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Neoadjuvant or perioperative immunochemotherapy versus chemotherapy alone for resectable non-small-cell lung cancer: a protocol for a systematic review and meta-analysis of surgical feasibility, pathological response, and perioperative outcomes

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Completed but not published.

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 21 May 2026 and was last updated on 21 May 2026.

INTRODUCTION

Review question / Objective Review question: In patients with resectable non-small-cell lung cancer, does neoadjuvant or perioperative PD-1/PD-L1 inhibitor-based immunochemotherapy improve pathological response, surgical feasibility, R0 resection, and perioperative outcomes compared with chemotherapy alone?

Objective: The objective of this systematic review and meta-analysis is to compare neoadjuvant or perioperative immune checkpoint inhibitor plus platinum-based chemotherapy with chemotherapy alone in patients with resectable non-small-cell lung cancer. The review will focus on pathological complete response, major pathological response, receipt of surgery, failure to undergo surgery, R0 resection, treatment-related adverse events, treatment discontinuation due to toxicity, and postoperative complications.

Rationale Neoadjuvant and perioperative immunochemotherapy has become an important treatment strategy for resectable non-small-cell lung cancer. Previous evidence syntheses have mainly focused on pathological response or survival outcomes. However, whether the improvement in pathological response is accompanied by impaired surgical feasibility or increased perioperative toxicity remains insufficiently clarified. In addition, randomized controlled trials and real-world comparative studies differ substantially in their denominators, surgical selection, and outcome-specific analysis populations. Therefore, a systematic review integrating treatment discontinuation, surgical feasibility, pathological response, and perioperative safety is needed to provide a clinically coherent assessment of this treatment strategy.

Condition being studied Resectable non-small-cell lung cancer. The review will focus on patients with potentially resectable early-stage to locally advanced NSCLC who received neoadjuvant or

perioperative systemic therapy before intended curative surgery.

METHODS

Search strategy A comprehensive search strategy will be developed using controlled vocabulary and free-text terms related to non-small-cell lung cancer, resectable disease, neoadjuvant or perioperative therapy, immune checkpoint inhibitors, chemotherapy, and comparative study design.

The search strategy will include four core concepts:
Disease: non-small-cell lung cancer, NSCLC, lung cancer.
Clinical setting: resectable, operable, neoadjuvant, perioperative, preoperative.
Intervention: immunotherapy, immune checkpoint inhibitor, PD-1, PD-L1, nivolumab, pembrolizumab, durvalumab, camrelizumab, toripalimab, tislelizumab, chemoimmunotherapy, immunochemotherapy.
Comparator and study design: chemotherapy, randomized controlled trial, cohort study, real-world study, comparative study.

The complete database-specific search strategies will be reported in the supplementary materials of the final review.

Participant or population Adult patients with histologically or clinically diagnosed resectable non-small-cell lung cancer, including patients with early-stage or locally advanced resectable disease. Studies enrolling patients with stage IB–IIIB disease will be considered eligible if the population is judged to be potentially resectable and the intervention and comparator meet the predefined criteria.

Studies involving mixed populations will be included only when data for eligible resectable NSCLC patients can be extracted separately or when the majority of the population meets the eligibility criteria and the treatment comparison is directly relevant.

Intervention Neoadjuvant or perioperative immunochemotherapy, defined as PD-1 or PD-L1 inhibitor-based immune checkpoint blockade combined with platinum-based chemotherapy before surgery. Perioperative strategies that include both preoperative immunochemotherapy and postoperative immunotherapy will also be eligible.

Eligible immune checkpoint inhibitors may include, but are not limited to, nivolumab, pembrolizumab, durvalumab, camrelizumab, toripalimab, tislelizumab, or other PD-1/PD-L1 inhibitors when combined with platinum-based chemotherapy.

Comparator Chemotherapy alone, preferably platinum-based chemotherapy, administered as neoadjuvant or perioperative systemic therapy without PD-1/PD-L1 inhibitor treatment.

Studies with mixed comparators, such as chemotherapy combined with radiotherapy or heterogeneous non-chemotherapy control regimens, will be excluded unless chemotherapy-alone data can be extracted separately.

Study designs to be included Randomized controlled trials and comparative real-world studies will be included. Comparative real-world studies may include retrospective or prospective cohort studies, propensity-score-matched studies, inverse probability treatment weighting studies, or other comparative observational designs.Single-arm studies, case reports, case series, reviews, editorials, conference abstracts without extractable comparative data, and non-comparative studies will be excluded.

Eligibility criteria Inclusion criteria:
Patients with resectable non-small-cell lung cancer.
Intervention consisting of neoadjuvant or perioperative PD-1/PD-L1 inhibitor plus platinum-based chemotherapy.
Comparator consisting of chemotherapy alone.
Randomized controlled trial or comparative real-world study design.
Reporting at least one predefined efficacy, surgical feasibility, pathological response, safety, or perioperative outcome.

Exclusion criteria:
Single-arm studies, case series, narrative reviews, systematic reviews, editorials, letters, or conference abstracts without usable comparative data.
Studies in which the intervention or comparator does not match the predefined PICO framework.
Studies without extractable paired comparative outcome data.
Duplicate publications or overlapping cohorts, unless the most complete or most relevant report can be identified.
Studies focusing exclusively on special surgical subgroups or rare pathological subtypes that are not representative of conventional resectable NSCLC.

Information sources PubMed/MEDLINE, Embase, Cochrane Library, Web of Science Core Collection, and Scopus will be searched from database inception to April 5, 2026. Reference lists of eligible studies and relevant reviews will also be screened to identify additional eligible studies.

Main outcome(s) The main outcomes will include:
Pathological complete response.
Major pathological response.
Proportion of patients who underwent surgery.
Proportion of patients who did not undergo surgery.
Grade 3–5 treatment-related adverse events.

Pathological complete response and major pathological response will be extracted according to the definitions used in the original studies. Surgical feasibility outcomes will preferentially be extracted from intention-to-treat or modified intention-to-treat populations when available.

Additional outcome(s) Additional outcomes will include:
R0 resection rate.
Grade 3–4 or grade ≥3 all-cause adverse events.
Treatment discontinuation or interruption due to treatment-related adverse events.
Postoperative complications or surgery-related adverse events.
Long-term outcomes, including event-free survival, disease-free survival, progression-free survival, and overall survival, when available.

Long-term outcomes will be synthesized narratively if quantitative pooling is inappropriate because of heterogeneity in endpoint definitions, time origins, treatment pathways, and follow-up maturity.

Data management All retrieved records will be imported into NoteExpress for deduplication and initial management. Two reviewers will independently screen titles and abstracts, assess full texts, and extract data. Disagreements will be resolved by discussion or by consultation with a third reviewer.

Extracted data will include first author, publication year, study design, country or region, study period, sample size, disease stage, intervention regimen, comparator regimen, treatment strategy, analysis population, outcome definitions, event counts, denominators, effect estimates, and follow-up information.

For each dichotomous outcome, the event number, total number, and analysis denominator will be recorded. If only percentages are reported with a clear denominator, event counts will be recalculated to the nearest integer and documented.

Quality assessment / Risk of bias analysis Randomized controlled trials will be assessed using the Cochrane Risk of Bias 2 tool. Comparative non-randomized studies will be assessed using the ROBINS-I tool. The certainty of evidence for key outcomes will be evaluated using the GRADE approach when appropriate.

Risk-of-bias assessment will consider randomization process, deviations from intended interventions, missing outcome data, outcome measurement, selective reporting, confounding, participant selection, and denominator-related indirectness.

Strategy of data synthesis Dichotomous outcomes will be pooled using odds ratios with 95% confidence intervals. The Mantel–Haenszel method will be used for meta-analysis. Because clinical and methodological heterogeneity is expected across randomized trials and real-world studies, random-effects models will be used as the primary analytical approach.

Heterogeneity will be assessed using Cochran's Q test and the I^2 statistic. Original event proportions and absolute differences per 1000 patients will also be reported to aid clinical interpretation, especially for high-frequency outcomes.

Single-zero-event studies will be handled using continuity correction when required. Double-zero-event studies will not contribute to odds-ratio pooling but will be considered in qualitative interpretation if clinically relevant.

If quantitative synthesis is inappropriate because of substantial heterogeneity or insufficient data, results will be summarized narratively.

Subgroup analysis Prespecified subgroup analyses will be performed when data are sufficient. Potential subgroup factors include:
Study design: randomized controlled trials versus real-world comparative studies.
Treatment strategy: purely neoadjuvant therapy versus perioperative therapy.
Analysis population or denominator: intention-to-treat or modified intention-to-treat population versus operated, postoperative, matched, or evaluable populations.

Outcome definition: standard versus non-standard definitions of pathological response, when applicable.

Sensitivity analysis Sensitivity analyses will include leave-one-out analyses for outcomes with sufficient numbers of studies and recoverable study-level event counts, especially pathological complete response and major pathological response.

Additional sensitivity analyses may be performed by excluding studies with non-standard outcome definitions, potential cohort overlap, high risk of bias, or denominator definitions that are not aligned with the target clinical question.

Language restriction No language restriction will be applied if sufficient data can be extracted. Studies published in languages other than English will be considered if the relevant data can be reliably interpreted.

Country(ies) involved China.

Keywords Non-small-cell lung cancer; resectable NSCLC; neoadjuvant therapy; perioperative therapy; immunochemotherapy; immune checkpoint inhibitor; chemotherapy; meta-analysis.Pulsed field ablation; persistent atrial fibrillation.

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