could have contributed to the heterogeneity of PFS and OS rates observed [27].

Complete responses were higher in the NACT group than the CCRT group [15, 16, 28]. The heightened CR rate in the NACT+CCRT group, compared to CCRT, can be attributed to several factors. Administering NACT prior to radiotherapy and concurrent chemotherapy may reduce tumor volume, thereby possibly improving radiosensitivity and response to subsequent treatments [29]. The combination of NACT with concurrent chemoradiotherapy may lead to a synergistic effect, enhancing tumor response and increasing the likelihood of a complete response. The NACT+CCRT group had a higher treatment completion rate, potentially contributing to better outcomes. Additionally, patient selection, including those with larger tumor masses, may have benefited from the NACT+CCRT approach [14]. Additionally, the combination of systemic chemotherapy followed by chemoradiotherapy could exert a complementary effect on tumor regression. Higher treatment completion rates reported in some NACT+CCRT cohorts may also contribute to improved outcomes.

Most adverse incidents recorded exhibited mild to moderate severity, underscoring the tolerability of both NACT+CCRT and CCRT alone in the treatment regimen for LACC. This observation aligns with findings from prior investigations [30, 31]. The comparable safety profiles demonstrated by NACT+CCRT and the CCRT group concerning adverse events instill confidence in the acceptability of these therapeutic modalities. However, it is noteworthy that Grade 3–4 fatigue was more frequently reported in the NACT + CCRT group. Fatigue has a well-established negative impact on the quality of life of cancer patients undergoing chemotherapy and may impair treatment adherence and daily functioning [32]. This highlights the importance of incorporating supportive care measures and routine fatigue assessment into treatment planning, particularly when considering intensified regimens. The absence of significant discrepancies in the incidence of adverse effects between the NACT and CCRT, as well as when contrasted with control populations in subgroup analyses, suggests that both treatment regimens can be considered as relatively safe options for patients [5, 14, 15].

However, it is crucial to recognize the limitation of this study, which encompasses potential biases intrinsic to meta-analyses and discrepancies in study methodologies. The overall sample size remains limited, reducing the power to detect small but potentially meaningful differences. Considerable heterogeneity was observed in complete response rates, PFS, and OS, which may be attributable to differences in neoadjuvant chemotherapy regimens, radiotherapy techniques (e.g., 2D vs. 3D vs. image-guided RT, which were not consistently reported), and variations in treatment protocols. Furthermore, the lack of uniform reporting on chemotherapy interruptions between cycles and histopathological subtypes limits our ability to fully assess their impact on treatment response. Finally, variability in disease stage at inclusion particularly the proportion of patients with more advanced disease—and the wide age distribution may have further contributed to outcome heterogeneity.

Future studies should aim to increase sample sizes and use rigorous methodological designs to enhance the reliability of treatment effect estimates. Specifically,

phase III randomized controlled trials comparing dose-intensified NACT regimens versus standard CCRT, particularly in stage IIIB–IVA populations, are warranted to determine efficacy across advanced disease stages. Prospective cohort studies stratified by overall treatment time (OTT), FIGO stage, histological subtype, and treatment protocol intensity will help identify prognostic subgroups and refine patient selection. In addition, future trials should incorporate predefined subgroup analyses based on demographic variables such as age, comorbidities, and geographic region to elucidate factors influencing response heterogeneity. Finally, long-term follow-up studies capturing progression-free and overall survival at multiple time points (e.g., 1-, 3-, and 5-year intervals) are crucial for understanding the durability of therapeutic benefits and informing evidence-based clinical decision-making.

In summary, this meta-analysis shows that NACT+CCRT offers comparable survival outcomes and a similar safety profile to standard CCRT alone, with a non-significant trend towards improved complete response. Although the current analysis did not find statistically significant differences, these findings remain valuable as they help clarify uncertainties in the treatment of LACC. Recognizing treatments with comparable efficacy and safety is essential, particularly in resource-constrained settings, where alternative treatment strategies may still offer meaningful clinical benefit.

Author Contribution Statement

Candra Novi Ricardo Sibarani, Siti Salima, and Dodi Suardi were involved in the conception and design of the study. Candra Novi Ricardo Sibarani, Siti Salima, Dodi Suardi, Nicholas Adrianto, and Ghea Mangkuliguna handled material preparation, data collection, and analysis. Candra Novi Ricardo Sibarani drafted the initial version of the manuscript, with all authors providing feedback on earlier drafts. All authors reviewed and approved the final version of the manuscript.

Acknowledgements

Scientific/Academic Approval

This study was not part of a student thesis or affiliated with any formal academic approval process.

Data Availability Statement

All data analyzed in this meta-analysis were extracted from previously published studies. The datasets supporting the findings are available in the article and its supplementary materials. Additional details can be provided by the corresponding author upon reasonable request.

Study Registration

The study protocol was registered with PROSPERO (registration number: CRD42024540599).

Conflict of Interest

The authors have no relevant financial or non-financial conflicts of interest to declare.

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