Efficacy and safety of neoadjuvant chemotherapy followed by radical surgery vs. radical surgery alone in locally advanced cervical cancer: A systematic review and meta-analysis

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Abstract. Locally advanced cervical cancer (LACC) poses a significant therapeutic challenge, particularly in defining the optimal role of neoadjuvant chemotherapy (NACT) followed by radical surgery (RS) relative to surgery alone. Existing literature offers conflicting evidence on survival benefits, highlighting the need for further clarification. In the present study, the PubMed, EMBASE, Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews databases were systematically searched for studies comparing NACT plus RS vs. RS alone in patients with International Federation of Gynecology and Obstetrics stage IB2-IIB cervical cancer. Eligible trials reported at least one major outcome [overall survival (OS) or disease-free survival (DFS)]. Odds ratios (ORs) were calculated using a random-effects model. Sensitivity analyses, assessment of publication bias and quality evaluations were performed. Seven studies encompassing 2,231 patients were included. The pooled estimate for DFS did not differ significantly between groups (OR, 0.98; 95% CI, 0.62-1.56; P=0.941), despite some individual studies showing improvements. Subgroup meta-analysis of OS found a significant advantage favoring NACT plus RS (OR, 0.53; 95% CI, 0.32-0.87; P=0.012). However, when all OS data were combined, the observed benefit approached but did not achieve statistical significance (OR, 0.74; 95% CI, 0.53-1.04; P=0.078). Leave-one-out sensitivity analyses confirmed the robustness of findings for OS and the consistent null effect for DFS. Publication bias assessments were largely negative, indicating minimal risk of missing or selectively reported studies. The NACT group had lower postoperative complications and radiotherapy needs but higher hematological toxicity and surgical complexity. In conclusion, NACT followed by RS may confer a borderline or subgroup-specific survival advantage over RS alone for LACC. However, the overall benefit remains inconclusive for DFS. Clinicians should balance potential gains against treatment-associated risks when considering NACT in routine practice.

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Introduction

Cervical cancer remains a significant global health concern, ranking as the fourth most common cancer among women worldwide. In 2020, ~604,000 new cases and 342,000 associated deaths were reported, with a disproportionate burden in low- and middle-income countries (1). The management of locally advanced cervical cancer (LACC), typically defined as International Federation of Gynecology and Obstetrics (FIGO) stages IB2 to IIB (2), presents a particular therapeutic challenge.

Concurrent chemoradiotherapy (CCRT) is the internationally accepted standard for FIGO IB2-IIB, resulting in superior overall survival (OS) and progression-free survival (PFS) compared with surgery alone or radiotherapy alone (e.g., higher response and survival rates; CCRT outperforms neoadjuvant therapy plus surgery in studies such as EORTC-55994) (3). However, the role of neoadjuvant chemotherapy (NACT) followed by radical surgery (RS) as an alternative treatment strategy has been a subject of ongoing debate. NACT involves administering chemotherapy before the primary treatment modality, such as RS in this case. The rationale behind this approach includes reducing tumor size to facilitate surgical resection, eradicating micrometastatic disease early and potentially improving surgical outcomes by decreasing the extent of disease (4).

Several studies have explored the efficacy and safety of NACT followed by RS compared with RS alone in patients with LACC (5-8). A systematic review and meta-analysis conducted by Zhao *et al* (9) evaluated the outcomes of NACT combined with RS vs. RS alone in patients with cervical cancer at all stages. The analysis included 13 studies with a total of 2,158 participants. The findings indicated that, with regard to OS, disease-free survival (DFS), PFS, local and distant recurrence, and parametrial infiltration, neoadjuvant chemotherapy plus radical surgery was similar to radical surgery alone (9). Nevertheless, a review by Gadducci and Cosio (4) assessed the impact of NACT followed by radical hysterectomy in patients with LACC. The study reported that this combined approach resulted in higher

PFS and OS times compared with primary radical hysterectomy. These benefits were observed regardless of the total cisplatin dose, chemotherapy cycle length or tumor stage (4).

Despite these promising results, the integration of NACT into standard treatment protocols for LACC is not universally accepted. Concerns have been raised regarding potential delays in definitive treatment, the risk of disease progression during chemotherapy, and the added toxicity associated with additional treatment modalities. Moreover, the heterogeneity of chemotherapy regimens and variations in surgical expertise across different centers contribute to the ongoing debate (1). Recent guidelines from the European Society of Gynecological Oncology (ESGO) highlight that while NACT followed by RS is a treatment option, it should not replace the standard CCRT approach. The guidelines emphasize the need for individualized treatment planning, considering factors such as tumor characteristics, patient comorbidities and resource availability (1,10).

Given the ongoing debate and the potential implications for patient care, a comprehensive systematic review and meta-analysis are warranted to critically evaluate the efficacy and safety of NACT followed by RS vs. RS alone in LACC. The present analysis aimed to provide clarity on the optimal treatment approach, thereby informing clinical practice and guiding future research endeavors.

Materials and methods

Study design. The present systematic review and meta-analysis were conducted to evaluate the efficacy and safety of NACT followed by RS vs. RS alone in patients with LACC. The methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (11).

Search strategy. A comprehensive literature search was performed across multiple databases, including PubMed (https://pubmed.ncbi.nlm.nih.gov/), EMBASE (https://www.embase.com/), the Cochrane Central Register of Controlled Trials (CENTRAL; https://www.cochranelibrary.com/central/about-central) and the Cochrane Database of Systematic Reviews (https://www.cochranelibrary.com/cdsr/about-cdsr). The search encompassed studies published from database inception up to March 2025, without language restrictions. The following medical subject headings (MeSH) terms and keywords were used: 'Cervical cancer', 'neoadjuvant chemotherapy', 'radical surgery', 'radical hysterectomy' and 'locally advanced'. The search had the following format in PubMed: ['Cervical Cancer'(MeSH) OR 'Cervical Neoplasms'(Title/Abstract) OR 'cervical carcinoma' (Title/Abstract)] AND ['Neoadjuvant Chemotherapy'(MeSH) OR 'neoadjuvant chemotherapy'(Title/Abstract) OR 'preoperative chemotherapy'(Title/Abstract)] AND ['Radical Surgery' (MeSH) OR 'radical hysterectomy'(Title/Abstract) OR 'surgical resection'(Title/Abstract)] AND ['Locally Advanced'(Title/Abstract) OR 'FIGO stage IB2'(Title/Abstract) OR 'FIGO stage IIB'(Title/Abstract)]. Similar strategies were applied to EMBASE, CENTRAL and the Cochrane database. Additionally, the reference lists of relevant articles (9) were manually screened to identify further pertinent studies. Although no language restrictions were applied during the database search, only articles published in English were ultimately included. Non-English studies were excluded if full translations were not available or if data extraction was not feasible due to language barriers.

Inclusion and exclusion criteria. Studies were considered eligible if they met the following criteria: i) Population: Women diagnosed with LACC, specifically FIGO stages IB2 to IIB. ii) Intervention: NACT followed by RS. iii) Comparison: RS alone. iv) Outcomes: Reported at least one of the following, namely, OS, PFS and DFS times, recurrence rate, lymph node metastasis or parametrial infiltration. v) Study design: Randomized controlled trials (RCTs), prospective non-RCTs or retrospective cohort studies.

Exclusion criteria included studies focusing on early-stage (FIGO stage IA to IB1) or metastatic cervical cancer, those lacking a comparison between the specified interventions and studies with insufficient data for extraction (1,9,12).

Data extraction and quality assessment. Two independent reviewers screened titles and abstracts for relevance, followed by full-text assessments to confirm eligibility. Discrepancies were resolved through discussion or consultation with a third reviewer. Data extracted included study characteristics (author, year, study design and sample size), patient demographics, treatment protocols and reported outcomes. Risk of bias was assessed using different tools depending on study design. For observational studies, the Newcastle-Ottawa Scale (NOS) (13) was applied. For randomized controlled trials, the Cochrane Risk of Bias (RoB) 2.0 tool (https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials) was used to assess the randomization process, allocation concealment, blinding, outcome measurement and completeness of data. The NOS scale assesses three aspects: i) Selection of the study groups (maximum of 4 stars); ii) comparability of groups (maximum of 2 stars), indicating appropriate matching or analysis to control for confounders; and iii) outcome/exposure (maximum of 3 stars), reflecting the adequacy of outcome measurement, length/adequacy of follow-up and attrition. A total of up to 9 stars can be awarded. Higher scores suggest a lower risk of bias.

Statistical analysis. All statistical analyses were conducted using comprehensive meta-analysis software, version 2 (Biostat International, Inc.). A random-effects model was employed to account for potential heterogeneity among studies, and odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated for dichotomous outcomes. Survival outcomes (OS and DFS) were summarized using ORs, as hazard ratios (HRs) were not consistently reported or extractable across the included studies. To distinguish between outcome-specific treatment effects, separate meta-analyses were performed for OS and DFS as distinct subgroups, rather than stratifying by study design or patient characteristics. This approach allowed the assessment of whether the treatment benefit varied according to the type of survival outcome. A number of studies provided dichotomized survival data (e.g., 5-year survival rates or recurrence status at follow-up) without time-to-event estimates or Kaplan-Meier curves suitable for HR reconstruction. Therefore, ORs were used to enable a

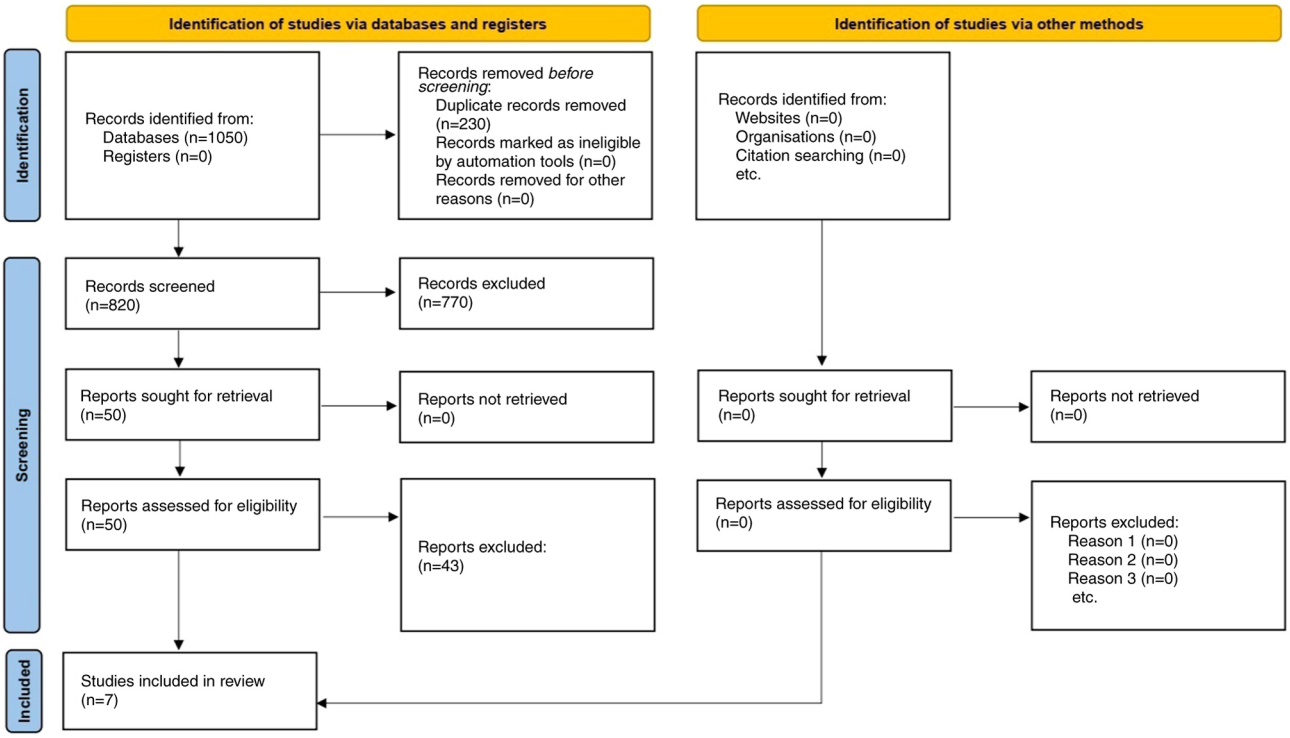

Figure 1. PRISMA flowchart of study selection. Flowchart illustrating the systematic search and selection process for included studies, detailing the number of records identified, screened, excluded and ultimately analyzed in the meta-analysis.

consistent pooled analysis, while acknowledging that ORs are less informative than HRs for time-to-event outcomes and that they may overestimate effect sizes when event rates are high. To assess the robustness of the results, sensitivity analyses were performed by systematically excluding each study to evaluate its impact on the overall findings.

Heterogeneity was assessed using precision interval analysis, which offers an alternative to the traditional I^2 statistic by focusing on the accuracy of the combined effect size estimate. Publication bias was evaluated through visual inspection of funnel plots, along with Begg and Mazumdar's rank correlation test (Kendall's τ values closer to zero indicate less serious publication bias) and Egger's regression test (if the intercept term is equal to or close to zero this indicates less serious publication bias). Furthermore, the fail-safe N test was used to determine how many missing studies would be needed to nullify the observed effect, and the Duval and Tweedie's trim-and-fill method was applied to adjust for potential publication bias by estimating and adding hypothetical missing studies. $P<0.05$ was considered to indicate a statistically significant difference for all analyses.

Results

Study selection. The initial database search yielded 1,050 records. After removing duplicates, 820 unique records remained. Following title and abstract screening, 50 articles were selected for full-text review. Of these, 43 were excluded for the following reasons: Early-stage or metastatic cervical cancer populations (n=13), absence of a comparator group matching the inclusion criteria (n=10), insufficient outcome data (n=9), duplicate or overlapping cohorts (n=6) and non-English publications without accessible translations (n=5), resulting in 7 studies being included in the final analysis (5-8,14-16). A PRISMA flow diagram illustrating the study selection process is provided in Fig. 1. Among the 7 included studies, 3 were RCTs (6,8,15), and 4 were observational cohort studies (5,7,14,16). Table I provides a comprehensive summary of the general characteristics and demographics of the included studies comparing NACT followed by RS vs. RS alone in LACC. The table presents key data on study sample sizes, patient demographics, FIGO staging, histological subtypes, treatment groups, lymph node metastasis rates, survival outcomes, and NACT chemotherapy regimens and doses. The total sample size of the included patients in this meta-analysis is 2,231.

Outcomes and synthesis of results. A subgroup-specific meta-analyses was performed based on survival outcome type (OS vs. DFS). Fig. 2 presents the survival outcome-specific meta-analyses for DFS and OS. For DFS, the pooled OR was 0.98 (95% CI, 0.62-1.56; P=0.941), indicating no significant benefit of NACT followed by RS compared with surgery alone. Although several individual studies reported improvements in DFS, these effects did not translate into a significant pooled estimate. By contrast, the pooled analysis of OS data showed a more favorable effect. When restricted to OS outcomes only, the pooled OR was 0.53 (95% CI: 0.32-0.87; P=0.012), suggesting a statistically significant survival benefit associated with NACT. However, when all studies contributing OS and DFS data are combined, the overall effect estimate becomes more modest and borderline significant (OR, 0.74; 95% CI, 0.53-1.04; P=0.078). These findings highlight a potential outcome-specific benefit of NACT for OS but not for DFS.

Table I. General characteristics and demographics of included studies.

First author, year	Sample size, n	Mean age (range), years	FIGO stages	Histological types	Treatment groups	Lymph node metastasis, %	Survival outcome	NAC regimen and doses	(Refs.)
Behtash *et al*, 2006	182	48 (26-75)	IB2-IIA	Squamous (majority), adenocarcinoma	NACT + RS (n=22) vs. RS alone (n=160)	36 RS; 47.1 NACT	OS not significantly different (P=0.06)	50 mg/m^2 cisplatin + 1 mg/m^2 vincristine (every 10 days for 3 cycles)	(5)
Chen *et al*, 2008	142	44 (25-74)	IB2-IIB	Squamous, adenocarcinoma	NACT + RS (n=72) vs. RS alone (n=70)	16.0 NACT responders; 45.5 non-responders	NACT responders ha better DFS and lower recurrence (P<0.001)	100 mg/m^2 cisplatin (day 1) + 4 mg/m^2 mitomycin C (IM, days 1-5) + 24 mg/kg/day 5-FU (IV, days 1-5)	(6)
Gong *et al*, 2016	800	Not specified	IB2-IIB	Squamous, adenocarcinoma	NACT + RS (n=411) vs. RS alone (n=389)	Not specified	5-year PFS 80.3% (NACT) vs. 81.0% (RS)	Carboplatin + cisplatin, Carboplatin + cisplatin, xpingyangmycin, ifosfamide, 5-FU, paclitaxel, vincristine (1-3 cycles)	(7)
Katsumata *et al*, 2013	134	Not specified	IB2-IIB	Squamous cell carcinoma	NACT + RS (n=67) vs. RS alone (n=67)	Not specified	5-year OS: 70.0% (NACT) vs. 74.4% (RS) (P=0.85)	7 mg Bleomycin (days 1-5) + 0.7 mg/m^2 vincristine (day 5) + 7 mg/m^2 mitomycin (day 5) + 14 mg/m^2 cisplatin (days 1-5)	(8)
Kim *et al*, 2011	524	50.6±11.5	IB1-IIA	Squamous (majority), non-squamous	NACT + RS (n=73) vs. RS alone (n=451)	23.9 RS; 23.3 NACT	Not specified	5-FU/cisplatin or paclitaxel/carboplatin (median, 3 cycles)	(16)
Yang *et al*, 2016	219	47 (23-66)	IB2-IIB	Squamous, adenocarcinoma, adenosquamous	NACT + RS (n=109) vs. RS alone (n=110)	Not specified	No significant difference in DFS/OS between groups	60 mg/m^2 irinotecan (IV, days 1, 8 and 15) + 70 mg/m^2 cisplatin (IV, day 1) or 175 mg/m^2 paclitaxel (IV, day 1) + 70 mg/m^2 cisplatin (IV, day 1) (1-2 cycles)	(15)

Table I. Continued.

First author, year	Sample size, n	Mean age (range), years	FIGO stages	Histological types	Treatment groups	Lymph node metastasis, %	Survival outcome	NAC regimen and doses	(Refs.)
Namkoong *et al*, 1995	230	48 (30-58)	IB-IIB	Squamous (majority), adenocarcinoma	NACT + RS (n=92) vs. RS alone (n=138)	18.5 NACT; 34.0 RS	4-Year tumor-free survival: 81.5% (NACT) vs. 66.7% (RS) (P=0.0067)	4 mg/m^2 vinblastine (days 1-2), 15 mg/m^2 bleomycin (days 1, 7 and 14), 60 mg/m^2 cisplatin (day 1); every 3 weeks	(14)

NACT, neoadjuvant chemotherapy; RS, radical surgery; OS, overall survival; DFS, disease-free survival; PFS, progression-free survival; 5-FU, 5-fluorouracil; IM, intramuscular; IV, intravenous.

Sensitivity analysis. In the leave-one-out sensitivity analysis for OS (Fig. 3A), removing each study one at a time resulted in ORs ranging from 0.45 to 0.62, all with statistically significant P-values of <0.05. The combined estimate remains significant (OR, 0.53; 95% CI, 0.32-0.87, P=0.012), indicating that no single trial primarily drives the benefit in OS. By contrast, for DFS (Fig. 3B), excluding individual studies yields summary ORs consistently near 1.0, with P-values from 0.467 to 0.990, highlighting the lack of a significant overall effect on DFS and confirming that the null finding is robust against the omission of any single study. The funnel plot of log ORs against standard error appears fairly symmetrical, suggesting no major signs of publication bias (Fig. 4). Begg and Mazumdar's rank correlation produces Kendall's τ values near 0.2 with non-significant P-values (two-tailed P>0.4), while Egger's regression test also shows no evidence of small-study effects (P>0.5). Duval and Tweedie's trim-and-fill analysis detects no missing studies on either side of the mean, leaving the pooled estimate unchanged. The fail-safe N similarly indicates that no additional studies are needed to bring the meta-analysis to a non-significant level. Overall, these findings suggest that the observed effect estimates are not heavily influenced by publication bias. The prediction-interval analysis (Fig. 5) indicates that, although the average effect size (OR, 0.98) has a 95% CI of 0.62-1.56 implying no clear departure from unity; the true effect across similar populations could range widely, from about 0.21 to 4.71. Therefore, even though the pooled estimate does not significantly differ from no effect, there is substantial heterogeneity; some settings might observe smaller effects (possibly null or worse), while others could see much larger effects.

Quality assessment. The quality of observational studies was evaluated using the NOS scale (Table II), and the quality of RCTs was evaluated using the Cochrane RoB 2.0 tool (Table III). Among the studies assessed, the study by Gong *et al* (7) received the highest total score (9 points), reflecting strong methodological rigor in terms of participant selection, group comparability and outcome assessment. Namkoong *et al* (14) achieved a score of 8, demonstrating a well-balanced design with appropriate controls for confounders and thorough outcome evaluation. Behtash *et al* (5) and Kim *et al* (16) received scores of 6, suggesting moderate quality due to potential limitations in comparability or outcome assessment. These studies may have had fewer controls for confounding factors or shorter follow-up periods compared with others in the analysis. The three RCTs (6,8,15) demonstrated generally low risk of bias in randomization, outcome assessment and data completeness, although blinding was not feasible in most surgical trials. No major threats to internal validity were identified. Overall, the included studies were of acceptable quality for meta-analysis, with most receiving high scores, indicating a low risk of bias. While some studies exhibited minor limitations in comparability or outcome assessment, the overall methodological rigor supports the reliability of the pooled findings.

Heterogeneity analysis. Meta-regression was conducted to assess whether study-level variables explained heterogeneity in OS estimates. The covariates included chemotherapy regimen, proportion of FIGO stage IIB patients, publication year, study design and sample size. None of the included covariates showed a statistically

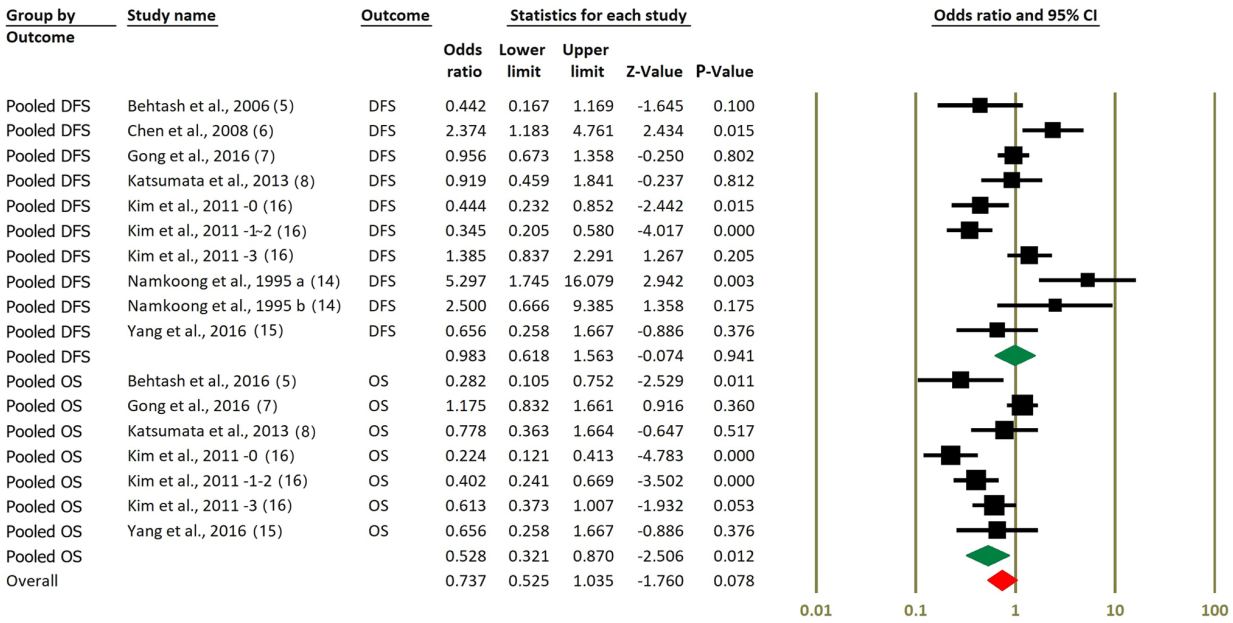

Figure 2. Forest plots comparing DFS and OS in NACT + RS vs. RS alone. Pooled ORs and 95% CIs for DFS are presented, showing no significant difference between NACT + RS and RS alone (OR, 0.98; P=0.941). Pooled OS data are presented, with a significant benefit shown in subgroup analysis (OR, 0.53; P=0.012); however, when all OS and DFS data were combined, the advantage approached but did not reach statistical significance (OR, 0.74; P=0.078). Kim *et al* (16) -0, -1~2 and -3 represent the number of metastatic lymph nodes; this study statistically analyzed OS and DFS after grouping based on the number of lymph node metastases. Namkoong *et al* (14) 1995 a and b represent squamous cell carcinoma and adenocarcinoma, respectively. DFS, disease-free survival; OS, overall survival; NACT, neoadjuvant chemotherapy; RS, radical surgery; OR, odds ratio; CI, confidence interval.

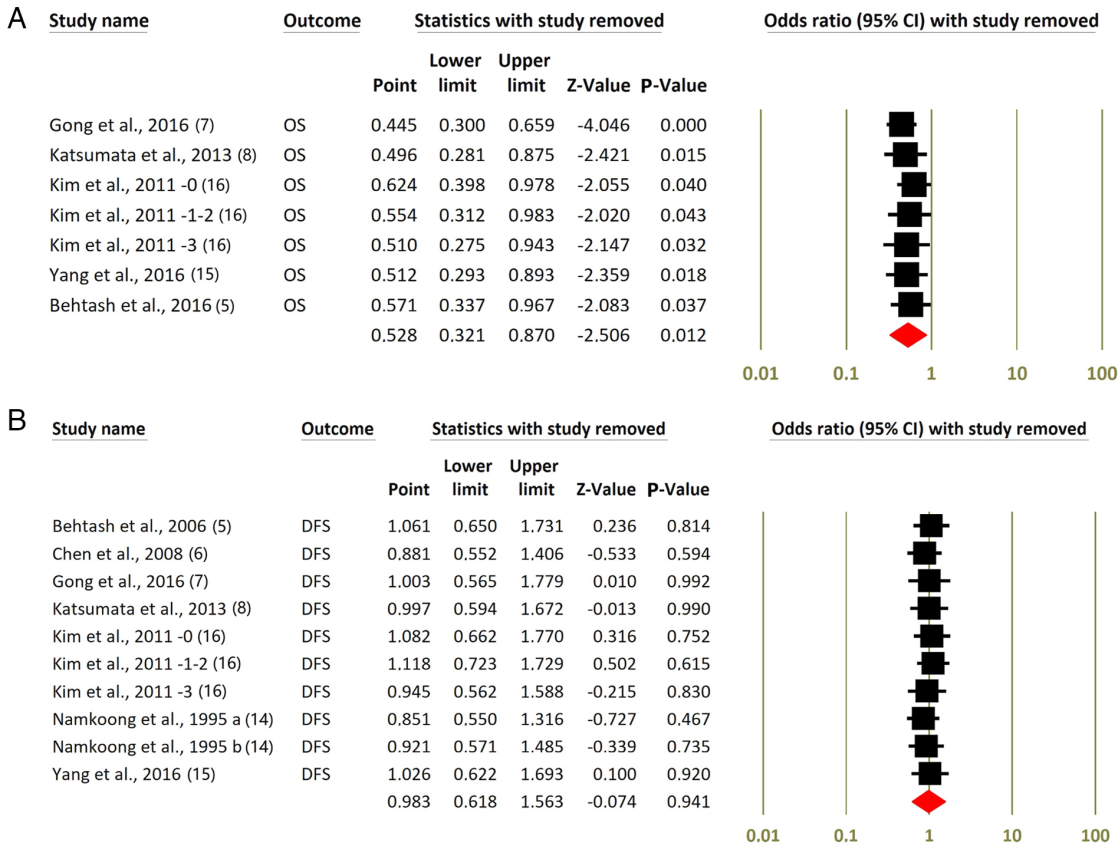

Figure 3. Leave-one-out sensitivity analysis for OS and DFS. Leave-one-out sensitivity analysis presented for (A) OS and (B) DFS in patients treated with NACT followed by RS vs. RS alone. (A) The exclusion of individual studies yields ORs consistently <1.0, with statistically significant P-values, indicating a stable OS benefit for NACT + RS. (B) By contrast, excluding individual studies does not meaningfully alter the DFS estimate, with ORs consistently near 1.0 and non-significant P-values, confirming the robustness of the null effect on DFS. Kim *et al* (16) -0, -1~2 and -3 represent the number of metastatic lymph nodes; this study statistically analyzed OS and DFS after grouping based on the number of lymph node metastases. Namkoong *et al* (14) 1995 a and b represent squamous cell carcinoma and adenocarcinoma, respectively. OS, overall survival; DFS, disease-free survival; NACT, neoadjuvant chemotherapy; RS, radical surgery; OR, odds ratio; CI, confidence interval.

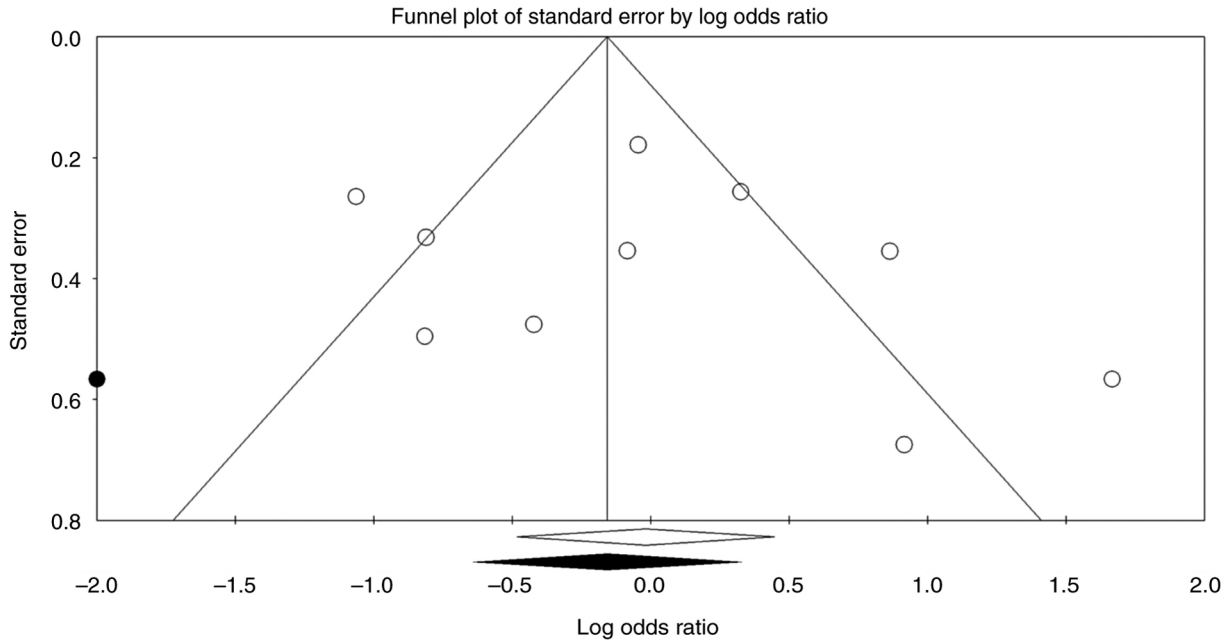

Figure 4. Funnel plot for publication bias assessment. Funnel plot evaluating potential publication bias in the included studies by plotting the standard error against the log odds ratio. The relatively symmetrical distribution of data points suggests minimal risk of bias. Further statistical tests, including Begg and Mazumdar's rank correlation, and Egger's regression test, support the absence of small-study effects, confirming that the overall meta-analysis results are unlikely to be influenced by publication bias.

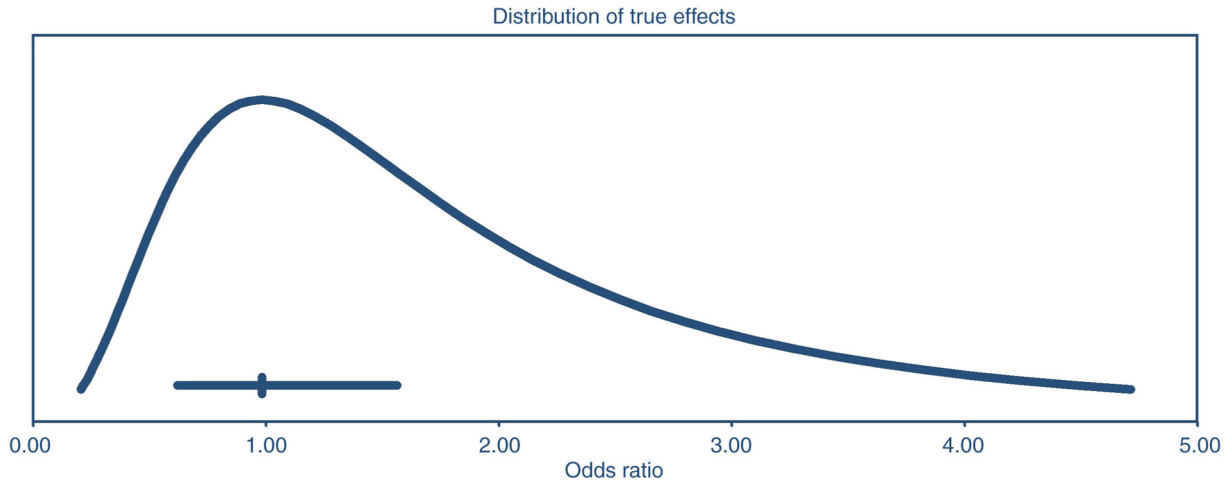

Figure 5. Prediction interval analysis of true effects. Distribution of true effects in the meta-analysis is presented. The mean effect size is 0.98, with a 95% confidence interval ranging from 0.62 to 1.56, indicating no significant overall effect of neoadjuvant chemotherapy followed by RS compared with RS alone. The prediction interval (0.21 to 4.71) highlights the potential variability of true effects in different populations, suggesting that while some subgroups may benefit, others may not. This emphasizes the heterogeneity in treatment outcomes across different clinical settings. RS, radical surgery.

significant association with the treatment effect. Specifically, the proportion of FIGO IIB patients (coefficient, -0.305; P=0.642), chemotherapy regimen (coefficient, 2.470; P=0.551), publication year (coefficient, 0.008; P=0.666), study design (coefficient, -5.735; P=0.559) and sample size (coefficient, 0.016; P=0.631) were not significant moderators. These findings suggest that the variability in OS effect sizes could not be adequately explained by these study-level characteristics, indicating residual unexplained heterogeneity (Table IV). Also, meta-regression analysis was performed to explore sources of heterogeneity in DFS outcomes using five covariates: Chemotherapy regimen, proportion of FIGO stage IIB patients, publication year, study design (randomized controlled trial vs. observational) and sample size. The proportion of FIGO IIB patients was significantly associated with effect size (coefficient, -0.049; P=0.027), suggesting that higher proportions of advanced-stage patients were linked to less favorable treatment effects. None of the other covariates, including chemotherapy regimen (coefficient, 0.098; P=0.289), publication year (coefficient, 0.003; P=0.936), study design (coefficient, -0.240; P=0.496) or sample size (coefficient, 0.0003; P=0.932), reached statistical significance. These results indicate that stage distribution may partially explain the observed heterogeneity (I^2=58%), whereas other study-level characteristics were not significant moderators (Table V).

Table II. Quality assessment of included studies using the Newcastle-Ottawa Scale.

First author, year	Selection (score 0-4)	Comparability (score 0-2)	Outcome/exposure (score 0-3)	Total score (score 0-9)	(Refs.)
Behtash *et al*, 2006	3	1	2	6	(5)
Gong *et al*, 2016	4	2	3	9	(7)
Kim *et al*, 2011	3	1	2	6	(16)
Namkoong *et al*, 1995	3	2	3	8	(14)

Higher scores suggest a lower risk of bias.

Table III. Risk of bias assessment for included randomized controlled trials using Cochrane RoB 2.0 tool[a].

First author, year	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in the measurement of the outcome	Overall risk of bias	(Refs.)
Chen *et al*, 2008	Low risk	Some concerns	Low risk	Low risk	Some concerns	(6)
Katsumata *et al*, 2013	Low risk	Low risk	Low risk	Low risk	Low risk	(8)
Yang *et al*, 2016	Some concerns	Low risk	Low risk	Low risk	Some concerns	(15)

[a]Risk of bias assessment across five domains for the three randomized controlled trials included in the meta-analysis. Assessments were made with ratings of low risk, some concerns or high risk. RoB, risk of bias.

Table IV. Meta-regression results for OS outcomes[a].

Covariate	Coefficient	Standard error	Z-value	P-value	95% CI (lower)	95% CI (upper)
Constant	-0.1140	0.1636	-0.70	0.5578	-0.8178	0.5897
Chemotherapy regimen	2.4702	3.4722	0.71	0.5506	-12.4694	17.4097
FIGO IIB patients (%)	-0.3046	0.5615	-0.54	0.6418	-2.7205	2.1112
Publication year	0.0080	0.0160	0.50	0.6664	-0.0607	0.0767
Study design (0=observational; 1=RCT)	-5.7345	8.2507	-0.70	0.5589	-41.2343	29.7652
Sample size	-0.0156	0.0278	-0.56	0.6307	-0.1352	0.1040

[a]Weighted least squares meta-regression results obtained using log odds ratios as the dependent variable for OS outcomes. Weights were calculated as the inverse of the variance for each study's effect size. OS, overall survival; RCT, randomized controlled trial; FIGO, International Federation of Gynecology and Obstetrics; CI, confidence interval.

Incidence of complications, adverse reactions, recurrence rate and distant metastasis rate. Several of the included studies evaluated the safety profile of NACT followed by RS compared with RS alone in LACC. Gong *et al* (7) found that patients in the NACT + RS group had a lower incidence of postoperative complications (7.30 vs. 13.62%; P=0.002) and postoperative radiotherapy/radiochemotherapy-related adverse effects (3.16 vs. 4.63%; P<0.001) compared with the RS-alone group. On the other hand, Behtash *et al* (5) reported similar recurrence rates in both groups, but the NACT group exhibited a slightly higher rate of distant metastases, although this was not statistically significant.

Operation time and intraoperative blood loss. Patients undergoing NACT followed by surgery in the study by Gong *et al* (7) had a longer operative time (233.66 vs. 224.37 min; P=0.008) and higher intraoperative blood loss (750.34 vs. 684.41 ml; P=0.011) compared with the RS alone group, indicating increased complexity in surgery. By contrast, Katsumata *et al* observed that surgical morbidity

Table V. Meta-regression results for DFS outcomes[a].

Covariate	Coefficient	Standard error	Z-value	P-value	95% CI (lower)	95% CI (upper)
Constant	-1.8372	2.0150	-0.91	0.3916	-6.1210	2.4460
Chemotherapy regimen	0.0975	0.0856	1.14	0.2888	-0.0854	0.2805
FIGO IIB patients (%)	-0.0486	0.0211	-2.30	0.0269	-0.0917	-0.0055
Publication year	0.0034	0.0411	0.08	0.9357	-0.0886	0.0954
Study design (0=observational; 1=RCT)	-0.2396	0.3393	-0.71	0.4958	-1.0358	0.5566
Sample size	0.0003	0.0031	0.09	0.9320	-0.0064	0.0071

[a]Weighted least squares meta-regression results obtained using log odds ratios as the dependent variable for DFS outcomes. Weights were calculated as the inverse of the variance for each study's effect size. RCT, randomized controlled trial; FIGO, International Federation of Gynecology and Obstetrics; CI, confidence interval.

rates were comparable between both groups, suggesting that pre-surgical chemotherapy did not necessarily complicate surgical outcomes (8).

Hematological toxicity. In the trial reported by Katsumata *et al* (8), grade 3 or 4 hematological toxicity was more frequent in the NACT group, particularly leukopenia (41%), neutropenia (56%) and thrombocytopenia (27%). Similarly, Yang *et al* (15) reported that neutropenia and diarrhea were significantly higher in the irinotecan-cisplatin (IP) chemotherapy group compared with that in the paclitaxel-cisplatin (TP) group, although both regimens had tolerable toxicities.

Postoperative radiation requirements. Katsumata *et al* (8) noted lower rates of postoperative radiation requirements in the NACT group (58 vs. 80%; P=0.015), which translated to fewer late radiation-related adverse events. Late adverse events such as urinary retention, lymphedema, vesicovaginal fistula and bowel obstruction were more frequent in the RS-alone group.

Discussion

The management of LACC has historically revolved around two main strategies: Primary CCRT or the combination of NACT followed by RS (1,4,17,18). In recent years, the potential role of NACT before surgery has garnered increasing interest, as it may offer advantages such as downstaging the tumor, facilitating more complete resections and potentially reducing distant metastases (5,6). However, the evidence supporting a definitive survival benefit, particularly when compared with the standard of care, remains inconsistent (7,8,19). The meta-analysis of the present study evaluated the efficacy and safety of NACT followed by RS relative to RS alone in women with LACC (FIGO stages IB2-IIB). These results confirm previous observations for OS while casting doubt on earlier claims regarding DFS improvement. In the present pooled analysis of 7 studies, encompassing a total of 2,231 patients, a complex picture concerning survival outcomes was observed. For DFS, the combined OR hovered near 0.98, with a 95% CI of 0.62-1.56 and a P-value of 0.941. This result indicates that there was no statistically significant difference in DFS between patients receiving NACT followed by RS and those undergoing surgery alone. Particularly, several individual studies within the meta-analysis did report improvements in DFS, but these positive effects did not translate into a significant advantage when pooled across all studies. By contrast, the meta-analysis of OS demonstrated a somewhat more favorable outcome, particularly in a subset of included data. In that subgroup, the OR for OS was 0.53 (95% CI, 0.32-0.87; P=0.012), indicating a statistically significant benefit of NACT plus RS over RS alone. However, when all OS data points were combined in the larger overall analysis, the OR shifted to 0.74 (95% CI, 0.53-1.04; P=0.078), crossing the threshold of statistical significance and thus suggesting only a borderline benefit. These findings suggest that NACT could be beneficial in selected cases; however, the evidence does not support a consistent survival advantage across all settings. Given that CCRT is the standard of care and consistently yields better outcomes than surgery-based approaches alone, the modest OS advantage of NACT + RS observed against RS should not be misinterpreted as an alternative to CCRT. Without direct comparisons to CCRT, the clinical implications of NACT + RS are most relevant in resource-limited settings or for patients unable to undergo radiotherapy.

In the present study, the leave-one-out sensitivity analyses for OS demonstrated that, upon excluding any individual trial, the pooled estimate remained comparatively stable (OR range, 0.45-0.62), consistently showing a significant or borderline-significant advantage for NACT plus RS. IBy contrast, the exclusion of individual studies in the DFS analysis consistently yielded ORs near 1.0 (P-values ranging from 0.467 to 0.990), emphasizing the lack of evidence for DFS benefit and the robustness of this null finding. Furthermore, no strong indications of publication bias were found based on Begg and Mazumdar's rank correlation test, Egger's regression test, the trim-and-fill method or the fail-safe N, all of which suggest that the conclusions about the overall effect estimates are not likely to be confounded by missing or selectively reported studies.

The results of the present study align in part with the those of the meta-analysis conducted by Zhao *et al* (9), which included 13 studies and found that the combination of NACT

and RS significantly improved OS and reduced local and distant recurrence, lymph node metastasis and parametrial infiltration in LACC. In that analysis, however, more consistent improvements in DFS were noted, whereas the pooled data of the present study did not show a statistically significant benefit in disease-free intervals. One possible explanation for this discrepancy is that Zhao *et al* (9) included a slightly different set of studies and varying DFS definitions, follow-up durations and timing of assessments, which may have influenced reported outcomes. Gadducci and Cosio (4) similarly identified improvements in both PFS, a surrogate closely related to DFS, and OS with NACT followed by RS in LACC. The meta-analysis emphasized that these benefits seemed to persist regardless of the total cisplatin dose, cycle length or tumor stage. The results of this study indicate that although neoadjuvant chemotherapy may improve OS rates, when all the data are taken into account, this advantage is not particularly clear. Such mixed results are not unusual in the setting of relatively heterogeneous treatment protocols; the variability in chemotherapy regimens, dosing and timing could attenuate any potential benefit in pooled analyses.

It is also instructive to situate the findings of the present study against the prevailing standard of CCRT. Although the analysis of the present study did not compare NACT plus RS against CCRT per se, several large RCTs and meta-analyses have established that CCRT is highly effective for LACC, leading to robust local control and improved survival rates (10,17). The 2023 ESGO/ESTRO/ESP guidelines (10) recognize that NACT followed by surgery can be an option for selected patients, but do not broadly recommend it as a replacement for CCRT. This stance echoes the ambivalence in the present study's findings, which do not show a consistent or statistically robust advantage of NACT in terms of DFS across the board, and only a borderline or context-dependent improvement in OS.

The lack of a significant improvement in DFS, compared with a borderline benefit in OS, raises several hypotheses. One possibility is that, while NACT may help debulk tumors and eradicate micrometastatic disease early, the subsequent RS and any adjuvant treatment might be sufficient to minimize local recurrences in both groups, thus balancing DFS outcomes over time (12,20). Another factor could be that patients who receive NACT but do not respond well might go on to have surgery delayed or complicated by chemotherapy-induced side effects, ultimately erasing some of the theoretical benefits on DFS. Additionally, DFS in LACC can be influenced by multiple confounders, such as tumor biology, patient comorbidities and post-surgical treatment decisions (e.g., radiotherapy after surgery in cases with high-risk features) (20). By contrast, the modest improvement in OS might suggest that some patients, perhaps those with highly chemosensitive tumors, experience eradication or substantial downstaging of micrometastatic disease, thus improving their overall life expectancy. It is conceivable that such a 'response subgroup' benefits disproportionately from early systemic therapy, tipping OS statistics in favor of NACT plus RS. Indeed, if a subset of patients is particularly responsive to neoadjuvant regimens, they might experience longer survival even if local recurrences (the primary driver of DFS) are not markedly affected at the population level. Additional research is needed to refine the identification of these potential responders based on tumor biology, molecular markers and precise imaging.

Moderate heterogeneity was noted across the included studies in the present analysis. The prediction-interval analysis for DFS indicated that while the summary effect size showed no significant difference from unity (OR, 0.98), the distribution of true effects across settings could range widely, from 0.21 to 4.71. This wide range suggests that while some centers or specific patient subgroups might observe a substantial benefit of NACT, others could see minimal or no advantage. Also, in some contexts, NACT + RS may be harmful. These findings highlight the uncertainty of generalizing the results of the present study and suggest that treatment decisions should be individualized and guided by context-specific factors, such as chemotherapy regimen, surgical expertise and patient characteristics. Factors influencing this variability likely include differences in chemotherapy regimens (e.g., platinum-based doublets vs. single-agent cisplatin), treatment duration (number of cycles), dosing intensity, and subsequent surgical technique and expertise. Further heterogeneity stems from differences in the baseline characteristics of patient populations: Tumor size, histological subtype (squamous vs. adenocarcinoma) and patient performance status can all modulate outcomes (1,4). To explore the sources of heterogeneity in OS outcomes, a meta-regression analysis was conducted incorporating key study-level variables, including chemotherapy regimen, study design, publication year, proportion of FIGO stage IIB patients and total sample size. None of these covariates demonstrated a statistically significant moderating effect on the observed treatment outcomes. For instance, the proportion of stage IIB patients (coefficient, -0.305; P=0.642) and chemotherapy regimen (coefficient, 2.470; P=0.551) showed no association with effect size. Similarly, neither study design nor sample size significantly explained between-study variability. These findings indicate that the moderate heterogeneity (I^2=58%) observed in the pooled OS estimate could not be accounted for by the tested moderators, suggesting the presence of residual clinical or methodological variability not captured in the model. Future trials should collect patient-level data and apply consistent reporting standards to resolve these uncertainties.

Despite these variations, the overall methodological quality of the included studies (as evaluated by the NOS and Cochrane RoB tool) was acceptable to high, with most of the studies having a score of ≥6. This finding suggests that the risk of bias at the study design level, especially selection bias and outcome assessment bias, was generally low. Even the studies with moderate scores (6 points) offered reasonably robust data. Hence, the observed inconsistencies are more likely attributable to genuine clinical heterogeneity than to methodological flaws.

From a clinical standpoint, the findings of the present study support the principle of individualized patient selection for NACT. Even if the benefit in DFS is not established, a borderline improvement in OS for certain populations indicates that NACT plus RS may be advantageous for carefully chosen patients. For instance, younger patients with good performance status and bulky but resectable tumors might derive greater benefit, particularly if their tumors are chemosensitive (5,6). Conversely, older patients or those with significant comorbidities may be at higher risk of toxicity from

chemotherapy, without a sufficient downstaging advantage to justify the addition of NACT.

The safety profile of NACT followed by RS is generally acceptable, with a lower incidence of postoperative complications and a reduction in the occurrence of adverse reactions related to radiotherapy (8). However, NACT is associated with increased hematological toxicity and chemotherapy-related side effects. Surgical complexity (operative time and blood loss) may be slightly increased in the NACT group, though this does not appear to impact long-term surgical morbidity. These findings suggest that while NACT offers some advantages in reducing post-surgical radiation complications, patient selection remains critical to balance the risks of chemotherapy toxicity and surgical challenges (8).

One strength of the present study is the consistent absence of publication bias across four complementary tests. The inclusion of both prospective and retrospective studies, while adding heterogeneity, broadens the generalizability of the results of the present study. A leave-one-out sensitivity analysis was also conducted, to ensure that no single study unduly influenced the conclusions of the present study.

The findings of the present should be interpreted in the context of certain limitations. First, the relatively small number of included studies (n=7) imposes constraints on the statistical power, particularly for subgroup analyses. Second, the analysis relied on available data for DFS and OS, but there was variation in how outcomes were defined and measured across studies. Some studies may have reported PFS or event-free survival as opposed to DFS, and they used different follow-up intervals. Third, heterogeneity in chemotherapy regimens, the number of treatment cycles and surgical expertise can all cause variations in effect sizes. This heterogeneity is partly captured by the wide prediction intervals, indicating that the true effect of NACT in a given clinical setting could deviate substantially from the pooled estimate. Additionally, one important methodological limitation of the present meta-analysis is the use ORs instead of HRs to analyze survival outcomes. While HRs are the preferred and statistically appropriate metric for time-to-event data such as OS and DFS, a number of the included studies reported survival outcomes in dichotomous form (e.g., 3- or 5-year survival status) without providing HRs, log-rank P-values or Kaplan-Meier curves suitable for reconstruction. Due to this constraint, ORs were used to ensure analytic consistency across all studies. However, it is important to recognize that ORs may overestimate the strength of association, particularly when event rates are high and they do not capture the time component of survival. This issue has been acknowledged in the statistical analysis section and it is recommended that future meta-analyses prioritize time-to-event metrics where available to provide more accurate estimates of treatment effects. Finally, NACT plus RS directly was not compared with the current standard treatment, CCRT. While such a comparison was beyond the scope of the present analysis, future systematic reviews might aim to include all three arms (NACT plus RS, RS alone and CCRT) to provide a more direct elucidation of optimal management strategies. Some studies have attempted such three-arm comparisons, albeit with incomplete data for direct head-to-head comparisons (4,17).

In conclusion, the present meta-analysis highlights the nuanced and, in some respects, inconclusive role of NACT followed by RS for the treatment of LACC. While there appears to be a borderline improvement in OS, the data do not demonstrate a clear, statistically significant advantage for DFS when all available studies are pooled. These findings are consistent with broader uncertainties in the literature, where some individual trials and meta-analyses reveal positive effects of NACT and others show limited or no benefits compared with upfront surgery or standard CCRT. Clinicians should interpret these results within the broader clinical context, weighing patient factors such as tumor bulk, performance status, comorbidities and treatment preferences. NACT plus RS may offer a meaningful therapeutic alternative in select populations or settings where radiotherapy resources are limited, but it is not currently poised to replace CCRT as the gold-standard treatment. Future well-designed randomized trials, possibly incorporating biological or molecular markers of chemosensitivity, may help refine patient selection and confirm or refute the borderline OS advantage observed in the present study.

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Availability of data and materials

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

Authors' contributions

FW designed the present study, performed data analysis and drafted the manuscript. FW collected data and contributed to manuscript writing. RP assisted with data collection and statistical analysis. FW and RP confirm the authenticity of all the raw data. YZ contributed to the data interpretation. YZ provided technical support and revised the manuscript. RZ supervised the study and reviewed the manuscript. YZ conceived the study, provided overall supervision and finalized the manuscript. 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.

Use of artificial intelligence tools

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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