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Three-dimensional conformal radiation therapy with concurrent chemotherapy for stage III non-small cell lung cancer: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Lung cancer continues to be a common form of cancer worldwide and a primary contributor to cancer-related fatalities. Non-small cell lung cancer (NSCLC) is the most prevalent form, making up 80% to 85% of newly identified malignant lung tumours, and remains a major concern for worldwide health. Surgical resection is the preferred treatment for localised NSCLC, but more than one-third of patients present with locally advanced, unresectable tumours. Concurrent radiation therapy and chemotherapy are believed to offer the potential for prolonged disease-free and overall survival to those patients. However, the results are inconsistent, and systematic meta-analysis is lacking to evaluate its treatment effect comprehensively. Therefore, we will conduct a meta-analysis to evaluate the efficacy and safety of 3D-CRT concurrent chemotherapy in unresectable stage III NSCLC to provide evidence-based medical support for clinical treatment.

Methods and analysis This systematic review and meta-analysis will adhere to the guidelines outlined in the PRISMA statement. Based on the predetermined criteria for inclusion, we will conduct a comprehensive search for randomised controlled trials (RCTs) examining the efficacy and safety of three-dimensional conformal radiation therapy (3D-CRT) concurrent chemotherapy in unresectable stage III NSCLC. The search will be performed across multiple databases including PubMed, Embase, Cochrane, Scopus and Web of Science from inception to 1 November 2024 using terms including NSCLC, 3D-CRT concurrent chemotherapy, radiation therapy, RCT and controlled clinical trial. Furthermore, relevant literature citations will be gathered, and relevant journals will be manually searched. The primary outcomes in the study were overall survival; progression-free survival; 1-, 3- and 5-year survival rates; event-free survival; and median survival time. Secondary outcomes included treatment effectiveness, all adverse events (AEs), all treatment-related adverse events (TRAEs), AEs (grade ≥3) and TRAEs (grade ≥3). Two separate reviewers will be responsible for screening, extracting data and evaluating quality. Our reviewers will perform subgroup analysis, sensitivity analysis and publication bias analysis to evaluate the heterogeneity and robustness. Review Manager 5.4 will be used for the analysis and synthesis process. The risk of bias will be assessed using the Cochrane Risk of Bias tool (RoB 2), and the Grading of Recommendations Assessment, Development and Evaluation will be employed to evaluate the study's overall evidence quality.

Ethics and dissemination This study is based on a secondary analysis of the literature, so ethical review approval is not required. The final report will be published in a peer-reviewed journal.

Trial registration The protocol of the systematic review has been registered on Open Science Framework, with a registration DOI https://doi.org/10.17605/OSF.IO/R7WCG.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This systemic review adheres to the guidelines outlined in the PRISMA-P.
⇒ Two reviewers will each conduct screening, extraction and quality assessment procedures separately to reduce the risk of bias.
⇒ To mitigate the potential risk of publication bias, we will search for both published and unpublished sources.
⇒ The Grading of Recommendations Assessment, Development and Evaluation tool will be used to evaluate the evidence quality of the studies found.
⇒ Combining the outcomes of various studies may lead to an increase in heterogeneity.

INTRODUCTION

Lung cancer remains one of the most prevalent types of cancer globally and a leading cause of cancer-related deaths.[1] According to Cancer Statistics 2024,[2] it is estimated that there will be 2 001 140 new cancer cases in the USA, with an estimated 611 720 deaths, among which lung cancer is the deadliest form of cancer, claiming the lives of approximately 340 people every day.[2]

Non-small cell lung cancer (NSCLC) is the most prevalent form, making up 80% to 85% of newly identified malignant lung tumours,[3 4] and remains a major concern for worldwide health.[5–10] However, NSCLC often exhibits no significant symptoms in its early stages, leading to a situation where most patients are diagnosed at an advanced stage of the disease.[11] Statistics reveal that approximately 40% of patients have distant metastases at the time of diagnosis, while 20% to 30% are in locally advanced, unresectable tumours. Consequently, the proportion of patients eligible for surgical treatment is low,[12] with roughly 80% requiring chemotherapy or radiotherapy as their primary therapeutic approach.[13]

Among the various treatment strategies, the combination of three-dimensional conformal radiation therapy (3D-CRT) with concurrent chemotherapy has emerged as a promising option for unresectable stage III NSCLC. 3D-CRT, an advanced radiation technique, allows for the precise delivery of radiation doses to the tumour while minimising exposure to surrounding healthy tissues. This precision is achieved through the use of computer-generated three-dimensional images of the tumour and surrounding anatomical structures. By conforming the radiation fields to the shape of the tumour, 3D-CRT enhances the chances of tumour control while reducing the risk of adverse effects. Concurrent chemotherapy, on the other hand, involves the administration of anticancer drugs in combination with radiation therapy. This approach is designed to enhance the antitumor effects of both modalities, potentially leading to improved outcomes. The drugs used in chemotherapy can work synergistically with radiation to damage tumour cells, making them more vulnerable to the effects of radiation.[14]

The combination of 3D-CRT with concurrent chemotherapy for unresectable stage III NSCLC may improve local tumour control and potentially prolong survival. However, it is important to note that this approach is associated with a higher risk of toxicity compared with single-modality treatments. Therefore, careful patient selection, close monitoring and appropriate management of toxicities are crucial for the success of this treatment strategy. Chemotherapy is an effective treatment method that can eliminate cancer cells and control the progression of the disease. However, the cytotoxic agents used in chemotherapy also cause damage to normal cells in the body, leading to a high risk of adverse side effects.[15] On the other hand, while 3D-CRT can significantly improve local control rates for NSCLC, it is challenging to effectively prevent the spread and metastasis of cancer cells, thus compromising long-term treatment outcomes.[16 17] Therefore, for patients with unresectable stage III NSCLC, it is crucial to balance the need for both systemic and local therapy to optimise treatment outcomes.

At present, the standard treatment for unresectable stage III NSCLC is concurrent chemoradiotherapy,[18–21] but there is still controversy regarding the selection of chemotherapy regimens. 3D-CRT has gradually received attention and is considered a potential treatment. However, studies have shown that patients with large primary lung tumours or mediastinal metastatic lymph nodes may not benefit from 3D-CRT. In addition, when 3D-CRT is performed concurrently with chemotherapy, if the dose is too high, it may lead to an incidence of acute radiation esophagitis of up to 30% and an incidence of radiation pneumonitis of 14%.[22–26] These toxic and side effects cannot be ignored, so further research and evaluation are needed to assess the efficacy and safety of 3D-CRT concurrent chemotherapy in unresectable stage III NSCLC.[27 28]

In recent years, several studies have suggested that 3D-CRT concurrent chemotherapy can enhance the local control rate and safety of unresectable stage III NSCLC. However, despite some relevant clinical trial data,[16 21 24 29–32] the results are not entirely consistent, and there is a lack of systematic meta-analysis to evaluate its treatment effect comprehensively. To investigate the efficacy and safety of 3D-CRT concurrent chemotherapy in unresectable stage III NSCLC, we will adopt an evidence-based medical approach to rigorously evaluate and analyse relevant clinical trial data, aiming to provide a more reliable basis for clinical treatment decisions.

METHODS

Protocol design and registration

This protocol was created following the guidelines outlined in the 2015 PRISMA-P guidelines. Our findings will be presented following the PRISMA statement for reporting systematic reviews and meta-analyses. The checklist can be found in online supplemental file 1. Our research protocol has been registered on Open Science Framework (OSF) (https://doi.org/10.17605/OSF.IO/R7WCG).

Eligibility criteria

Population: Unresectable stage III NSCLC.
Intervention: 3D-CRT concurrent chemotherapy.
Comparison: 3D-CRT or chemotherapy.

Outcomes

The primary outcomes in the study were overall survival; progression-free survival; 1-, 3- and 5-year survival rates; event-free survival; and median survival time. Secondary outcomes included treatment effectiveness, all adverse events (AEs), all treatment-related adverse events (TRAEs), AEs (grade ≥3) and TRAEs (grade ≥3). The effectiveness of the treatment was assessed based on the Response Assessment Criteria in RECIST 1.0. The total clinical benefit rate included complete response, partial response and stable disease.

Study design

This review will focus on including only randomised controlled trials (RCTs) to gather studies with strong evidence and reduce variability. Other types of trials such as crossover trials, cluster-randomised, quasi-randomised

and non-randomised trials will be excluded. Additionally, non-randomised interventional studies, prospective or retrospective cohort studies, case-control studies, letters, editorials, review articles and case reports will also be excluded.

Information sources and search strategy

A search will be conducted using databases including PubMed, Embase, Cochrane, Scopus and Web of Science from inception to 1 November 2024 using terms including NSCLC, 3D-CRT concurrent chemotherapy, radiation therapy, RCT and controlled clinical trial. There will be no limitations on language or country. The full search strategy is presented in online supplemental file 2. In addition, manual searches including reviewing reference lists and exploring conference proceedings will be included to reduce the chances of overlooking clinical studies.

Two reviewers will conduct a thorough search without limitations on the gender of the subjects or the publication date. The search will commence after the protocol is approved for publication. All search terms and their combinations use the Boolean operators 'AND' and 'OR'.

Selection process

The first step in reviewing studies involves evaluating their titles and abstracts (after removing duplicates), which will be done by two authors independently. If a study is deemed potentially relevant, its full text will be obtained and screened separately by the two authors to determine eligibility. Any reasons for excluding studies will be documented. If there is a disagreement between the two reviewers, they will try to resolve it. If they cannot reach an agreement, a third reviewer will step in to make the final decision.

Data collection process

Two authors will independently conduct data extraction. They will extract and summarise the following information from each study into spreadsheets: study identification, methodological characteristics, sample characteristics, outcomes measured, length of follow-up after intervention and main findings. The data that was gathered included various initial characteristics, and these characteristics are detailed in table 1. In cases where outcome data is unclear or missing in the original article, the corresponding author will be contacted via email for clarification.

Table 1 General information of the included studies

Authors
Publication year
Country
Study design
Sample size (males/females)
Sample characteristics (age and ethnicity)
Intervention
Comparison
Include or exclude
Reason(s) for exclusion
Length of follow-up after intervention (months) (mean and range)
Gross tumour volume mean (cm^3) (range)
Tumour stage
Primary outcomes
①Overall survival
②Progression-free survival
③1-, 3- and 5-year survival rates
④Event-free survival
⑤Median survival time
Second outcomes
①Treatment effectiveness
②All adverse events
③All treatment-related adverse events
④Adverse events (grade ≥3)
⑤Treatment-related adverse events (grade ≥3)

Risk of bias in individual studies

The risk of bias will be assessed using the Cochrane Risk of Bias tool (RoB 2),[33] which categorises randomised trials as having low, some concerns, or high risk based on five domains: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result.[34 35] If there are any missing data, the bias will be considered 'unclear', and efforts will be made to contact the authors for clarification. Two authors will independently evaluate the risk of bias, with any discrepancies resolved by a third author. All studies meeting the inclusion criteria will be included in the analyses, but the interpretation and discussion of results will take into account the RoB2 assessments.

Confidence in cumulative evidence

The evidence's quality will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method.[36–39] Two independent reviewers will use the five GRADE criteria (risk of bias, consistency of effect, imprecision, indirectness and publication bias) to determine the certainty of evidence. The classification will be described as high, moderate, low or very low.

DATA SYNTHESIS

Statistical analysis

If the studies have similar designs and comparators, we will conduct meta-analyses using RevMan 5.4 software, following the statistical guidelines outlined in the current edition of the Cochrane Handbook for Systematic Reviews of Interventions. The Mantel-Haenszel method will be

used for the fixed effect model in cases where tests for heterogeneity are not significant.[40 41] In instances where statistical heterogeneity is present (I^2>50% or p<0.05), the random effects model will be employed.[42 43] If the level of heterogeneity is high, a meta-analysis will not be conducted, and instead, a narrative qualitative summary will be provided.

The analysis of time-to-event results will be done using HR, and for dichotomous data, risk ratio (RRs) with 95% CIs will be used for comparison. Statistical significance will be considered at p<0.05.[44 45] Continuous results will be assessed using weighted mean differences (with 95% CI) or standardised mean differences (with 95% CI) in case of varying measurement scales.

Subgroup analyses and sensitivity analyses

Subgroup analyses or sensitivity analyses will be conducted to investigate the reasons for differences. If the findings can be quantitatively analysed, a meta-regression prediction will be carried out. Sensitivity analyses will take into account quality factors and risk of bias assessed by specific tools.

Assessment of reporting biases

If there are more than 10 studies included, a funnel plot will be used to assess publication bias.[46 47] An uneven or asymmetrical shape of the plot suggests the existence of publication bias. The Egger test will then be employed to examine the asymmetry of the funnel plot.

Narrative synthesis

If a quantitative synthesis is not suitable, a systematic narrative synthesis will be conducted. This synthesis will involve presenting information from the text and tables to summarise and clarify the characteristics and results of the studies included. The narrative synthesis will investigate the connections and findings within and across the studies, following the recommendations from the Centre for Reviews and Dissemination.

Updates to study protocol

If any changes need to be made to the review protocol, these modifications will be recorded and added as additional material with the final manuscript and will also be updated on the OSF register.

Patient and public involvement

This study will not involve patients or the public in any aspect of the design, implementation, reporting or preparation for sharing the results.

Ethics and dissemination

As the data for this study is gathered from published research in databases and does not involve interacting with patients, ethical approval is not necessary. The research results will be disseminated in respected academic journals.

DISCUSSION

This systematic review is focused on assessing the effectiveness of 3D-CRT concurrent chemotherapy in unresectable stage III NSCLC. A thorough search method and specific criteria for inclusion and exclusion will be employed to find pertinent studies. The findings will consolidate the current evidence on 3D-CRT concurrent chemotherapy for unresectable stage III NSCLC and guide future research in this field.

There are several advantages in our study, such as conducting a thorough search of literature with no limitations on language or country. Additionally, two reviewers will independently carry out screening, extraction and quality assessment steps. The GRADE tool will be used to evaluate the evidence quality of the studies found. Nevertheless, it is important to take into account various restrictions as well. First, combining the outcomes of various studies may lead to an increase in heterogeneity. Furthermore, the issue of publication bias, which involves a tendency for positive results to be favoured in publication, is also a concern. To mitigate this bias, we will proactively seek out unpublished studies and investigate sources of grey literature to ensure a thorough and inclusive representation of the available evidence. Other factors, such as variations in patient race, diverse treatment approaches, varying durations of monitoring and differing rates of loss to follow-up, may confer limitations on this study.

We anticipate that this comprehensive review will enhance the understanding of the use of 3D-CRT concurrent chemotherapy for unresectable stage III NSCLC, potentially leading to further research and improved treatment strategies for these conditions.

Contributors XH conceived the study. XH and QC registered the protocol. XH and JZ drafted the protocol. YR and JX revised it. XH and WL developed the search strategies and ran them. LX and SH selected the studies and extracted data. XH and JX analysed the data. All authors contributed to the article and approved the submitted version. XH is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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