Efficacy of induction chemotherapy combined with standard chemoradiotherapy vs. standard chemoradiotherapy monotherapy in locally advanced cervical cancer: A systematic review and meta-analysis

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Abstract. Concurrent chemoradiotherapy (CCRT) is the standard treatment for locally advanced cervical cancer (LACC); however, the role of additional induction chemotherapy (IC) remains debated. The present study performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to comparatively assess therapeutic outcomes and safety profiles between induction chemotherapy followed by concurrent chemoradiotherapy (IC + CCRT) versus CCRT alone in patients with locally advanced cervical cancer (LACC) (International Federation of Gynecology and Obstetrics 2018 stage IB2-IVA). The study screened relevant literature published up to March 2025 and ultimately included 6 RCTs, where 1,006 patients were stratified (504 in the IC + CCRT regimen vs. 502 in the CCRT alone regimen). Compared with CCRT alone, IC + CCRT significantly improved the complete response (CR) rate [odds ratio (OR), 1.95; 95% confidence interval (CI), 1.20-3.17; P=0.007] and 1-year progression-free survival rate (OR, 1.82; 95% CI, 1.14-2.90; P=0.01). A consistent trend favoring IC+CCRT was observed for overall survival, although this was not statistically significant. Hematological toxicities, notably thrombocytopenia (OR, 1.76; 95% CI, 1.06-2.90; P=0.03) and neutropenia (OR, 2.69; 95% CI, 1.09-6.61; P=0.03), were more frequent with IC+CCRT, while non-hematological toxicity profiles were comparable. In conclusion, the addition of modern, short-course induction chemotherapy to CCRT enhances the CR rate and 1-year progression-free survival rate in LACC, establishing a promising intensified treatment strategy.

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Abbreviations: CCRT, concurrent chemoradiotherapy; CR, complete response; IC, induction chemotherapy; LACC, locally advanced cervical cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RCT, randomized controlled trial

Key words: induction chemotherapy, cervical cancer, meta-analysis, PFS, adverse events

Introduction

Epidemiological statistics confirm cervical carcinoma as a leading global health burden, ranking fourth in incidence among all malignancies worldwide (with an estimated 661,021 new cases and 348,189 deaths globally in 2022) preceded only by breast, colorectal and lung cancer, and with significant female morbidity and mortality across all regions, including China (with ~150,700 new cases and 55,700 deaths in 2022) (1,2). Although cervical cancer screening and human papillomavirus vaccination programs have been successfully implemented and a significant decline in incidence rates has been observed in high-income countries (3,4), cervical cancer remains a persistent global health challenge, disproportionately impacting low- and middle-income countries, where disease burden reaches critical levels (5,6).

Findings from five large-scale randomized controlled trials (RCTs) conducted between 1999 and 2000 demonstrate that concurrent chemoradiotherapy (CCRT) significantly enhances local disease control in locally advanced cervical cancer (LACC), with corresponding improvements in both progression-free survival (PFS) and overall survival (OS)

rates compared with conventional radiotherapy alone (7-11). For instance, a systematic review and meta-analysis revealed that CCRT led to a 10.2% increase in complete response (CR) rates, an 8.4% increase in local regional control and a 7.5% enhancement in OS rates (12). Notwithstanding these advances, the 5-year OS rate for LACC treated with CCRT remains suboptimal, ranging from 65 to 70%, with distant metastasis representing a primary mode of treatment failure (10,13-15). This persistent efficacy ceiling underscores the imperative to intensify and optimize systemic therapy within the standard CCRT framework.

In recent years, in order to improve the treatment outcome of LACC, research has shifted from merely adjusting empirical treatment plans to a deeper understanding of tumor biology and heterogeneity. Molecular studies are elucidating factors underlying differential treatment responses and prognosis. For example, the identification of specific gene mutations (such as DCHS2, DNAH10, RYR1 and WDFY4) and the assessment of tumor mutational burden (TMB) have enabled the construction of a recurrence-related score (RRS) that stratifies patients by distinct immune microenvironment features, such as increased infiltration of activated $CD8^+$ T cells and NK cells in high-risk groups versus exhausted $CD8^+PD\text{-}1^+$ T cells in low-risk groups, and correlates with clinical outcomes, thus underscoring the potential of biomarker-driven strategies (16).Concurrently, the exploration of novel agents, such as bioactive natural compounds capable of inducing dual cell death pathways, points to alternative mechanisms to overcome therapeutic resistance (17). These insights into the molecular determinants of tumor invasiveness and treatment failure further strengthen the theoretical basis for enhancing and optimizing systemic treatment within the framework of standard concurrent radiotherapy and chemotherapy.

In this context, the intensification of systemic treatment has been investigated through both adjuvant and neoadjuvant approaches. The adjuvant strategy, exemplified by the OUTBACK trial, demonstrated that adding chemotherapy after CCRT significantly increased treatment-related toxicity without conferring OS benefits (18,19). By contrast, the neoadjuvant approach, termed induction chemotherapy (IC) prior to CCRT, aims to reduce primary tumor burden and eradicate microscopic metastases earlier. However, the historical role of IC has been fraught with contradiction and controversy (20). Early meta-analyses, most notably an individual patient data meta-analysis of 21 trials, concluded that IC (often followed by radiotherapy alone) provided no survival benefit over radiotherapy alone and might even increase the risk of local recurrence (21). This was largely attributed to suboptimal, protracted IC regimens that delayed definitive CCRT, potentially allowing for tumor repopulation (22).

This long-standing negative perception has been fundamentally challenged and reversed by recent high-quality evidence, which highlights that the schedule and dose-intensity of IC are pivotal determinants of its efficacy (23). The landmark phase III INTERLACE trial (NCT01566240) demonstrated that a short, dose-intense course of weekly carboplatin and paclitaxel for 6 weeks, followed immediately by standard CCRT, significantly improved 5-year PFS (72 vs. 64%) and OS (80 vs. 72%) rates compared with CCRT alone, representing a 40% relative reduction in the hazard (risk) of dying (24). Critically, despite an increased incidence of hematological adverse events, this regimen did not compromise radiotherapy compliance and, importantly, did not lead to a clinically significant detriment in patient quality of life compared with CCRT alone (25). Other modern, dose-dense IC regimens, such as weekly cisplatin and paclitaxel, have also shown promising efficacy and feasibility (26,27). This evolving evidence signifies a paradigm shift, transforming IC from a historically discouraged strategy into a promising new standard of care, yet it simultaneously introduces new questions regarding the optimal integration of different IC regimens and the identification of patients who derive the greatest benefit. Therefore, the central clinical question has evolved. The contradiction is no longer about whether IC can be effective, but rather how to analyze the totality of modern evidence to clearly define the magnitude of benefit and safety profile of contemporary, dose-intense IC+CCRT versus CCRT alone. Older meta-analyses are outdated as they cannot incorporate these practice-changing trials (28). To provide contemporary and evidence-based clarity, the present systematic review and meta-analysis was performed to compare the efficacy and safety of modern IC+CCRT versus CCRT alone in patients with LACC.

Materials and methods

Protocol and registration. This systematic review with meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol was registered in PROSPERO (CRD42024613530).

Eligibility criteria [population, intervention, comparison, outcomes and study (PICOS)]. The PICOS criteria were as follows. i) Population: Patients with histologically or cytologically confirmed LACC according to the International Federation of Gynecology and Obstetrics 2018 staging system (stages IB2-IVA) (29). ii) Intervention: Patients receiving sequential IC followed by standard CCRT, i.e., the IC + CCRT regimen. iii) Comparison: Patients receiving standard CCRT alone. iv) Outcomes: Primary outcomes of OS and PFS. OS was defined as the time from randomization to death from any cause. PFS was defined as the time from randomization to documented tumor progression (radiological or clinical) or death. Treatment response was evaluated per the Response Evaluation Criteria in Solid Tumors version 1.1 (30), where CR indicated disappearance of all target lesions, while partial response (PR) required ≥30% reduction in the sum of target lesion diameters. The objective response rate (ORR) comprised CRs and PRs. Secondary outcomes were the incidence of adverse reactions, which were classified into hematological toxicity (such as anemia and myelosuppression) and non-hematological toxicity (including gastrointestinal toxicity, such as diarrhea, nausea and vomiting). v) Study design: Published or unpublished RCTs with no restrictions on country or language were included.

Exclusion criteria. The exclusion criteria consisted of the following: i) Reviews, systematic evaluations, animal-based experiments or case reports; ii) non-RCTs, observational studies or retrospective studies; iii) duplicate publications, studies with methodologically flawed designs or inconsistent/incomplete

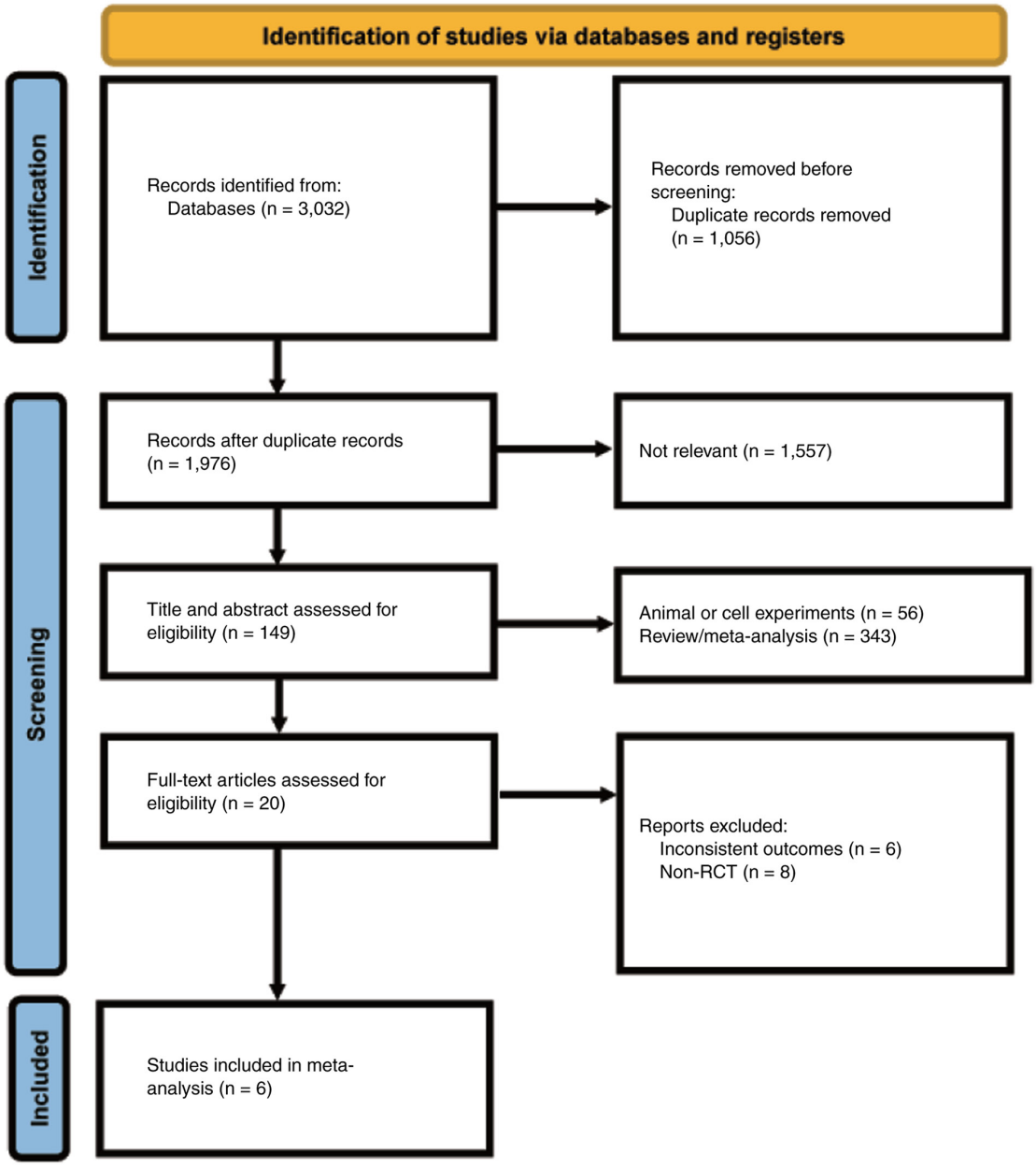

Figure 1. Flow diagram of study selection process for the meta-analysis. RCT, randomized controlled trial.

outcome reporting; iv) ongoing trials lacking published results; and v) studies not fulfilling the inclusion criteria.

Literature search and study screening. Two independent investigators systematically searched the PubMed (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (https://www.embase.com/), Cochrane Library (https://www.cochranelibrary.com/central), Web of Science (https://www.webofscience.com/wos/woscc), CNKI (https://www.cnki.net/), SinoMed (https://www.sinomed.ac.cn/), WanFang (https://www.wanfangdata.com.cn/) and VIP (http://qikan.cqvip.com/) databases up to March 2025. Concurrent searches were performed in the World Health Organization International Clinical Trials Registry Platform (https://trialsearch.who.int/) and the Chinese Clinical Trial Registry (http://www.chictr.org.cn/). The search strategy incorporated medical subject headings for ((‘Uterine Cervical Neoplasms’[Mesh]) AND (‘Chemoradiotherapy’[Mesh]) AND (‘Induction Chemotherapy’ [Mesh] OR ‘Neoadjuvant Therapy‘[Mesh])). Retrieved records were screened against predefined eligibility criteria by both researchers. Discrepancies in study selection were resolved through third-party adjudication.

Data extraction and quality appraisal. Two independent reviewers performed dual extraction of study characteristics from eligible trials, encompassing first author, publication year, sample size, patient age, treatment protocols (radiotherapy dosing and chemotherapy regimens) and clinical outcomes. The Cochrane (RoB 2.0) tool (https://www.riskofbias.info/welcome/rob-2-0-tool) was employed to assess risk of bias across the following key domains: Selection bias (randomization and allocation concealment), performance bias (blinding), attrition bias (incomplete data), reporting bias and other sources. Studies were categorized as low, high or unclear risk for each domain.

Table I. Baseline characteristics of included studies.

First author, year	Country	Study design	Number of patients		Age, years		FIGO	Pathology	(Refs.)
			IC + CCRT	CCRT	IC + CCRT	CCRT			
Tripathi and Rawat, 2019	India	RCT	40	40	Mean ± SD, 46.85± 8.448	47.13± 10.281	IIA-IIIB	SCC	(33)
Banerjee *et al*, 2022	India	RCT	21	30	NA	NA	IIB-IVA2	SCC	(34)
Li *et al*, 2023	China	RCT	73	68	Median, 51	Median, 53	IB2-IVA	SCC/AC/ ASC	(35)
McCormack *et al*, 2024	Multicenter	RCT	250	250	Median, 46	Median, 46	IB2-IVA	SCC/AC/ ASC	(24)
Singh *et al*, 2019	India	RCT	54	62	Median, 50	Median, 49	IIB-IIIB	SCC	(36)
da Costa *et al*, 2019	Brazil	RCT	55	52	Median, 48	Median, 45	IIB-IVA	SCC/AC/ ASC	(37)

FIGO, International Federation of Gynecology and Obstetrics; RCT, randomized controlled trial; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; SCC, squamous cell carcinoma; AC, adenocarcinoma; ASC, adenosquamous carcinoma.

Table II. Treatment regimens across included studies.

First author, year	RT regimens	Interventions		(Refs.)
		IC+CCRT	CCRT	
Tripathi and Rawat, 2019	EBRT [50 Gy/25 f (5 f/week)]+ ICRT (HDR 700 cGy x 3 f)	Paclitaxel + cisplatin + CCRT	Cisplatin + RT	(33)
Banerjee *et al*, 2022	EBRT [50 Gy/25 f (5 f/week)]+ ICRT (HDR 700 cGy x 3 f)	Paclitaxel + cisplatin + CCRT	Cisplatin + RT	(34)
Li *et al*, 2023	EBRT/IMRT [56.35-60.2 Gy for LN, 50.4 Gy for CTV/28 f (5 f/week)] + ICRT (600 cGy x 5 f)	Paclitaxel + cisplatin + CCRT	Cisplatin + RT	(35)
McCormack *et al*, 2024	EBRT [45.0-50.4 Gy/20-28 f (5 f/week)] + ICRT	Paclitaxel + carboplatin + CCRT	Cisplatin + RT	(24)
Singh *et al*, 2019	EBRT [46 Gy/23 f (5 f/week)]+ ICRT (HDR 700 cGy x 3 f)	5-Fu + carboplatin + CCRT	Cisplatin + 5-Fu + RT	(36)
da Costa *et al*, 2019	EBRT [45-50.4 Gy/25-28 f (5 f/week)] + ICRT (HDR 700-750 cGy x 4 f)	Gemcitabine + cisplatin + CCRT	Cisplatin + RT	(37)

f, fractions; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; 5-Fu, 5-fluorouracil; EBRT, external beam radiotherapy; ICRT, intracavitary radiotherapy; RT, radiotherapy; CTV, clinical target volume; HDR, high-dose-rate.

GRADE assessment. The certainty of evidence for each outcome was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework (31,32). Two reviewers independently assessed the following domains: Risk of bias, inconsistency, indirectness, imprecision and publication bias. Evidence certainty was categorized as high, moderate, low or very low. For each outcome, reasons for downgrading (such as imprecision due to limited sample sizes or wide confidence intervals and inconsistency due to high heterogeneity) were documented. Summary tables

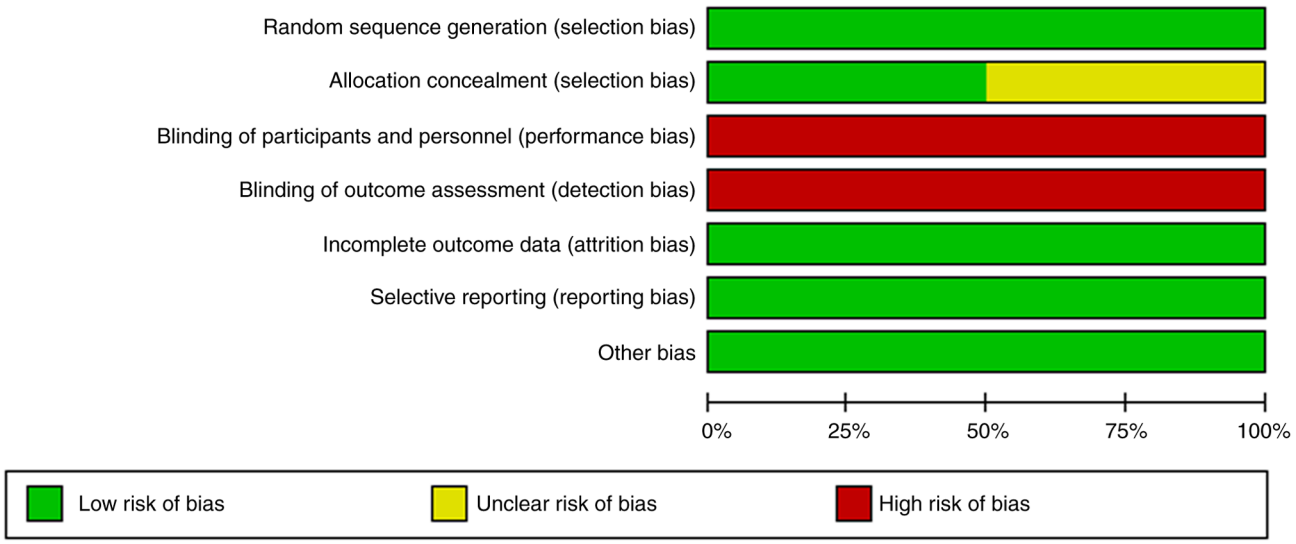

Figure 2. Risk of bias graph for the 6 randomized controlled trials.

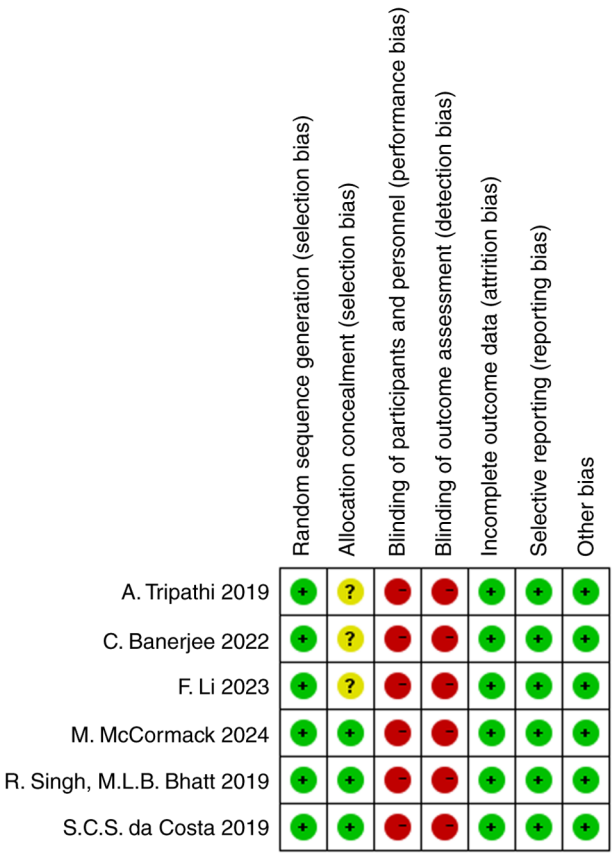

Figure 3. Risk of bias summary for the 6 randomized controlled trials.

were generated using GRADEpro GDT software (https://www.gradepro.org/), and the full evidence profile is presented in Table SI.

Statistical analysis. All meta-analyses were performed using Cochrane RevMan (version 5.4) (The Cochrane Collaboration; https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman) and R (version 4.5.2) (R Core Team; https://www.r-project.org/). The results were reported as pooled odds ratios (ORs) with 95% confidence intervals (95% CIs). Cochran's Q test and I^2 statistics were used to evaluate the heterogeneity of all the studies. Taking into account the diversity in both clinical and methodological aspects, regardless of the degree of heterogeneity, the random-effects model was adopted to provide more conservative and more general estimates. Sensitivity analyses were conducted to explore the influence of individual studies and to assess the robustness of the findings. Funnel plots were created using Egger's/Begg's regression tests for outcomes including ≥10 studies. For outcomes with fewer studies, the potential for publication bias was acknowledged as a limitation. Two-tailed $P<0.05$ was considered to indicate a statistically significant difference.

Results

Literature search and study inclusion. A total of 3,032 records were initially retrieved: PubMed (n=515), EMBASE (n=408), Web of Science (n=1,085), Cochrane Library (n=124), CNKI (n=330), SinoMed (n=287), WanFang (n=150) and VIP (n=133). After excluding 1,056 duplicate articles, the titles and abstracts of the remaining studies were reviewed. A total of 1,557 articles were excluded due to irrelevant content and 399 articles were not included as they were systematic reviews, animal studies or case reports. Full-text articles were excluded for the following reasons: Inconsistent outcomes (6 articles) and non-RCT (8 articles). Following eligibility assessment, 6 trials involving 504 experimental and 502 control participants were included (24,33-37). Fig. 1 illustrates the literature screening workflow, while Tables I and II summarize the key characteristics of the included studies.

Quality assessment. The methodological quality was evaluated using the Cochrane Risk of Bias Assessment Tool (RoB 2.0) (Figs. 2 and 3). Random sequence generation performed well. However, in terms of allocation concealment, some studies showed unclear risks. Due to the nature of the treatment regimens, blinding of participants ,researchers and

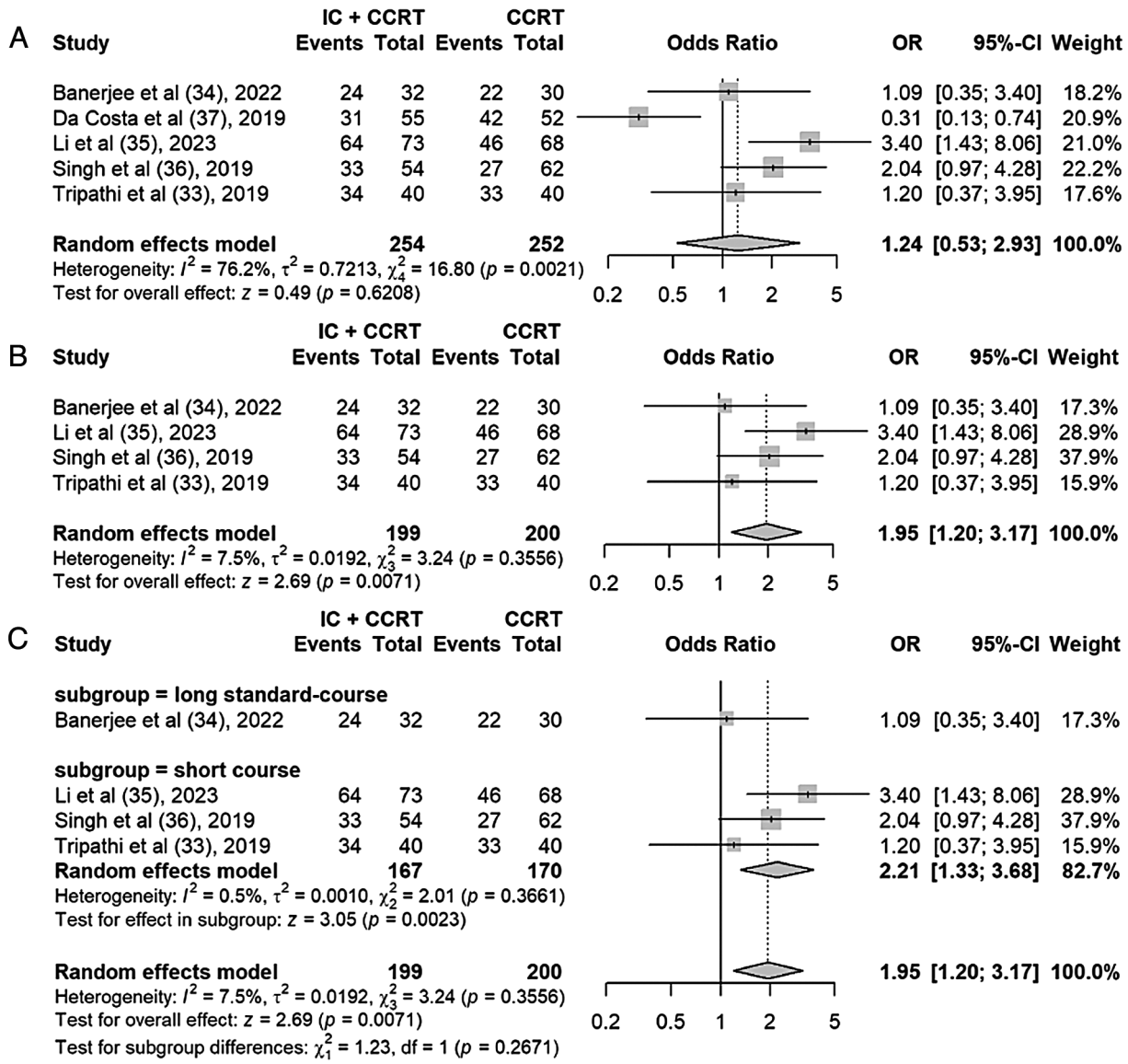

Figure 4. Forest plots for CR. Forest plots (A) including all studies and (B) excluding the study by da Costa *et al* (37) 2019. (C) Subgroup analysis of CR. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; CR, complete response.

outcome assessors presented practical difficulties, resulting in a relatively high risk of bias in this area. It is worth noting that all studies demonstrated low risks in terms of the completeness of outcome data, selective reporting and other biases.

Rationale for risk of bias judgments. The assessments of high or unclear risk in specific domains are detailed as follows. There was a high risk of bias in blinding. All six trials were judged as high risk concerning the blinding of participants, personnel and outcome assessment. This stems from their open-label design, where the distinct treatment pathways (IC + CCRT involving additional chemotherapy cycles versus CCRT alone) were impossible to mask. Furthermore, the characteristic toxicities of induction chemotherapy (such as hair loss and more pronounced bone marrow suppression) acted as overt unblinding factors. This knowledge of allocation introduces a potential for expectancy bias in the assessment of subjective outcomes such as tumor response and adverse event grading.

There was an unclear risk of bias in allocation concealment. Three studies [Li *et al* (35) 2023; Banerjee *et al* (34) 2022; and Tripathi and Rawat (33) 2019] were rated as having an unclear risk regarding allocation concealment. While describing randomization, their reports omitted the specific methods used to conceal the allocation sequence (for example, sealed envelopes and central randomization) until after participants were enrolled. This lack of detailed reporting prevents a definitive judgment on whether selection bias was prevented, reflecting a common limitation in methodological transparency rather than evidence of actual bias.

CR. In total, 5 of the included studies reported the CR rate (33-37). The random-effects model was adopted for the meta-analysis, which showed higher CR rates in the IC + CCRT group compared with those in the CCRT alone group (OR, 1.24; 95% CI, 0.53-2.93; P=0.62), but there was significant heterogeneity (P=0.002; I^2=76%) (Fig. 4A). A sensitivity analysis conducted using the leave-one-out method demonstrated

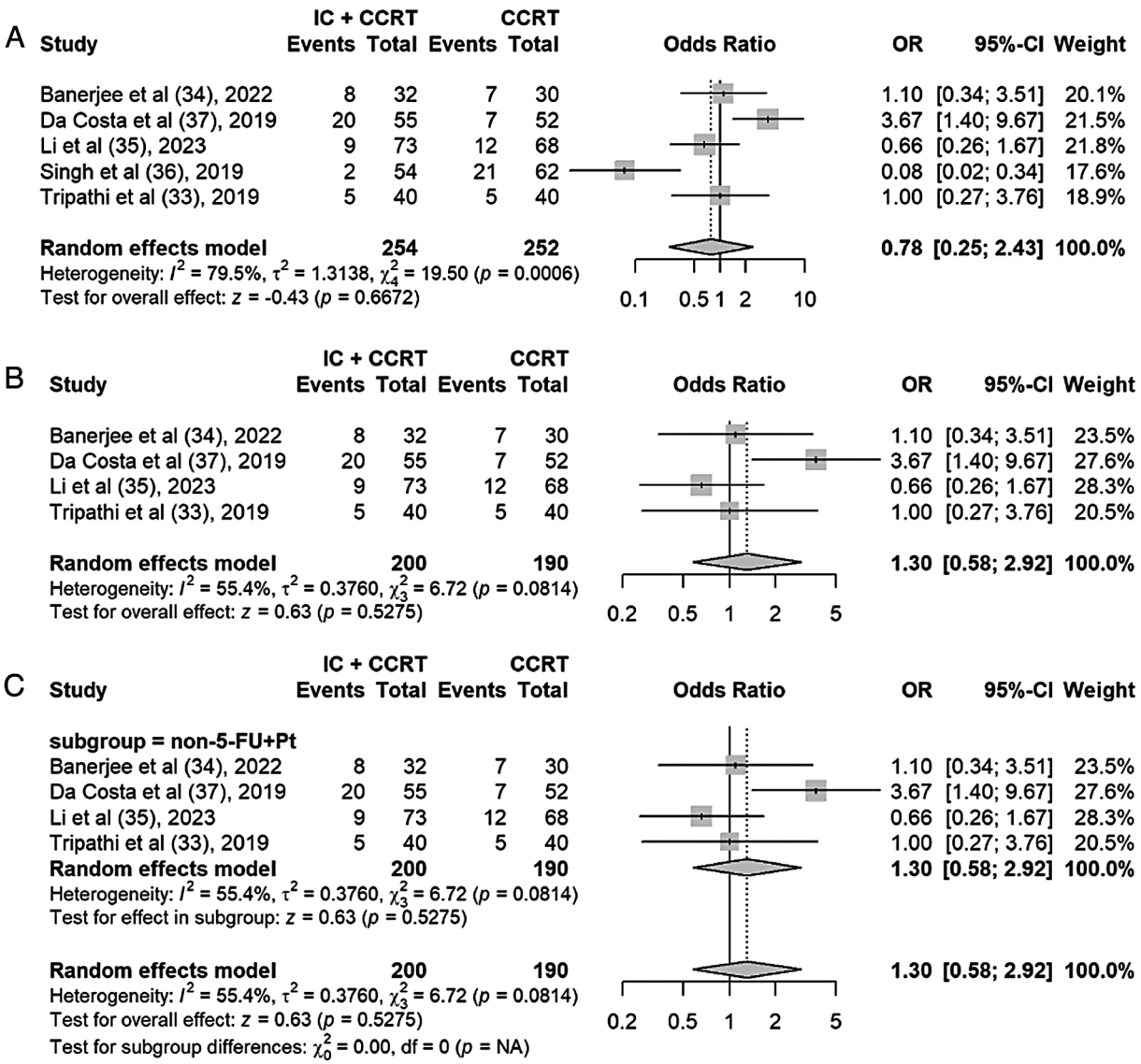

Figure 5. Forest plots for partial response. Forest plots (A) including all studies and (B) excluding the study by Singh *et al* (36) 2019. (C) Subgroup analysis of partial response. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; FU, fluorouracil; pt, platinum-based drugs (cisplatin in all included studies); CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

that excluding the study by da Costa *et al* (37) 2019 markedly reduced this heterogeneity, with the I^2 statistic decreasing from 76 to 7%. The overall effect size shifted to 1.95 (95% CI, 1.20-3.17; P=0.007), indicating statistically significant results (Fig. 4B). These findings suggest that the study by da Costa 2019 was a substantial contributor to the observed heterogeneity, and its exclusion improved the consistency of the pooled estimates.

Based on the impact on overall treatment timeline, induction chemotherapy regimens were categorized into long standard-course (3 cycles of 3-weekly chemotherapy, extending over ~9 weeks) and short-course regimens. The latter included protocols designed to minimize delay to definitive chemoradiation, characterized by either a reduced number of cycles (1-2 cycles) or an intensive weekly schedule over a shorter total duration. A subgroup analysis was performed (Fig. 4C). The short-course subgroup demonstrated a significant improvement in CR with IC + CCRT (OR, 2.21; 95% CI, 1.33-3.68; P=0.002). This indicates that the total duration and intensity of the induction regimen, which directly affect the timing of definitive therapy, have a significant impact on treatment outcome.

Partial response. A total of 5 of the included studies reported the PR rate. In the meta-analysis of PR rates, the initial random-effects model showed high heterogeneity (I^2=79%) (Fig. 5A). Sensitivity analysis revealed that the study by Singh *et al* (36) in 2019 significantly influenced the results. The control group in this study used a two-drug regimen of cisplatin + 5-fluorouracil, while the other studies all used single-agent cisplatin. This difference may be the main reason for it becoming an outlier and causing high heterogeneity. After excluding this study, the heterogeneity decreased to a moderate level (I^2=55%) (Fig. 5B), and the control group regimens of the remaining studies tended to be consistent.

Further subgroup analysis, stratified by the inclusion of fluorouracil in the control regimen, revealed that in the non-fluorouracil subgroup (four studies), heterogeneity

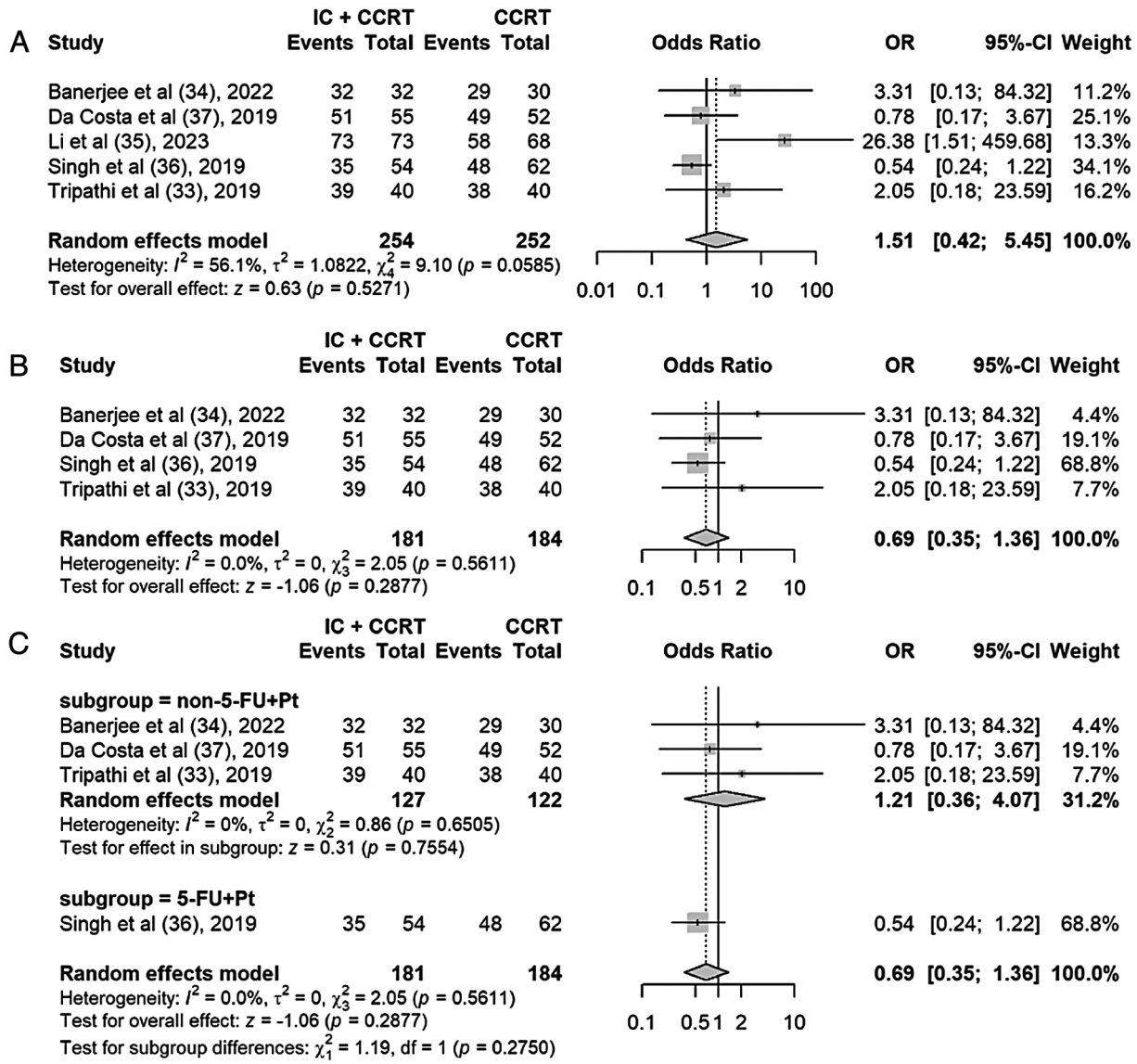

Figure 6. Forest plots for the objective response rate. Forest plots (A) including all studies and (B) excluding the study by Li *et al* (35) 2023. (C) Subgroup analysis of objective response rate. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; FU, fluorouracil; pt, platinum-based drugs (cisplatin in all included studies); CI, confidence interval; df, degrees of freedom; M-H,Mantel-Haenszel.

decreased to a moderate level (I^2=55%), whereas the fluorouracil subgroup consisted of a single study (Singh *et al* 2019), precluding the calculation of within-subgroup heterogeneity. The test for subgroup differences was significant (P=0.0011), confirming that the difference in control regimens (cisplatin + 5-fluorouracil vs. cisplatin alone) was a major source of the initial high heterogeneity. Both subgroup analyses did not show that IC + CCRT had a significant advantage in improving the PR rate. Given the remaining heterogeneity, a random-effects model was used for the pooled analysis. The results showed that IC + CCRT did not significantly improve the PR rate compared with simple CCRT (combined OR, 1.30; 95% CI, 0.58-2.92; P=0.53) (Fig. 5C).

ORR. A total of 5 studies reported the ORR. The pooled analysis using the random-effects model showed that there was no statistically significant difference in ORR between the IC + CCRT group and the CCRT group (OR, 1.51; 95% CI, 0.42-5.45; P=0.53), but there was moderate heterogeneity among the studies (I^2=56%; P=0.06) (Fig. 6A). Sensitivity analysis using the leave-one-out method identified the study by Li *et al* (35) as the primary source of heterogeneity. After excluding this study, the I^2 statistic decreased from 56 to 0%, while the pooled OR remained non-significant (OR, 0.69; 95% CI, 0.35-1.36; P=0.29) (Fig. 6B). The extreme ORR (100%) in the experimental arm of the study by Li *et al* (35) may be attributable to the later assessment time point (1 year post-treatment versus 4-12 weeks in other studies) and a more intensive radiotherapy regimen (higher nodal dose and more brachytherapy fractions). Notably, the remaining four studies still included one trial with an intensified CCRT regimen (cisplatin + 5-fluorouracil) in the control arm (36). A further subgroup analysis restricted to studies using single-agent cisplatin CCRT [Tripathi and Rawat (33), Banerjee *et al* (34) and da Costa *et al* (37)] yielded a pooled OR of 1.21 (95% CI, 0.36-4.07; P=0.76), with low heterogeneity (I^2=0%) (Fig. 6C).

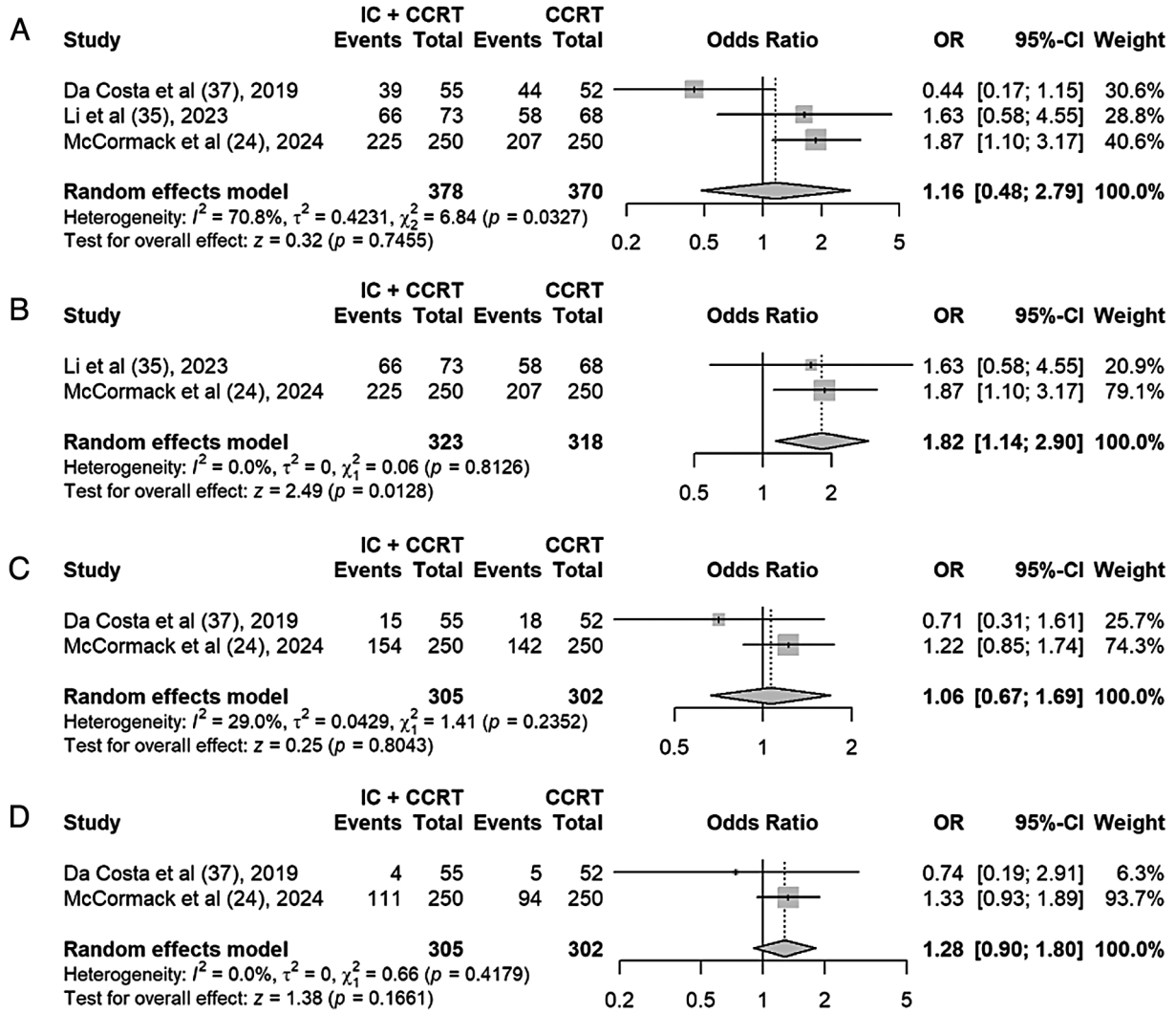

Figure 7. Forest plots for the PFS rates. Forest plots for 1-year PFS rate (A) including all studies and (B) excluding the study by da Costa *et al* (37) 2019. Forest plots for (C) 3-year and (D) 5-year PFS rates. PFS, progression-free survival; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

These findings indicate that while IC may show a non-significant trend toward improved ORR in the context of single-agent cisplatin CCRT, the overall evidence does not support a statistically significant benefit.

1-, 3- and 5-year PFS and OS rates. A total of 3 studies reported the 1-year PFS and OS rates, while 2 studies reported the 3- and 5-year PFS and OS rates.

Based on a preliminary meta-analysis, the addition of IC to standard CCRT showed a non-significant trend toward improved 1-year PFS (OR, 1.16; 95% CI, 0.48-2.79; P=0.75), with substantial heterogeneity (I^2=71%) (Fig. 7A). Given that the outlier study [da Costa *et al* (37) 2019] employed a long standard-course regimen, a sensitivity analysis was performed excluding it to reduce protocol-related heterogeneity. After exclusion, heterogeneity was eliminated (I^2=0%), and IC + CCRT demonstrated a significant improvement in 1-year PFS rate compared with CCRT alone (OR, 1.82; 95% CI, 1.14-2.90; P=0.01) (Fig. 7B).

For longer-term outcomes, random-effect models showed non-significant point estimates favoring IC + CCRT at 3 years (P=0.80) (Fig. 7C) and 5 years (P=0.17) (Fig. 7D), with the magnitude of benefit appearing to increase over time, although neither reached statistical significance.

OS. A random-effects model was applied for the meta-analysis of OS rate. The pooled analysis demonstrated consistent but non-significant improvements in OS rate favoring IC + CCRT: 1-year OS rate (OR, 1.55; 95% CI, 0.64-3.76; P=0.33), 3-year OS rate (OR, 1.15; 95% CI, 0.82-1.60; P=0.42) and 5-year OS rate (OR, 1.21; 95% CI, 0.86-1.70; P=0.27). These results were not statistically significant (Fig. 8A-C).

Although the initial 1-year OS rate combined analysis did not show statistical significance, it was observed that the results of the study by da Costa *et al* (37) were in contrast to those of the other two studies. In the study by da Costa *et al* (37), which utilized a 'long-course standard type' induction regimen comprising three cycles of cisplatin and gemcitabine administered every 3 weeks (extending over ~9 weeks and delaying the initiation of definitive chemoradiation by 3-4 weeks after the last chemotherapy cycle), the odds ratio was <1, favoring CCRT alone. By contrast, both the study by Li *et al* (35) 2023 and that by McCormack *et al* (23) 2024

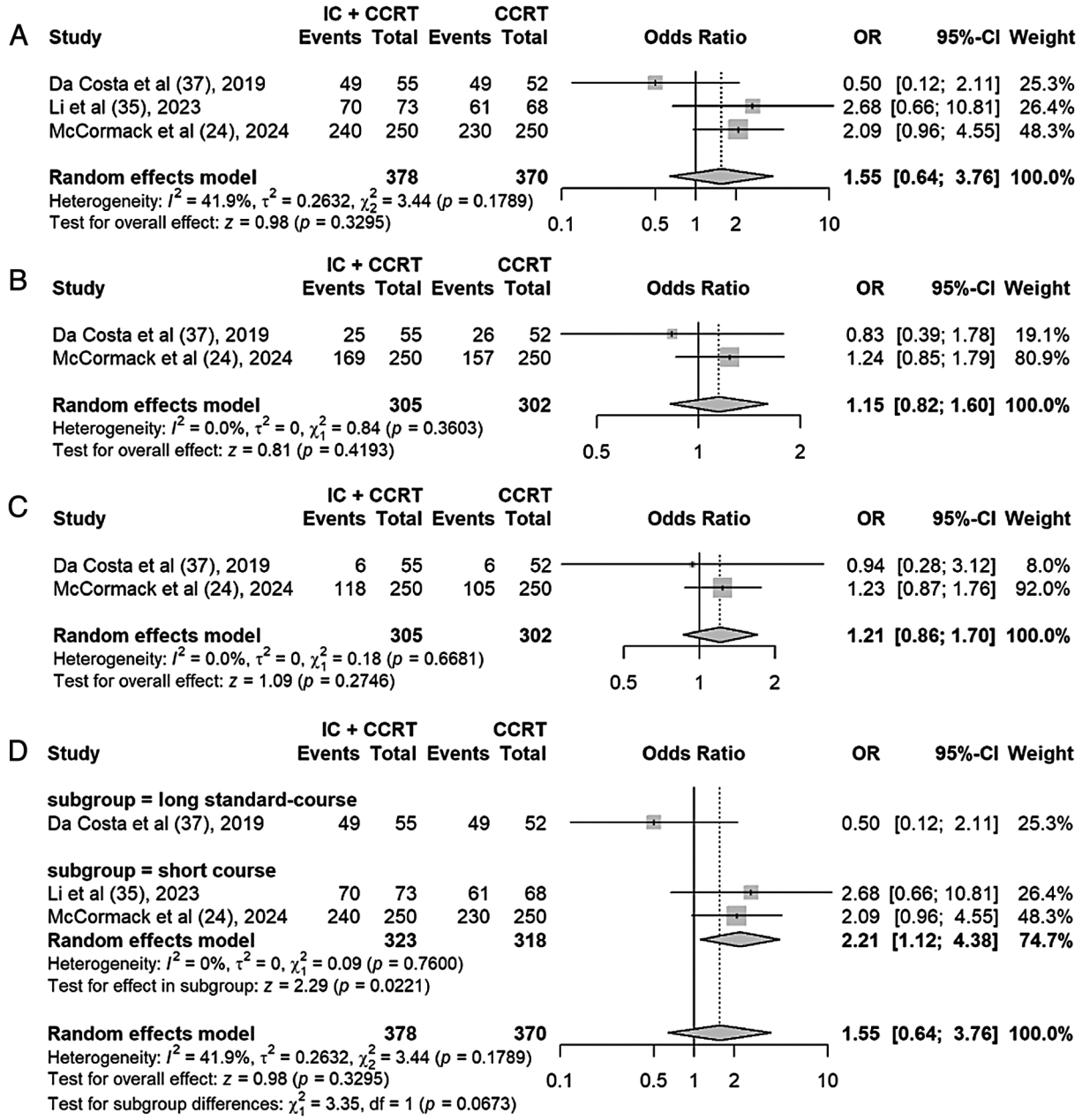

Figure 8. Forest plots for the OS rates. Forest plots for (A) 1-year, (B) 3-year and (C) 5-year OS rates, and (D) subgroup analysis of 1-year OS. OS, overall survival; CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

employed 'short-course type' regimens designed to minimize delays to definitive chemoradiation, and both reported odds ratios >1, favoring IC+CCRT. Considering that this study used the 'long-course standard type' induction regimen, while the other studies used the 'short-course type' regimen, a subgroup analysis was conducted based on treatment course design. In the 'short-course type' subgroup (n=2), IC + CCRT significantly improved 1-year OS rate (OR, 2.21; 95% CI, 1.12-4.38; P=0.02) (Fig. 8D), and there was no heterogeneity (I^2=0%). This result suggests that the benefit of induction chemotherapy on survival may be limited to the 'short-course type' regimen.

Local recurrence rate and distant metastasis rate. Local recurrence rates were reported in 3 out of the 6 studies, and distant metastasis rates were reported in 4 out of the 6 articles. A random-effects model was used for the meta-analysis, and it was found that the local recurrence rate was higher in the IC + CCRT group than that in the CCRT group (OR, 1.32; 95% CI, 0.83-2.11; P=0.24), but that the distant metastasis rate was lower in the IC + CCRT group than that in the CCRT group (OR, 0.74; 95% CI, 0.33-1.69; P=0.48). There were no statistically significant differences in the local recurrence rate and distant metastasis rate groups (Fig. 9A and B).

Safety and adverse events. The adverse events that occur during treatment mainly come under two categories: Hematological toxicity and non-hematological toxicity. Regarding hematological toxicity, thrombocytopenia was documented in 3 studies, neutropenia in 5, leukopenia in 3 and anemia in 6. Regarding hematological toxicity, the IC +

Table III. Summary of adverse events in IC+CCRT versus CCRT for locally advanced cervical cancer.

Adverse event category	Number of studies	Odds ratio (95% CI)	P-value	Interpretation
Hematological toxicities				
Thrombocytopenia	3	1.75 (1.10-2.79)	0.02	Significantly higher in IC+CCRT
Neutropenia	5	2.89 (2.03-4.12)	<0.01	Significantly higher in IC+CCRT
Leukopenia	3	1.62 (0.96-2.72)	0.07	Not significant
Anemia	6	1.81 (1.15-2.84)	0.01	Significantly higher in IC+CCRT
Non-hematological toxicities				
Fatigue	3	1.39 (0.91-2.11)	0.13	Not significant
Radiation cystitis	3	0.70 (0.38-1.27)	0.24	Not significant
Nephrotoxicity	4	0.58 (0.36-0.92)	0.02	Significantly lower in IC+CCRT
Abdominal pain	3	0.84 (0.53-1.33)	0.46	Not significant
Gastrointestinal toxicity	3	1.01 (0.66-1.55)	0.97	Not significant
Diarrhea	3	0.66 (0.44-1.00)	0.05	Borderline significance
Nausea	3	0.58 (0.22-1.50)	0.26	Not significant
Skin reaction	4	1.21 (0.65-2.27)	0.55	Not significant

CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; CI, confidence interval.

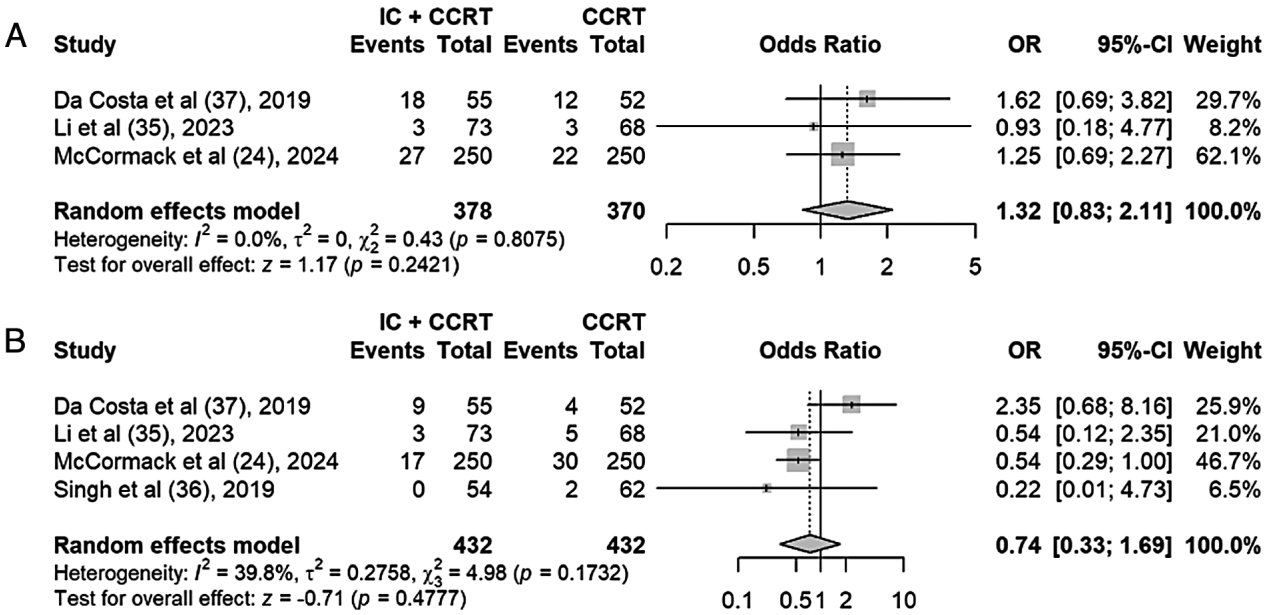

Figure 9. Forest plots for recurrence and metastasis. Forest plots for (A) local recurrence rate and (B) distant metastasis rate. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

CCRT group demonstrated a significantly higher incidence of thrombocytopenia (OR, 1.76; 95% CI, 1.06-2.90; P=0.03) and neutropenia (OR, 2.69; 95% CI, 1.09-6.61; P=0.03) (Fig. 10A). However, for leukopenia (OR, 1.55; 95% CI, 0.51-4.69; P=0.44) and anemia (OR, 1.43; 95% CI, 0.54-3.82; P=0.47), although the IC + CCRT group showed a numerically higher incidence, this difference did not reach statistical significance. With regard to non-hematological toxicity, fatigue was mentioned in 3 studies, radiation cystitis in 3, nephrotoxicity in 4, abdominal pain in 3, gastrointestinal toxicity in 3, diarrhea in 3, nausea in 3 and skin reaction in 4. The pooled analysis demonstrated no statistically significant differences between the IC + CCRT and CCRT groups in the incidence of fatigue (OR, 1.32; 95% CI, 0.67-2.58; P=0.42), radiation cystitis (OR, 0.76; 95% CI, 0.33-1.76; P=0.52), abdominal pain (OR, 0.84; 95% CI, 0.53-1.35; P=0.47), gastrointestinal toxicity (OR, 1.18; 95% CI, 0.51-2.73; P=0.71), diarrhea (OR, 0.66; 95% CI, 0.44-1.00; P=0.05), nausea (OR, 0.59; 95% CI, 0.22-1.56; P=0.29) or skin reaction (OR, 1.16; 95% CI, 0.43-3.12; P=0.77). The only exception was nephrotoxicity, which occurred significantly less frequently in the IC+CCRT group (OR, 0.58; 95% CI, 0.36-0.92; P=0.02) (Fig. 10B). The pooled odds ratios

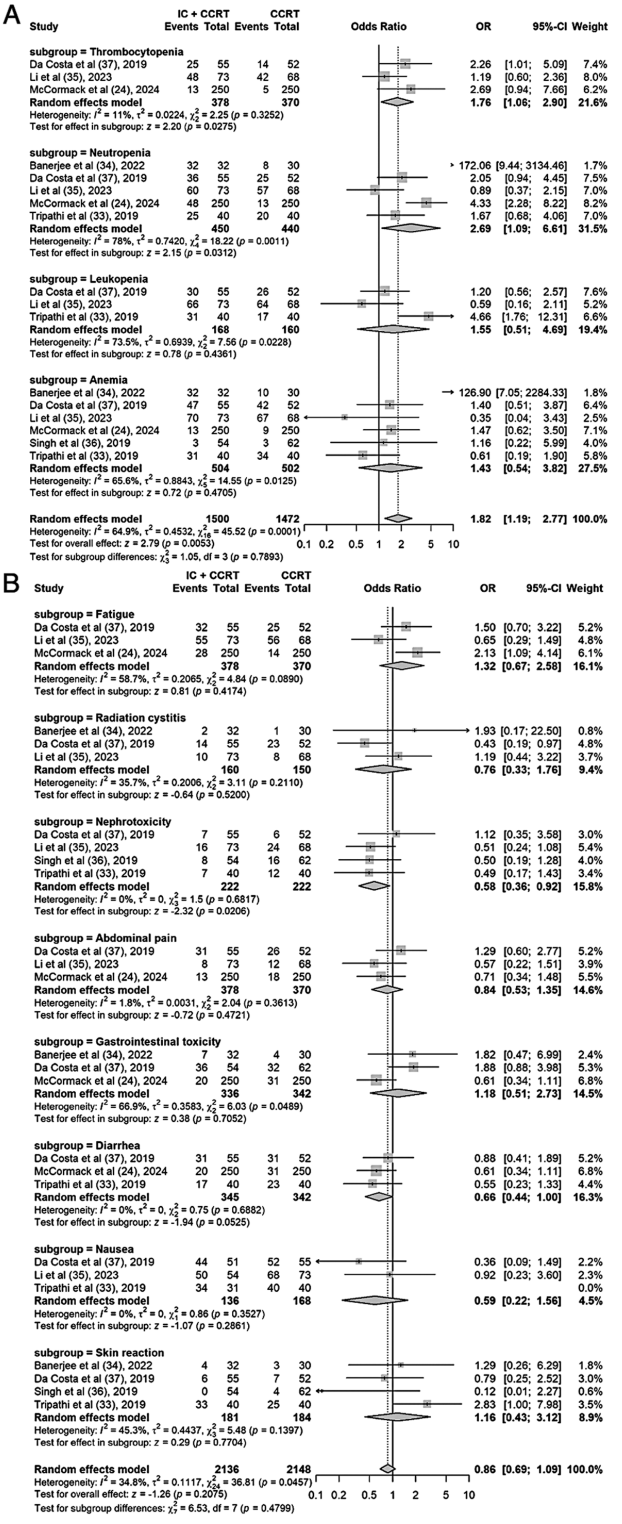

Figure 10. Forest plots for toxicity. Forest plots for (A) hematological and (B) non-hematological toxicity. CCRT, concurrent chemoradiotherapy; IC, induction chemotherapy; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

for hematological and non-hematological adverse events are summarized in Table III. The certainty of evidence for each outcome was assessed using the GRADE framework. The evidence profile summarizing the certainty ratings is provided in Table SI. Overall, the certainty of evidence was high for hematological and non-hematological toxicity outcomes, and moderate for most survival outcomes, with downgrading primarily due to imprecision (from limited sample sizes) or inconsistency (from high heterogeneity) in several endpoints.

Sensitivity analysis and publication bias assessment. Sensitivity analyses were performed using a leave-one-out approach, systematically excluding each study in sequence to determine its individual impact on the pooled outcomes. The results indicated that, with the exception of the CR, PR, ORR, and 1-year PFS analyses, the removal of any single study did not substantially influence the overall results (Figs. S1A-11A). This indicates that the meta-analysis results are relatively robust. Furthermore, after performing Begg's and Egger's tests on the funnel plots of all outcome indicators, the publication bias analysis of the 6 included studies demonstrated no significant publication bias with regard to the CR, PR and ORR, the 1-, 3- and 5-year PFS and OS rates, or the LRR and DMR (all P>0.05) (Figs. S1B-11B). However, for outcomes with only a small number of studies (for example, 3-5 studies), the statistical power to detect publication bias is inherently low, which is an important methodological limitation. Therefore, while the available quantitative tests did not detect significant bias, the possibility of unpublished data or small-study effects cannot be definitively ruled out, particularly for the outcomes with very few studies. The interpretation of funnel plots for these outcomes is also highly challenging. Consequently, the conclusions, especially those reliant on a small number of trials, should be interpreted with caution regarding potential publication bias.

Discussion

A systematic review and meta-analysis was conducted to evaluate the efficacy and safety of adding IC before standard CCRT for LACC. The core results indicated that the IC + CCRT strategy, especially when using modern short-course, dose-dense regimens, significantly improved the CR rate and 1-year PFS rate of patients compared with CCRT alone, but with a higher risk of hematological toxicity; although the OS rate showed an improving trend, it did not reach statistical significance. These findings mark the transformation of IC from a historically controversial strategy due to long-term and delayed radical treatment to a promising treatment enhancement option based on precise protocol design. Subgroup analysis confirmed that short-course intensive regimens (1-2 cycles therapy or weekly therapy) are key to achieving survival benefits, which is highly consistent with the conclusion of the INTERLACE III phase trial that changed clinical practice (24). The trial demonstrated that immediate continuation of CCRT after 6 weeks of carboplatin/paclitaxel induction therapy could significantly increase the 5-year OS rate from 72 to 80%, and its successful model lies in rapidly reducing tumors through dose-dense weekly therapy while minimizing the risk of tumor recurrence due to long treatment intervals, thereby converting the potential theoretical advantages of IC into definite survival benefits (24). This principle, solidified by modern practice-changing trials, finds precedent in earlier exploratory studies (38,39). For instance, a phase II trial demonstrated that a dense schedule of paclitaxel-cisplatin administered every 10 days over ~1 month achieved a high

clinical response rate (90.7%) in patients with locally advanced disease without delaying subsequent definitive treatment (39). This early evidence underscores the feasibility and activity of compressing the induction period to rapidly reduce tumor volume, a foundational concept for contemporary protocols.

Based on the confirmation of the effectiveness of the short-term treatment plan, an in-depth analysis was conducted to investigate the 'incremental value' of adjuvant chemotherapy prompts. It was found that this value is not absolute and is largely influenced by the intensity of the subsequent comprehensive CCRT. The present sensitivity analysis and subgroup analysis revealed that when the control group in the study adopted intensified dual-drug CCRT (such as cisplatin + 5-fluorouracil), the trend of additional benefits brought by increasing IC was not obvious. This finding aligns with the existing evidence-based medical evidence. In the context of CCRT, multiple studies and network meta-analyses have shown that the dual-drug combination based on cisplatin does not demonstrate a clear superiority over cisplatin monotherapy in terms of survival outcomes (12,40). This suggests that there may be a 'yield reduction' effect in the treatment intensity sequence for LACC. In other words, if the radical CCRT stage itself is a potent treatment plan, then the expected additional survival benefit from adding IC before it may be relatively limited; conversely, in the clinical context where the standard CCRT is based on single-agent cisplatin, adding short-term IC can provide a clear improvement in treatment intensity, which is consistent with the observed trend of ORR improvement in the present study. Therefore, the clinical decision-making for IC should be a meticulous balance process, with the core purpose not being simply to stack chemotherapy drugs, but rather to strategically utilize the systemic effect of IC to early clear micrometastases and create more favorable local conditions for subsequent radiotherapy by reducing the primary tumor size based on the individual patient's condition and the treatment background.

From the perspective of the mechanism, the benefits of IC may go beyond the simple cytotoxic effect. Basic research suggests that chemotherapy drugs such as platinum may have certain immunomodulatory effects, such as reducing immunosuppressive cells in the tumor microenvironment (41). This may partially explain the positive trend observed in the present study of IC+CCRT in reducing the rate of distant metastasis. Of course, the present study also has several limitations. The total number and sample size of the included RCTs are still limited, and in particular, there are few studies reporting long-term survival outcomes. This may affect the statistical confidence in the OS results. In addition, the heterogeneity in radiotherapy techniques, specific chemotherapy doses and adverse reaction recording standards among the studies, although handled through random-effects models and sensitivity analyses, may still affect the accuracy of some combined estimates.

In conclusion, the present study provides important evidence-based support for the application of modern short-course intensive IC combined with CCRT in LACC, especially in patients who subsequently receive standard-intensity CCRT. The future research direction should focus on integrating multi-dimensional information, such as tumor molecular characteristics, radiomics and immune microenvironment markers, to construct a precise predictive model, in order to more accurately identify the patient groups most likely to benefit from this intensified treatment strategy. At the same time, it should carefully explore the timing and sequence of combining immunotherapy and other new modalities, ultimately achieving individualized treatment and breaking through the treatment bottleneck of LACC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Author's contributions

YS and XL contributed to the conception, design and writing of the manuscript. WX and TT were responsible for data extraction and analysis. The first draft of the manuscript was written by YS. FZ and DY contributed to the statistical analysis and interpretation of results, ensuring the robustness of the meta-analysis methodology. Manuscript revision and proofreading were conducted by WX, XL, FZ, and DY. YS and XL confirm the authenticity of all the raw data. YG, WX and YX contributed to the study design and provided critical feedback on the methodology. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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