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Comparative Efficacy of Induction Chemotherapy and Immune Checkpoint Inhibitor Intensification Strategies in Locally Advanced Cervical Cancer: A Systematic Review and Network Meta-Analysis

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 4 June 2026 and was last updated on 4 June 2026.

INTRODUCTION

Review question / Objective The objective of this network meta-analysis is to evaluate and compare the relative efficacy and safety of novel therapeutic strategies—specifically concurrent immunotherapy combined with chemoradiotherapy (ICI+CCRT) and induction chemotherapy followed by chemoradiotherapy (IC→CCRT)—versus standard cisplatin-based concurrent chemoradiotherapy (CCRT) alone in patients with locally advanced cervical cancer (LACC).

Specifically, this study aims to address the following clinical questions:
1. Which treatment regimen (ICI+CCRT, IC→CCRT, or CCRT) yields the optimal survival outcomes regarding progression-free survival (PFS) and overall survival (OS) in the overall population?
2. Do these novel combination strategies significantly increase the risk of toxicities compared to standard CCRT?
3. To perform explore potential clinical and methodological heterogeneity across the evidence network, pre-specified subgroup analyses will be conducted based on key clinical characteristics, including patient baseline FIGO stages, age groups,etc.

Rationale Concurrent cisplatin-based chemoradiotherapy (CCRT) has long been the standard of care for locally advanced cervical cancer (LACC). However, a substantial proportion of patients still experience disease recurrence or distant metastasis, underscoring an urgent need for more effective therapeutic strategies. Recently, multiple landmark phase III randomized controlled trials (RCTs) have introduced promising intensive approaches, notably adding immune checkpoint inhibitors to CCRT (ICI+CCRT) or integrating induction chemotherapy prior to CCRT (IC→CCRT).

Despite these individual advances, a critical clinical dilemma remains: there is a complete lack of direct, head-to-head randomized trials comparing

ICI+CCRT against IC→CCRT. Consequently, clinicians lack high-level evidence to determine which treatment intensification strategy yields superior long-term survival, or whether their increased toxicities compromise their therapeutic benefits. Furthermore, it remains ambiguous whether specific patient sub-populations derive divergent benefits from these distinct mechanisms of action.

Therefore, a network meta-analysis (NMA) is robustly rationalized to bridge this evidence gap. By utilizing a frequentist graph-theoretical approach, this study will indirectly compare these contemporary regimens, balance their efficacy and safety profiles, and explore potential clinical heterogeneity through pre-specified subgroup analyses.

Condition being studied Locally advanced cervical cancer (LACC).

METHODS

Search strategy 1. Databases to be searched:
We will systematically search the following electronic databases from their inception to the present: PubMed, Scopus, Web of Science and ClinicalTrials.gov. Additionally, we will manually screen the reference lists of relevant reviews and included studies to identify potential missing trials. ClinicalTrials.gov will also be searched for ongoing or unpublished studies.

2. Search strategy example (for PubMed):
#1 "Uterine Cervical Neoplasms"[Mesh] OR "cervical cancer"[Title/Abstract] OR "cervical carcinoma"[Title/Abstract] OR "cervical tumor"[Title/Abstract] OR "cervical neoplasm"[Title/Abstract]
#2 "immunotherapy"[Title/Abstract] OR "immune checkpoint inhibitor"[Title/Abstract] OR "pembrolizumab"[Title/Abstract] OR "durvalumab"[Title/Abstract] OR "atezolizumab"[Title/Abstract] OR "nivolumab"[Title/Abstract] OR "cemiplimab"[Title/Abstract] OR "induction chemotherapy"[Title/Abstract] OR "neoadjuvant chemotherapy"[Title/Abstract]
#3 "chemoradiotherapy"[Title/Abstract] OR "chemoradiation"[Title/Abstract] OR "radiotherapy"[Title/Abstract] OR "radiation"[Title/Abstract] OR "CCRT"[Title/Abstract]
#4 "randomized controlled trial"[Publication Type] OR "randomized"[Title/Abstract] OR "randomised"[Title/Abstract] OR "RCT"[Title/Abstract] OR "clinical trial"[Title/Abstract]
#5 #1 AND #2 AND #3 AND #4.

Participant or population 1. Inclusion Criteria:
– Population: Adult female patients (aged >= 18 years) with a histologically or cytologically confirmed diagnosis of primary cervical cancer.
– Disease Stage: Diagnosed with locally advanced cervical cancer (LACC), defined as FIGO (International Federation of Gynecology and Obstetrics) stages IB2-IIB with lymph node metastasis, or stages III-IVA based on the updated staging classification.

2. Exclusion Criteria:
– Patients with early-stage cervical cancer suitable for primary surgery (e.g., FIGO stage IA to IB1) or those with distant organ metastasis (FIGO stage IVB).
– Patients with recurrent or secondary cervical malignancies.
– Patients who have received prior pelvic radiation or systemic oncological therapies.

Intervention The primary interventions to be evaluated are intensive therapeutic regimens for locally advanced cervical cancer (LACC), which include:
1. Immune checkpoint inhibitor combined with standard concurrent chemoradiotherapy (ICI+CCRT).
2. Induction chemotherapy followed by standard concurrent chemoradiotherapy (IC→CCRT).
Regimens involving different sequences, specific agents, or dosages within these two broad categories will be eligible for inclusion.

Comparator The primary comparator is standard-of-care definitive concurrent chemoradiotherapy (CCRT) alone, typically consisting of platinum-based chemotherapy (usually weekly cisplatin) administered concurrently with external beam radiotherapy (EBRT) and encapsulated by subsequent brachytherapy. Studies comparing ICI+CCRT or IC→CCRT directly against each other will also be included as active comparators.

Study designs to be included This review will exclusively include prospective randomized controlled trials (RCTs), encompassing both phase II and phase III designs, that evaluate the predefined interventions in LACC patients. Observational studies, retrospective cohort studies, case series, non-randomized trials, and laboratory/animal experiments will be strictly excluded to ensure the highest level of clinical evidence.

Eligibility criteria Additional inclusion criteria:

1. Studies must report at least one of the predefined survival outcomes (PFS, OS) or toxicity outcomes.
2. Only peer-reviewed, full-text publications will be included.

Additional exclusion criteria:
1. Studies lacking extractable efficacy or safety data.
2. Duplicate publications or updated reports from the same trial population. In such cases, the most recent and comprehensive dataset was included.

Information sources A comprehensive literature search will be conducted across electronic databases including PubMed, Scopus, Web of Science and ClinicalTrials.gov. To ensure a thorough harvest of data, clinical trial registries such as ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) will be manually screened to track ongoing, recently completed, or unpublished studies. Additionally, the reference lists of all eligible RCTs and relevant systematic reviews will be manually reviewed to identify any potentially missed articles.

Main outcome(s) The primary efficacy outcomes are Progression-Free Survival (PFS) and Overall Survival (OS). PFS is defined as the time from randomization to objective disease progression or death from any cause. OS is defined as the time from randomization to death from any cause. Survival outcomes will be extracted as Hazard Ratios (HRs) along with their corresponding 95% Confidence Intervals (CIs). The timing of these effect measures will be based on the maximum follow-up reported in each primary trial.

Additional outcome(s) The secondary outcomes focus on safety and treatment-related toxicities. Toxicity outcomes will be evaluated using Odds Ratios (ORs) with their corresponding 95% CIs as the standard effect measures, evaluated at the completion of the active treatment phase.

Data management Literature search records will be imported into rayyan to facilitate duplicate removal and initial screening. Two investigators will independently perform title/abstract screening and subsequent full-text assessment based on predefined eligibility criteria. Data extraction will be conducted independently using a standardized Excel spreadsheet. Extracted items will include study characteristics, baseline patient demographics, intervention details, and outcome data. Any discrepancies throughout the selection and extraction process will be resolved through discussion or consultation with a third senior investigator.

Quality assessment / Risk of bias analysis The methodological quality and risk of bias of the included randomized controlled trials will be independently evaluated by two investigators using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool. Five core domains will be assessed: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Each trial will be categorized as having 'low risk', 'some concerns', or 'high risk' of bias. Disagreements will be adjudicated by a third investigator.

Strategy of data synthesis A network meta-analysis (NMA) will be performed using a frequentist graph-theoretical approach via the 'netmeta' package in R software. Given the expected variations in patient cohorts and clinical settings across different multi-center trials, a random-effects model will be implemented. For survival endpoints (PFS, OS), pooled HRs and 95% CIs will be estimated. For binary toxicity outcomes (Any AE, Grade 3+ AE), pooled ORs and 95% CIs will be calculated. Global and local inconsistency between direct and indirect evidence will be rigorously assessed using the design-by-treatment interaction model and the node-splitting method. Treatment regimens will be quantitatively ranked using P-scores.

Subgroup analysis To systematically explore potential clinical and methodological heterogeneity within the evidence network, pre-specified subgroup analyses will be conducted for the primary survival outcomes (PFS, OS) based on the following standard clinical strata and prognostic factors, subject to data availability in the primary trials:
1. Tumor baseline staging and burden: exploring variations across different FIGO stages (e.g., lower-risk vs. higher-risk advanced stages) and status of pelvic/para-aortic lymph node metastasis.
2. Histological subtypes: comparing therapeutic effects between squamous cell carcinoma and adenocarcinoma/adenosquamous carcinoma.
3. Patient demographic characteristics: evaluating potential disparities across different age groups or geographical regions.
4. Methodological and treatment variations: assessing the impact of different external beam radiotherapy (EBRT) modalities (e.g., advanced intensity-modulated techniques vs. conventional radiotherapy).

Sensitivity analysis To guarantee the stability and reliability of the synthesis, pre-specified sensitivity analyses will be conducted to identify potential sources of methodological heterogeneity. We will sequentially restrict the evidence network to studies characterized by low risk of bias, high methodological quality, and definitive trial designs. Additionally, a standard leave-one-out sensitivity analysis will be executed by systematically omitting one trial at a time to determine whether the final efficacy and safety hierarchies are driven by any individual study or specific evidence loop.

Language restriction No language limits or restrictions will be imposed on the literature search.

Country(ies) involved China.

Keywords Cervical cancer; immunotherapy; induction chemotherapy; chemoradiotherapy; network meta-analysis.

Contributions of each author

Author 1 - Qianru Yang - Author 1 drafted the manuscript, developed the study protocol and search strategy, and will be responsible for literature screening and statistical data synthesis.
Email: 18191379349@163.com
Author 2 - Pengtao Yang - Author 2 will perform literature screening and quality assessment.
Author 3 - Yali Wang - Author 3 revised the manuscript and will resolve discrepancies as a third reviewer.